Dynamics of Parathyroid Hormone Secretion in Health and Secondary Hyperparathyroidism

Arnold J. Felsenfeld,* Mariano Rodríguez,† and Escolástico Aguilera-Tejero‡

*Department of Medicine, VA Greater Los Angeles Healthcare System and University of California Los Angeles, Los Angeles, California; and †Department Nefrología y Unidad de Investigación, Hospital Universitario Reina Sofia, and ‡Department Medicina y Cirugía Animal, Universidad de Córdoba, Córdoba, Spain

This review examines the dynamics of parathyroid hormone secretion in health and in various causes of secondary hyperparathyroidism. Although most studies of parathyroid hormone and calcium have focused on the modification of parathyroid hormone secretion by serum calcium, the relationship between parathyroid hormone and serum calcium is bifunctional because parathyroid hormone also modifies serum calcium. In normal animals and humans, factors such as phosphorus and vitamin D modify the basal parathyroid hormone level and the maximal parathyroid hormone response to hypocalcemia. Certain medications, such as lithium and estrogen, in normal individuals and sustained changes in the serum calcium concentration in hemodialysis patients change the set point of calcium, which reflects the serum calcium concentration at which parathyroid hormone secretion responds. Hypocalcemia increases the basal/maximal parathyroid hormone ratio, a measure of the relative degree of parathyroid hormone stimulation. The phenomenon of hysteresis, defined as a different parathyroid hormone value for the same serum calcium concentration during the induction of and recovery from hypo- and hypercalcemia, is discussed because it provides important insights into factors that affect parathyroid hormone secretion. In three causes of secondary hyperparathyroidism—chronic kidney disease, vitamin D deficiency, and aging—factors that affect the dynamics of parathyroid hormone secretion are evaluated in detail. During recovery from vitamin D deficiency, the maximal parathyroid hormone remains elevated while the basal parathyroid hormone value rapidly becomes normal because of a shift in the set point of calcium. Much remains to be learned about the dynamics of parathyroid hormone secretion in health and secondary hyperparathyroidism.


This review examines the dynamics of parathyroid hormone (PTH) secretion in health and in various causes of secondary hyperparathyroidism with an emphasis on chronic kidney disease (CKD). For better understanding of factors that affect PTH secretion, the PTH–calcium relationship is evaluated with respect to (1) PTH secretion in the baseline state (basal PTH) and its sensitivity to the serum calcium concentration; (2) the maximal PTH response to hypocalcemia and factors that have been reported to modify the maximal PTH response to hypocalcemia; (3) shifts in the set point of calcium for PTH secretion in normal individuals as a result of treatment with medications such as lithium and estrogen and in hemodialysis patients during sustained changes in the serum calcium concentration; (4) the dynamics of PTH secretion in the secondary hyperparathyroidism of CKD, vitamin D deficiency, and aging; and (5) the phenomenon of hysteresis, defined as a different PTH value for the same serum calcium concentration during the induction of and recovery from both hypo- and hypercalcemia. A focus on hysteresis is justified because it provides important insights into how PTH secretion is modified by rate and directional changes in the serum calcium concentration.

Bifunctional Relationship Between PTH and Serum Calcium

Although PTH secretion is controlled by the serum calcium concentration, it is also important to recognize that through its calcemic actions, PTH regulates the serum calcium concentration. As such, the stimulation of PTH secretion in response to hypocalcemia acts to restore the serum calcium concentration to normal. Similarly, the increase in the serum calcium concentration that is seen with an infusion of PTH or during abnormally high PTH values such as in primary hyperparathyroidism are examples of PTH acting to control the serum calcium concentration. For full understanding of the dynamics of PTH secretion, it is first necessary to appreciate the bifunctionality of the PTH–calcium relationship. As such, the serum calcium concentration controls PTH secretion while simultaneously PTH regulates the serum calcium concentration. Unfortunately, because the infusion of PTH in humans is rarely studied, the vast majority of modern clinical studies are limited to the evaluation of the PTH response to changes in the serum calcium concentration. In general, changes in the serum calcium concentration are induced in normal humans by the use of a...
calcium-chelating agent and a calcium infusion and in hemodialysis patients by the use of low- and high-calcium dialysate concentrations during dialysis sessions.

The importance of integrating the PTH response to changes in the serum calcium concentration with the serum calcium response to PTH is shown in Figure 1 (1). The serum calcium response to PTH is shown as curve 1, and the PTH response to changes in the serum calcium concentration is shown as curve 2. Although the term in general use for curve 2 is the PTH–calcium curve, in actuality, it is the calcium–PTH curve because PTH is the dependent variable. The serum calcium response to PTH (curve 1) is almost linear between 5 and 10 mg/dl, but the calcemic response to PTH decreases when the serum calcium exceeds 10 mg/dl. Reasons for the decreased calcemic response to PTH above a serum calcium of 10 mg/dl include (1) the greater gradient of calcium against which PTH must function; (2) the decrease in serum phosphorus is maximal at PTH values two to three times normal and does not decrease much more at higher PTH values; (3) the deterioration in renal function resulting from hypercalcemia decreases phosphorus excretion, which, in turn, increases the serum phosphorus concentration, thereby compromising the calcemic action of PTH (2–4); and (4) the proportional increase in the percentage of carboxy-terminal and large truncated amino-terminal PTH fragments of which 7-84 PTH is the prototype (5,6). These PTH fragments seem to antagonize the calcemic action of PTH by binding to the carboxy-terminal PTH (C-PTH) receptor (7–9) and possibly by inducing internalization of the PTH1 receptor (10).

As shown in curve 2 (PTH as dependent variable) in Figure 1, hypercalcemia suppresses PTH, and PTH values approach but do not reach zero. The suppression of PTH by hypercalcemia acts to restore serum calcium to normal by increasing renal excretion of calcium through both the effect of reduced PTH values and activation of the calcium-sensing receptor in the loop of Henle. A reduced PTH value also decreases calcium efflux from bone, renal phosphorus excretion, and calcitriol production, all of which act to restore the serum calcium concentration to normal (11). Conversely, when hypocalcemia develops, the resulting increase in PTH restores the serum calcium value to normal by increasing calcium efflux from bone, serum calcitriol production, renal reabsorption of calcium, and renal phosphorus excretion. The effect of the last is mediated through the reduction of the serum phosphorus concentration (11).

The equilibrium operating point (EOP) for the bifunctional relationship is the intersection of curve 1 (calcium as dependent variable) and curve 2 (PTH as dependent variable; Figure 1). It is modified by several factors. Phosphorus restriction and an increased serum calcitriol shift the EOP to the left (12–14) because less PTH is needed to maintain the same serum calcium concentration. Conversely, phosphorus loading, a deficiency of calcitriol, and renal failure shift the EOP to the right (15–19) because more PTH is needed to maintain the same serum calcium concentration.

Measurement of PTH
With the advent of the dual antibody, immunometric assay for the measurement of intact PTH (iPTH) in the late 1980s (20), it was thought that the bioactive form of PTH (1-84 PTH) could be measured with great accuracy. Also, the contemporary prevailing opinion was that the previous PTH assays that measured C-PTH and amino-terminal fragments were no longer needed. In the early 1990s, D’Amour et al. (21) showed that when PTH secretion was stimulated during the induction of hypercalcemia, the ratio of iPTH to C-PTH fragments increased, and when PTH secretion was suppressed during the induction of hypercalcemia, the ratio of iPTH to C-PTH fragments decreased. In a subsequent study, the same authors showed that besides 1-84 PTH, the iPTH assay also detected a non−1-84 PTH fragment of which 7-84 PTH is the prototype (22). In normal humans, the non−1-84 PTH fragment represented approximately 20% of the total iPTH measured with the iPTH assay, but in renal failure, the non−1-84 PTH fragment accounted for approximately 50% of the measured PTH (22,23). In the late 1990s, a second-generation iPTH assay was developed in which the amino-terminal antibody was directed against the first six amino acids, in contrast to the first-generation iPTH assay in which the binding sites for the amino terminal have ranged from epitopes 12 to 34 (6,10). Thus, the second-generation assay eliminated the detection of the large, truncated amino-terminal fragments that were being measured with the first-generation iPTH assay (7,24); however, more recent studies showed that the second-generation iPTH assay also detects an N-form of PTH, different from

---

**Figure 1.** Concept of the equilibrium operating point (EOP) for regulation of the serum calcium concentration. The representation is that of a bifunctional relationship between serum calcium and parathyroid hormone (PTH). In curve 1, serum calcium is a function of PTH; in curve 2, PTH is a function of serum calcium. The intersection of the two function curves determines the EOP for the serum calcium concentration. Factors that decrease the need for PTH, such as hypophosphatemia (↓PO4) and increased serum calcitriol (CTR) values, shift the EOP to the left. Factors that increase the need for PTH shift the EOP to the right. These factors include renal failure, hyperphosphatemia (↑PO4), and decreased serum calcitriol values. Adapted from reference 14 with permission from the American Society of Nephrology.
1-84 PTH. The N-form of PTH accounts for approximately 8% of measured 1-84 PTH in normal individuals and 15% in patients with renal failure (6,25). In a recent study (6) in normal humans, the change in circulating PTH immunoheterogeneity during the induction of hypocalcemia at maximal PTH stimulation and hypercalcemia at maximal PTH suppression was measured by different PTH assays that, in general, were in agreement with HPLC results. The approximate values by PTH assay were (1) baseline state: 1-84 PTH accounted for 23%, non–1-84 PTH for 4.5%, and C-PTH fragments for 73%; (2) hypocalcemia: 1-84 PTH accounted for 33%, non–1-84 PTH for 5%, and C-PTH fragments for 62%; and (3) hypercalcemia: 1-84 PTH accounted for 10%, non–1-84 PTH for 5%, and C-PTH fragments for 85% (6). In dialysis patients, only measurements of 1-84 PTH and non–1-84 PTH have been performed. The respective ratios of 1-84 PTH to non–1-84 PTH in dialysis patients (26) versus normal volunteers (6) were as follows: (1) Baseline state: 1.61 versus 5.09; (2) hypocalcemia (maximal PTH stimulation): 1.89 versus 5.99; and (3) hypercalcemia (maximal PTH suppression): 1.12 versus 2.26. Thus, non–1-84 PTH values are considerably greater as a percentage of 1-84 PTH in dialysis patients than in normal volunteers.

Interest in PTH fragments has increased because Slatopolsky et al. (7) and Nguyen-Yamamoto et al. (8) showed that the C-PTH fragments and the 7-84 PTH fragment (prototype for non–1-84 PTH) inhibited the calcemic action of PTH. It has also been shown that the action of 7-84 PTH and C-PTH fragments were most likely mediated by their binding to the C-PTH receptor (9,27). Moreover, 7-84 PTH may act to internalize the PTH1 receptor in selected target cells in kidney and bone (10).

In this review, the first-generation iPTH assay was used for most of the studies that are presented and evaluated. Even though as cited in the previous paragraph, certain differences are present between the first- and second-generation assays for iPTH, the correlations between the two assays in the basal state (28) and during the induction of hypocalcemia and hypercalcemia remain highly significant both in normal individuals and in patients with CKD (6,26).

Serum Calcium as a Modifier of PTH Secretion
Because we often refer to the PTH–calcium relationship, it is important to define the terms used to analyze and evaluate the PTH–calcium curve. From data obtained during the induction of hypo- and hypercalcemia, the following terms are used to define the PTH–calcium curve: (1) Basal PTH is the PTH level in the baseline state before the induction of hypocalcemia or hypercalcemia. (2) Maximal PTH is the highest PTH value observed in response to hypocalcemia and that an additional reduction of the serum calcium does not further increase PTH. The basal PTH value, 25 pg/ml, and the maximal PTH value, 100 pg/ml, shown in Figure 1 represent values from one of the first studies in normal young adults in whom PTH was measured with the first-generation iPTH assay (29). Subsequent studies (18,30–34) that used the same PTH assay reported similar basal and maximal PTH values in normal humans. (3) Basal serum calcium is the serum calcium concentration at the basal PTH. (4) The ratio of basal to maximal PTH is the basal PTH divided by the maximal PTH. When this fraction is multiplied by 100 in normal volunteers, it is between 20 and 30% (18,29–34). By correcting the basal PTH for the overall capacity to produce PTH (maximal PTH), a measure of the relative degree of PTH stimulation is obtained. When hypocalcemia is present, the basal-to-maximal PTH ratio should be high, indicating that the parathyroid gland is using more of its overall capacity to correct the low calcium. Conversely, hypercalcemia should be accompanied by a decrease in the basal-to-maximal PTH ratio. (5) The set point of calcium is defined as the serum calcium concentration at the mid-range of the PTH–calcium curve. It is used to reflect the sensitivity of the parathyroid gland (PTH secretion) to the serum calcium concentration and also indicates corresponding shifts in the PTH–calcium curve. (6) Minimal PTH is the lowest PTH concentration measured during induction of hypercalcemia. Even in healthy individuals, PTH secretion is not completely suppressed by hypercalcemia.

Basal PTH
From a comparative physiology perspective, basal PTH values seem to be more constant than those of basal calcium. Some mammals, such as the rabbit and the horse, have higher serum calcium values than humans but have PTH concentrations similar to those in humans both in absolute values and as a percentage of maximal PTH (35–39).

Our focus is on the effect of factors—primarily the serum calcium concentration but other factors as well—that have been shown to modify basal PTH levels. Although studies in dialysis patients have shown that calcitriol and its analogs are effective in reducing basal PTH values in many patients, a review of such studies is not our goal. Also, calcimimetics, which greatly reduce basal PTH values in patients with CKD, are not discussed in this review.

Effect of Dietary Phosphate and Vitamin D Status on Basal PTH
Dietary phosphate and vitamin D status are known to affect the development of hyperparathyroidism in both the normal and the azotemic state. Studies in normal and azotemic rats have shown that high dietary phosphate greatly increases PTH values (15,40). Conversely, dietary phosphate restriction reduces PTH values in normal rats and minimizes increases in PTH values in azotemic rats (13,41). Even in normal rats and humans who are given a single meal that contains a high phosphate content, it has been shown that postprandial PTH values increase (42–44). A high-phosphate diet has also been shown to increase prepro-PTH mRNA independent of calcium and calcitriol in normal rats (42). Besides an effect on resistance to the calcemic action of PTH, there is in vitro evidence that phosphorus directly stimulates PTH secretion in intact rat parathyroid glands or slices of hyperplastic human parathyroid glands (45–49). Finally, in hemodialysis patients, high serum phosphorus has been shown to interfere with suppression of PTH by serum calcium (50).

The vitamin D status is another important determinant of the basal PTH value. Vitamin D deficiency is a widely known cause of secondary hyperparathyroidism (51,52). Studies (53,54) have shown that values of 25(OH)D that previously
were thought to be normal are associated with increases in PTH values. As a result, the concept of vitamin D insufficiency has been introduced for 25(OH)D values <30 ng/ml (52,55). Studies (56–58) in patients with CKD have emphasized the importance of repleting vitamin D stores as part of the treatment of hyperparathyroidism.

**Basal PTH and the Effect of Acute Metabolic and Respiratory Acidosis and Alkalosis.** In a series of studies (59–61), we evaluated the effect of acute metabolic and respiratory acidosis and that of acute metabolic and respiratory alkalosis on basal PTH levels. During a 60-min induction of both metabolic and respiratory acidosis during which ionized calcium was clamped at a normal value as blood pH progressively decreased, PTH values rapidly increased by approximately three-fold in both groups (Figure 2A) (59). In a subsequent study (60), during a 60-min induction of both metabolic and respiratory alkalosis in which the ionized calcium concentration was clamped at a normal value as blood pH progressively increased, PTH values rapidly decreased to <25% of basal PTH values in both groups (Figure 2B). These studies showed that acute changes in blood pH rapidly affect PTH secretion.

Although our studies (59–61) showed that acute changes in blood pH directly affect PTH secretion, the possibility that acute changes in blood pH directly affect bone dissolution was not evaluated. Previous in vitro and in vivo studies (62–64) showed that even in the absence of PTH, metabolic acidosis increases calcium efflux from bone. Moreover, Fraley and Adler (65) showed that the administration of PTH to parathyroidectomized animals that received an acid load increased survival; therefore, the results of these studies suggest not only that in acute metabolic acidosis calcium release from bone is increased independent of PTH but also that PTH acts to enhance calcium release further from bone and to increase buffering capacity. Consequently, there is good evidence to suggest that acute metabolic acidosis besides increasing PTH secretion increases the bone response to PTH. As do phosphate depletion and high

---

**Figure 2.** Effect of acute metabolic and respiratory acidosis and acute metabolic and respiratory alkalosis on PTH values during a normocalcemic clamp and the induction of hypocalcemia. (A) Blood pH, ionized calcium (iCa), and PTH values during the induction of metabolic and respiratory acidosis in which a normocalcemic clamp (60 min) was followed by the induction of hypocalcemia (30 min) and a hypocalcemic clamp (30 min). Both metabolic and respiratory acidosis rapidly increased PTH values during the normocalcemic clamp. Metabolic acidosis increased PTH values during the induction of hypocalcemia to values greater than those seen with hypocalcemia alone. (B) Blood pH, iCa, and PTH values during the induction of metabolic and respiratory alkalosis in which a normocalcemic clamp (60 min) was followed by the induction of hypocalcemia (30 min) and a hypocalcemic clamp (30 min). Both metabolic and respiratory alkalosis rapidly decreased PTH values during the normocalcemic clamp. During the induction of hypocalcemia, PTH values increased more rapidly in the control group, but the maximal PTH value that was achieved during hypocalcemia was similar among the three groups. Data are means ± SEM. Results were published previously in references 59 and 60. Reprinted with permission from the American Society for Bone and Mineral Research.
serum calcitriol levels, acute metabolic acidosis seems to shift the EOP (integration of curve 1 and curve 2 in Figure 1) to the left; however, in contrast to phosphate depletion and high serum calcitriol levels that reduce PTH values, metabolic acidosis besides increasing the calcemic action of PTH increases PTH secretion. An explanation for the stimulatory effect of metabolic acidosis on PTH secretion was provided by Quinn et al. (66), who showed that the calcium-sensing receptor was pH sensitive and metabolic acidosis increased PTH secretion by reducing the sensitivity of the calcium-sensing receptor to calcium.

Maximal PTH

Because the PTH–calcium relationship is a sigmoidal curve (curve 2 in Figure 1), the maximal PTH response to hypocalcemia is observed after only a moderate reduction in the serum calcium concentration, and further lowering of serum calcium does not result in any additional increase in PTH values. In clinical disorders such as CKD, vitamin D deficiency, and primary hyperparathyroidism, an increase in parathyroid gland mass from hyperplasia in the former two disorders or an adenoma in most cases of primary hyperparathyroidism is associated with increases in the maximal PTH response to hypocalcemia (18,19,30,33,67). In CKD, calcitriol and its analogs decrease PTH transcription and upregulate vitamin D receptors (68); therefore, it is not surprising that prolonged calcitriol treatment in CKD often results in a reduction in maximal PTH values (69,70). Moreover, treatment with calcitriol besides reducing iPTH values may enhance the intraglandular degradation of iPTH (71).

In a study of the development of CKD (18), a progressive increase in maximal PTH values from 80 to 138 to 312 pg/ml was observed as the creatinine clearance decreased from 110 to 63 to 26 ml/min. Similar results were reported by Cardinal et al. (33). In maintenance hemodialysis patients, the maximal PTH value is often 10 to 20 times greater than normal (70,72,73) and sometimes even greater (74). In a study of vitamin D deficiency in dogs, maximal PTH values increased by more than five-fold as vitamin D deficiency evolved during a 2-yr period (19). In contrast to CKD, in which despite high PTH values normal or high serum phosphorus values are seen, the increase in PTH in vitamin D deficiency results in a decrease in serum phosphorus (19). The decrease in the serum phosphorus value probably increases the calcemic action of PTH and, in turn, reduces the demand for PTH.

In studies (75) of primary hyperparathyroidism in the United States, the weight of the average tumor removed has been approximately five times greater than that of the total weight of all of the normal parathyroid glands, which is approximately 140 mg; however, when primary hyperparathyroidism was first studied in detail in the 1930s and 1940s, the average tumor weight was often 40-fold greater than the total weight of the normal glands (75–77). Today, in China and India and in other developing countries with large populations who often do not have ready access to medical care, the weights of the removed parathyroid adenomas have been reported to be similar to those seen in the United States in the 1930s and 1940s (75–77).

In studies of primary hyperparathyroidism from China and India, (75,78,79) basal PTH values are often 10 to 20 times normal in contrast to values of 1.5 to 2.0 times normal reported in recent American studies. In these patients with great increases in parathyroid gland mass and basal PTH values 10 to 20 times normal, maximal PTH values probably approach and may even exceed values seen in dialysis patients with severe secondary hyperparathyroidism.

Factors that Modify the Maximal PTH Response to Hypocalcemia

Studies in animals have shown that several factors modify the maximal PTH response to acutely induced hypocalcemia. The induction of metabolic acidosis in dogs almost doubled the subsequent maximal PTH (59) (Figure 2A). Similarly, the infusion of parathyroid hormone related peptide (PTHrP) more than doubled the maximal PTH response in both normal and azotemic rats (80,81). In patients who had primary hyperparathyroidism and in whom several days of bisphosphonate treatment corrected the hypercalcemia, the maximal PTH response to hypocalcemia increased by more than twofold (67). Similarly, a single dose of a bisphosphonate given to hemodialysis patients induced a modest but significant increase in the maximal PTH response (82).

In metabolic acidosis, a possible explanation for the increased maximal PTH value is that acidemia decreases the sensitivity of the calcium-sensing receptor (66,83), but even with decreased calcium-sensing receptor sensitivity, it is still necessary to postulate that the PTH response can be enhanced beyond that with hypocalcemia alone. Explanations for the increase in maximal PTH values after the infusion of PTHrP (80) and the correction of the hypercalcemia in patients with primary hyperparathyroidism from bisphosphonate treatment (67) remain unknown. For the former, the presence of a PTH/ PTHrP receptor in the rat parathyroid gland (81) may be important but does not define a mechanism. In the induction of metabolic acidosis, the infusion of PTHrP, and the treatment of hypercalcemia with bisphosphonates, the increases in maximal PTH were dramatic and in the first two developed in <2 hr. Whether the need for more bioactive PTH reduced the intraglandular degradation of 1-84 PTH, as was shown previously in a partial parathyroidectomy model in dogs (71), requires further study.

Another attractive hypothesis for the capacity to increase maximal PTH secretion was suggested a number of years ago on the basis of results from an in vitro study (84). In contrast to classical stimulation-secretion theory in which all hormonal cells respond to a stimulus, only 48% of the parathyroid cells secreted PTH when PTH secretion was stimulated by a low calcium concentration. On rechallenge to a low calcium concentration, additional parathyroid cells were recruited and secreted PTH. If such results are applicable to in vivo PTH secretion, then it could potentially allow a greater response to hypocalcemia if stimuli such as metabolic acidosis, PTHrP infusion, and bisphosphonate-induced lowering of serum calcium result in the recruitment of more secreting parathyroid cells. Another potential mechanism for increased PTH release is the increased posttranscriptional release of PTH mRNA conferred by the regulatory protein adenosine-uridine-rich binding
protein (AUF1). Such a mechanism was shown to contribute to the increase in PTH values in rats that were maintained on a low-calcium diet (85). Although it was possible that the regulatory protein AUF1 could be a factor in the bisphosphonate study in which 5 to 10 d elapsed before restudy (67), it would seem less likely to be a factor in short-term studies such as acute metabolic acidosis or PTHrP infusion.

Other factors have been shown to decrease the maximal PTH response to hypocalcemia. In animals, the induction of hypercalcemia for 2 hr before hypocalcemia was induced reduced the maximal PTH response to hypocalcemia by 40 to 50% (39,86). Furthermore, this effect of hypercalcemia was shown to be dependent on both its degree and its duration (87). The infusion of 7-84 PTH in rats reduced the maximal PTH response to hypocalcemia by approximately 40% (88). Finally, in five-sixths nephrectomized rats on a high-phosphate diet for 20 wk, the maximal PTH level of 1045 pg/ml was reduced to 274 pg/ml, a value not different from normal, when rats were restudied 3 wk after an isogenic kidney transplant and removal of the high-phosphate diet (89).

These inhibitory responses suggest that the PTH response to hypocalcemia can be modified by several factors besides a direct effect of calcium. The amount of PTH available for secretion is controlled by an intraglandular calcium-dependent degradation process (5). Acute hypercalcemia is known to increase the relative proportion of C-PTH and 7-84 PTH fragments as compared with 1-84 PTH (6,21). The possibility that an increase in 7-84 PTH during hypercalcemia may blunt the 1-84 PTH response to the subsequent induction of hypocalcemia is supported by the study in which a 7-84 PTH infusion reduced the maximal PTH response to hypocalcemia (88). The regulatory protein AUF1 could also potentially reduce 1-84 PTH secretion during hypercalcemia (85), but because of the short duration of the hypercalcemia, it is a less likely explanation for the reduction in the PTH response to hypocalcemia in the cited studies (39,86). Similarly, increases in calcitriol have been shown to reduce levels of 1-84 PTH and increase C-PTH fragments (71), but such increases would not be expected during such a short study; therefore, the possibility that 7-84 PTH alone or in combination with C-PTH fragments is responsible for the reduced 1-84 PTH response to hypocalcemia after 2 hr of hypercalcemia must be entertained.

Effect of Rate of Calcium Decrease and the Hypocalcemic Clamp on Maximal PTH. Whether the rate of calcium decrease affects the maximal PTH response to hypocalcemia has been a topic of interest. In one of the first studies in which the iPTH assay was used in normal volunteers, there was no difference in the maximal PTH response to hypocalcemia when the same degree of hypocalcemia was induced over 60 or 120 min (29). In a subsequent study, the PTH response to a 120-min mostly linear decrease in serum calcium was compared with that of a stepwise decrease in which short, rapid decreases in serum calcium were interspersed with short but stable periods of hypocalcemia during the same 120-min period (Figure 3). The latter design resulted in higher PTH peaks during the short, more rapid decreases in the serum calcium concentration, but the PTH value at the end of the induction of hypocalcemia was similar (90). In essence, this pattern of rapid decreases in serum calcium followed by short, constant levels of hypocalcemia is different from a continuous, linear decrease in the serum calcium concentration; however, it is difficult to determine whether the higher PTH value during the accelerated decreases in serum calcium was from a rate effect or from the greater degree of hypocalcemia seen in the normal volunteers who received the episodic decreases in the serum calcium (Figure 3A).

In a study in dogs (91), we did not find any difference in the maximal PTH value whether the linear reduction in ionized calcium was induced over 30 or 60 min (Figure 4, A and B). In another study in dogs (92), a comparison of the PTH response to a linear decrease in the ionized calcium concentration in-
duced over 30 or 120 min showed that the maximal PTH response was modestly but significantly greater at the end of the 30-min induction (Figure 5A); however, when after a 30-min induction of hypocalcemia a more rapid reduction in serum calcium was induced, the PTH value did not increase further (Figure 5B). Conversely, in the group in which the induction of hypocalcemia was over 120 min, a more rapid reduction of serum calcium did further increase PTH to values not different from the maximal PTH value seen when hypocalcemia than during the induction of hypocalcemia is known as hysteresis. Results of PTH hysteresis from dogs in the 60-min cycle were similar (data not shown). Data are means ± SEM. Results were published previously in reference 91. Reprinted with permission from the American Society of Bone and Mineral Research.

Figure 4. PTH response to the sequential induction of and recovery from hypocalcemia and the resulting hysteresis of PTH. The PTH response to the sequential induction of and recovery from hypocalcemia is shown for 30-min (A) and 60-min (B) cycles in the dog. PTH values were similar during the first and second cycles both in the 30- and 60-min groups. (C) Results obtained from dogs in the 30-min cycle are shown. The lower PTH values for the same serum calcium concentration during the recovery from hypocalcemia than during the induction of hypocalcemia is known as hysteresis. Results of PTH hysteresis from dogs in the 60-min cycle were similar (data not shown). Data are means ± SEM. Results were published previously in reference 91. Reprinted with permission from the American Society of Bone and Mineral Research.

Several studies have shown that a hypocalcemic clamp results in a reduction in PTH values as compared with those achieved at maximal PTH even though the same degree of hypocalcemia is maintained (92–94). Some (95–97) have suggested that the reduction in PTH values during a hypocalcemic clamp is due to depletion of PTH stores; however, we have a different explanation for the reduction in PTH levels seen during a hypocalcemic clamp. Figure 5D shows that after a 30-min induction of hypocalcemia, PTH values decreased when a hypocalcemic clamp was initiated between 30 and 60 min. At 60 min, when a further reduction in hypocalcemic values was induced, PTH values increased to levels similar to those seen at 30 min before the hypocalcemic clamp was started. These results suggest that the lower PTH value during the hypocalcemic clamp was not due to depletion of PTH stores but may have resulted from a deceleration in the rate of calcium reduction (92). Moreover, the results of the study by Grant et al. (90), shown in Figure 3B, suggest the possibility that PTH responds to changes in the rate of acceleration and deceleration of the reduction in serum calcium. During the constant serum calcium concentration that followed the rapid decrease in serum calcium, PTH values decreased from the peak values that were seen during the rapid decrease in serum calcium (Figure 3B); therefore, PTH changes that are seen during the acceleration and deceleration of the decrease in the serum calcium concentration may be analogous to the changes in PTH that are seen with the hypocalcemic clamp. Whether an increase in the production of PTH fragments has any role in the decrease in iPTH that is seen during a hypocalcemic clamp remains to be determined.

Finally, results of the study already shown in Figure 4 also suggest that the changes in PTH secretion after a hypocalcemic
clamp or from changes in the rate of calcium acceleration or deceleration are not due to depletion of PTH. In that study, two sequential inductions of hypocalcemia followed by either a 30- or 60-min recovery from hypocalcemia resulted in similar maximal PTH values during the first and second inductions of hypocalcemia, suggesting that PTH stores are not easily depleted.

**Set Point of Calcium**

The set point of calcium is defined as the serum calcium concentration at the mid-range of the PTH–calcium curve and is used to indicate the sensitivity of the parathyroid gland (PTH secretion) to the serum calcium concentration and, as such, also indicates shifts in the PTH–calcium curve. In studies in normal animals and humans, certain conditions have been associated with changes in the set point of calcium. Almost 30 yr ago, Keaton et al. (98) showed that the neonatal calf had an increase in the set point of calcium and thus a right shift of the PTH–calcium curve as compared with the older calf. Whether this result was due to a change in the calcium-sensing receptor remains to be shown. Patients who were treated with lithium had higher ionized calcium values than control subjects and an increase in the set point of calcium with a right shift of the PTH–calcium curve (99). Despite the higher serum calcium concentration, the basal PTH value was greater in the lithium-treated group even though maximal PTH values were similar in the two groups. This result suggests a reduced sensitivity to calcium in the lithium-treated group even though maximal PTH values were similar in the two groups. This result suggests a reduced sensitivity to calcium in the lithium-treated group. In a study in healthy postmenopausal women, 23 wk of estrogen treatment reduced the ionized calcium concentration and decreased the set point of calcium, shifting the PTH–calcium curve to the left even though basal and maximal PTH values did not change (100). A confounding variable in that study was that PTH was measured with a carboxy-terminal assay. In another study (101) in
which an intact assay for PTH was used, estrogen treatment also shifted the PTH–calcium curve to the left. Finally, Mizunashi et al. (102) studied patients with hypoparathyroidism and with pseudohypoparathyroidism. In these patients, hypocalcemia is characterized by low PTH values in the former and high PTH values in the latter. Treatment with calcitriol or its analogs increased the serum calcium concentration and increased the set point of calcium, shifting the PTH–calcium curve to the right in both disorders. In summary, these studies in humans with normal renal function show that medications or treatments that change the existing serum calcium concentration result in a change in the set point of calcium with a shift of the PTH–calcium relationship to the right or left depending on the corresponding change in the serum calcium concentration. Whether these changes in the set point of calcium are mediated through changes in the calcium-sensing receptor, as has been shown in patients with activating and inhibitory mutations of this receptor, or by other mechanisms remains to be determined.

Hysteresis
Studies in normal animals and humans and in hemodialysis patients have shown the presence of hysteresis with respect to PTH secretion (91,103–107). Hysteresis for PTH secretion is defined as a higher PTH value for the same serum calcium concentration during the induction of hypocalcemia than during the recovery from hypocalcemia. An example of PTH hysteresis to the induction of and recovery from hypocalcemia is shown in normal dogs (Figure 4C). The majority of the studies of PTH hysteresis (91,103–107) have evaluated the response to hypocalcemia, but some studies (87,103,107) have evaluated the induction of and recovery from hypercalcemia. In contrast to studies (87,103,107) of hypocalcemia in which PTH values are greater during the induction of hypocalcemia than during the recovery from hypocalcemia, studies of hypercalcemia have shown that PTH values are less during the induction of hypercalcemia than during the recovery from hypercalcemia.

Hysteresis is a widely known physiologic phenomenon that is not unique to PTH secretion. Hysteresis has been reported in such diverse physiologic conditions as papillary muscle contraction (108,109), pressure volume loops of the lung (110,111), regulation of intracranial pressure (112), and autoregulation of renal blood flow (113). Some (95–97) have suggested that the hysteresis of PTH secretion is simply due to a depletion of PTH stores; however, on the basis of results already shown in Figures 3 through 5, it is our hypothesis that hysteresis results from a sensing by the parathyroid gland of a directional change or a deceleration or acceleration in the rate of change in the serum calcium concentration. Moreover, although a reasonable a priori argument could be made for depletion of PTH stores during the induction of hypocalcemia, such an argument cannot be made for hysteresis during the induction of and recovery from hypercalcemia. In the latter, suppression of PTH would not be expected to deplete PTH stores, and PTH values are greater during the recovery from hypercalcemia. Whether directional changes in the serum calcium concentration affect the intracellular degradation of PTH needs to be evaluated. It is possible that during the recovery from hypocalcemia, an increase in C-PTH and 7-84 PTH fragments results in a reduction in 1-84 PTH. Conversely, during the recovery from hypercalcemia, whether a decrease in C-PTH and 7-84 PTH fragments contribute to higher 1-84 PTH values needs to be studied. An extension of studies of induced hypocalcemia and hypercalcemia in normal humans (6) and in hemodialysis patients (26) to include directional changes should help to answer these questions.

If indeed PTH secretion is changed by directional changes in the serum calcium concentration, then the next question should be to decide whether there is a biologic advantage to such a response. Our hypothesis is that hysteresis is a mechanism that prevents an overcorrection of the serum calcium during recovery from hypocalcemia or hypercalcemia (91,104). It is the action of PTH that regulates the serum calcium concentration. In the normal human, the maximal increase in PTH during hypocalcemia is approximately four-fold greater than normal PTH values (18,30–34). At this level of PTH increase, the calcemic actions of PTH, such as the efflux of calcium from bone, enhanced renal reabsorption of calcium, increased phosphorus excretion, and stimulation of 1,25(OH)2D production, are probably maximized. Presumably it takes time before any reduction in PTH values is translated to reduced activity at the tissue/receptor level. Consequently, during the recovery phase from hypocalcemia, it would seem reasonable that a reduction in PTH secretion is necessary to prevent an overcorrection of the serum calcium from hypocalcemia to hypercalcemia by blunting the aforementioned calcemic actions of PTH. Similarly, during the recovery from hypercalcemia, in which PTH values are greater than during the induction of hypercalcemia, more PTH is needed to slow renal calcium excretion and probably to increase phosphorus excretion and bone buffering of calcium to prevent an overcorrection from hypercalcemia to hypocalcemia. Finally, it should be asked whether during the recovery from hypocalcemia an increase in C-PTH and 7-84 PTH fragments retard the calcemic action of 1-84 PTH (7,8) and, conversely, during the recovery from hypercalcemia whether a reduction in C-PTH and 7-84 PTH fragments potentiate the calcemic action of 1-84 PTH.

Effect of Vitamin D Deficiency and Old Age on PTH Secretion
The effects of vitamin D deficiency and of age on the development of hyperparathyroidism are important subjects. Because dividing the effects of vitamin D deficiency and of age into the previously listed categories—1) maximal PTH, 2) basal PTH, and 3) shift of the PTH–calcium curve—would dilute the impact and understanding of these subjects, we present each as a single unit in which maximal PTH, basal PTH, and shift of the PTH–calcium curve are discussed together.

Effect of Vitamin D Deficiency and Repletion
In an important study that was performed in dogs, Cloutier et al. (19,114) showed how vitamin D depletion and repletion affected the development and resolution of secondary hyperparathyroidism. In that study, dogs were placed on a vitamin D– and calcium-deficient diet for 2 yr, after which the repletion...
of vitamin D was studied for 19 mo. During the study, PTH responses to the induction of hypocalcemia and hypercalcemia were performed at regular intervals.

During the induction of vitamin D deficiency, 25(OH)D values progressively fell to very low values, reaching a nadir at 9 mo (Figure 6A). Values of 1,25(OH)D increased during the first 6 mo, fell to normal values at 9 mo, and then declined to modestly subnormal values during the remainder of the 24 mo of the vitamin D–deficient diet. In contrast to the marked deficiency of 25(OH)D, the reason for the only modest decrease in 1,25(OH)D was presumably because the high PTH value and the coexisting hypophosphatemia acted in concert to increase the rate of conversion of 25(OH)D to 1,25(OH)D. Such an action also would act to accelerate the depletion of 25(OH)D (115,116). Ionized calcium values remained normal for the first 6 mo, decreased slightly at 9 mo, and then further decreased at 21 and 24 mo. The basal PTH value (5.09 pM) progressively increased, first becoming significantly elevated at 3 mo and reaching 40.3 pM at 24 mo (Figure 6B).

The maximal PTH value increased from 11.1 pM at the start of the study to 60.1 pM at 24 mo. Although a measurement of the basal/maximal PTH ratio was not provided in the study, we divided the mean value for basal PTH by the mean value for maximal PTH to provide an estimate of the basal/maximal PTH at the various time intervals. As such, the basal/maximal PTH ratio increased from 46% at the start of study to 67% at 24 mo. Also, the increase in iPTH was greater than that of C-PTH fragments in the basal state and also during the induction of hypocalcemia. Such a result could potentially augment the action of iPTH by minimizing the inhibitory effects on C-PTH fragments (7,8).

Treatment of the vitamin D deficiency started at 24 mo. Calcitriol was given for 1 mo and then stopped, after which normal food supplemented with vitamin D was started. During the month of calcitriol treatment, ionized calcium and basal PTH values became normal and 1,25(OH)D increased to supranormal values (Figure 6, A and B). When calcitriol was

Figure 6. PTH and calcium homeostasis during induced vitamin D deficiency and vitamin D repletion. Dogs were placed on a vitamin D– and calcium-deficient diet for 24 mo, after which 1,25(OH)D was given for 1 mo and then vitamin D was given for 18 mo. (A) iCa, 25(OH)D, and 1,25(OH)D values are shown during the development and treatment of vitamin D deficiency. (B) The basal and maximal PTH values are shown. The maximal PTH value was determined during the induction of hypocalcemia with sodium-EDTA. During vitamin D repletion, basal PTH values decreased rapidly to baseline values similar to those before vitamin D deficiency, whereas maximal PTH values decreased slowly and remained three times greater than normal after 19 mo of treatment. (C) The three parathyroid function curves shown are at baseline (A), after 24 mo of vitamin D deficiency (B), and after 19 mo of vitamin D repletion (C). During vitamin D deficiency, hypocalcemia developed and the basal PTH as a percentage of maximal PTH increased (curve B). With vitamin D repletion (curve C), basal PTH as a percentage of maximal PTH decreased to a very low value, which, in turn, resulted in a normal basal PTH level. It should be noted that the scale on the x axis for A and B is not linear. The figure was produced using results published previously in references 19 and 114. Reprinted with permission from the American Society of Bone and Mineral Research.
stopped after 1 mo and vitamin D supplementation was started, ionized calcium and PTH values remained normal, 25(OH)D values increased to normal, and 1,25(OH)D gradually decreased to normal values (Figure 6A).

Whereas basal PTH values rapidly normalized during vitamin D repletion, maximal PTH values decreased very slowly, and 19 mo after vitamin D repletion was started, the maximal PTH value had decreased from only 601 pm to 33.7 pm, a value still three times greater than normal (Figure 6B). Because basal PTH values decreased much more than maximal PTH values, the basal/maximal PTH ratio decreased from 67% at 24 mo to 11% 19 mo after vitamin D repletion was started (Figure 6C). This ratio of 11% was considerably less than the basal/maximal PTH ratio at the start of the study. Moreover, the dramatic reduction in the basal/maximal PTH ratio was rapid. It was seen after 1 mo of calcitriol treatment and continued unchanged when vitamin D treatment was started. In contrast to the development of vitamin D deficiency in which the increase in iPTH exceeded that of C-PTH fragments, the reduction in iPTH during vitamin D repletion was greater than that of C-PTH fragments. The resultant increase in the ratio of C-PTH to iPTH could have potentially acted to reduce the calcemic action of iPTH.

As shown in Figure 6C, the set point of calcium decreased, resulting in a shift to the left of the PTH–calcium curve during the hypocalcemia of vitamin D deficiency (curve B). The expected increase in the basal/maximal PTH ratio that was induced by hypocalcemia was seen with a value of 67%; however, even after vitamin D repletion, the PTH–calcium curve remained shifted to the left of the normal curve throughout the 19 mo of vitamin D treatment (curve C). Moreover, despite the continued left shift of the PTH–calcium curve after vitamin D repletion, the basal/maximal PTH ratio was surprisingly low at 11% (curve C). Because of the low basal/maximal PTH ratio, the serum calcium concentration and the basal PTH value were normal (curve C). In the presence of a high maximal PTH, it is necessary to have both a persistent left shift of the PTH–calcium curve and a low basal/maximal PTH ratio to maintain both a normal basal PTH and a normal serum calcium value; however, even today, >10 yr after the completion of the study, the mechanism for such an adaptation remains unexplained. An attractive possibility is that the increase in C-PTH is responsible for the greater reduction in basal PTH and that the decrease in the set point of calcium is mediated by changes in the calcium-sensing receptor.

This important study of vitamin D deficiency clearly shows that at least in the dog model, the secondary hyperparathyroidism reflected by the high maximal PTH, which is presumably due to parathyroid hyperplasia, takes a long time, if ever, to resolve completely. In the presence of high maximal PTH values, it is necessary for certain adaptations in the PTH–calcium curve to occur to return ionized calcium and basal PTH values to normal. Whether the adaptations described in the dog also apply to vitamin D-deficient patients after treatment has not, to our knowledge, been studied in detail.

**Effect of Old Age**

Many studies have reported that PTH values are higher in elderly than in young adults (117–119). Similar results have also been reported in animals such as the dog and the rat (38,120). Contributing to the higher PTH values in the elderly are several factors that are intrinsic to aging, such as decreased renal function (121), less efficient intestinal absorption of calcium (122), resistance to the calcemic action of PTH (32), a greater prevalence of vitamin D insufficiency (123–125), and perhaps the acidotic tendency of old age (126,127). Three studies used dynamic testing of the PTH–calcium relationship to evaluate whether the age-associated increase in basal PTH values is also associated with an increase in the maximal PTH response to hypocalcemia, which, if present, would indicate a greater secretory capacity in the elderly than in the young adult (31,32,34).

In one study (31), only women were studied; in the second (32), only men were studied; and in the third (34), both men and women were studied. Ledger et al. (31) showed that both basal and maximal PTH values were increased in elderly women. It was also shown that a short course of calcitriol treatment decreased basal and maximal PTH values in both elderly and young women, but both of these values remained greater in elderly women. The other two studies (32,34) also showed that basal PTH values were greater in elderly than in young adults; however, although maximal PTH values tended to be greater, they did not reach significance in the last two studies.

The study by Portale et al. (32) is particularly intriguing because it provides a detailed analysis of PTH action. In the baseline state, the PTH value was almost two-fold greater in elderly men even though ionized calcium values were similar (Table 1). Reflecting the higher PTH values, there was a 25% decrease in the serum phosphorus concentration and a greater nephrogenous cAMP value. Thus, despite a two-fold elevation in PTH and a reduction in serum phosphorus, neither the ionized calcium concentration nor the serum calcitriol value in elderly men was different from values in young men. In other words, a high PTH value even with a decreased serum phosphorus, which should increase the efficiency of PTH, did not increase the serum calcium concentration in elderly men, suggesting the presence of resistance to the calcemic action of PTH. Also supporting such an interpretation was a lesser calcemic response to a PTH infusion in the elderly group. Thus, in the elderly, it seems that there is a dissociation between the calcemic action and phosphaturic effect of PTH. A discussion on how such a dissociation might occur has been described in detail elsewhere (10). These results suggest that age, by virtue of a reduced calcemic response to PTH presumably acting at the bone, should be added to the list of factors that include renal failure, hyperphosphatemia, and calcitriol deficiency, shown in Figure 1, which shift the EOP to the right.

**PTH Response to Serum Calcium in Hemodialysis Patients**

The predialysis or basal PTH value is the primary tool used to evaluate the magnitude of hyperparathyroidism in hemodialysis patients. The purpose of this section is to show that in hemodialysis patients and presumably in patients with advanced CKD, several factors affect the basal PTH value and need to be considered to evaluate appropriately the magnitude of hyperparathyroidism, to understand the physiology of PTH secretion, and to design strategies for the treatment of hyper-
parathyroidism. As such, we discuss (1) the sensitivity to increases in the serum calcium concentration as the severity of secondary hyperparathyroidism increases; (2) the effect that sustained hypocalcemia has on basal and maximal PTH values and the treatment of hyperparathyroidism; (3) the use of the basal/maximal PTH ratio to understand better the dynamics of PTH secretion in patients with CKD and hemodialysis patients; (4) the adaptation of the set point for PTH secretion to sustained changes in the predialysis serum calcium concentration, which, in turn, results in a shift of the entire PTH–calcium curve to the direction of the change in the serum calcium concentration; and (5) the effect of sustained changes in the serum calcium concentration on hysteresis in hemodialysis patients, which serves to highlight features of PTH secretion.

**Sensitivity to Serum Calcium and Increases in Serum Calcium in Hemodialysis Patients**

Low- and high-calcium dialysates were used both before and after calcitriol treatment to obtain PTH–calcium curves in a large group (n = 50) of hemodialysis patients (70). All of the patients had a predialysis (basal) iPTH value >300 pg/ml, and the mean basal PTH value was considerably greater at 773 pg/ml. Patients were designated as responders or nonresponders to calcitriol treatment on the basis of whether the predialysis PTH value decreased by at least 40%. The basal PTH value was less in responders (n = 25) than in nonresponders (n = 25; 586 ± 51 versus 959 ± 80 pg/ml; P < 0.01). The maximal PTH value was also less in responders than in nonresponders (1172 ± 108 versus 1899 ± 170 pg/ml; P < 0.01). Our results were similar to those of Malberti et al. (128), who reported that basal and maximal PTH values as well as parathyroid gland volumes that were obtained by imaging techniques were greater in nonresponders than in responders to calcitriol treatment.

In the responder group, treatment with calcitriol shifted the PTH–calcium curve to the right with a set point of calcium increase from 1.08 ± 0.02 to 1.13 ± 0.02 mM (P < 0.01), and both basal and maximal PTH values decreased (Table 2). As shown by the decrease in the basal/maximal PTH ratio, basal PTH decreased proportionally more than maximal PTH. The greater decrease in basal PTH suggests that basal PTH was more sensitive to the increase in serum calcium than maximal PTH. Conversely, during calcitriol treatment in the nonresponder group, despite a similar shift to the left of the PTH–calcium curve as represented by an increase in the set point of calcium from 1.08 ± 0.03 to 1.13 ± 0.02 mM (P < 0.01), neither basal nor maximal PTH values decreased. As a result, the basal/maximal PTH ratio remained unchanged (Table 2).

For better delineation of the sensitivity of PTH secretion to the serum calcium concentration, the maximal PTH, basal PTH, and basal/maximal PTH ratio were evaluated in greater detail in three groups of hemodialysis patients: (I) Patients who had severe hyperparathyroidism and did not respond to calcitriol treatment (basal PTH 959 ± 80 pg/ml, nonresponders to calcitriol treatment).

### Table 1. Morning fasting blood and 24-h urine composition in healthy elderly and young men

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Elderly (n = 9)</th>
<th>Young (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>74 ± 2</td>
<td>39 ± 1</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>84 ± 2</td>
<td>78 ± 2</td>
</tr>
<tr>
<td>Blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>creatinine (mg/dl)</td>
<td>0.96 ± 0.04</td>
<td>0.92 ± 0.03</td>
</tr>
<tr>
<td>ionized calcium (mg/dl)</td>
<td>4.84 ± 0.04</td>
<td>4.84 ± 0.03</td>
</tr>
<tr>
<td>total calcium (mg/dl)</td>
<td>9.2 ± 0.1b</td>
<td>9.5 ± 0.1</td>
</tr>
<tr>
<td>magnesium (mg/dl)</td>
<td>2.06 ± 0.03</td>
<td>2.00 ± 0.04</td>
</tr>
<tr>
<td>phosphorus (mg/dl)</td>
<td>2.7 ± 0.1c</td>
<td>3.6 ± 0.1</td>
</tr>
<tr>
<td>iPTH (pg/ml)</td>
<td>42 ± 4b</td>
<td>23 ± 4</td>
</tr>
<tr>
<td>1,25(OH)2D (pg/ml)</td>
<td>37 ± 2</td>
<td>31 ± 2</td>
</tr>
<tr>
<td>25(OH)D (ng/ml)</td>
<td>20 ± 2</td>
<td>22 ± 1</td>
</tr>
<tr>
<td>Urine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>calcium (mg/24 h)</td>
<td>190 ± 25</td>
<td>174 ± 19</td>
</tr>
<tr>
<td>phosphorus (mg/24 h)</td>
<td>1071 ± 66</td>
<td>1144 ± 55</td>
</tr>
<tr>
<td>magnesium (mg/24 h)</td>
<td>116 ± 14d</td>
<td>166 ± 11</td>
</tr>
<tr>
<td>FEPi (%)</td>
<td>28.2 ± 1.4c</td>
<td>16.8 ± 1.2</td>
</tr>
<tr>
<td>cAMP (nmol/100 ml GF)</td>
<td>2.75 ± 0.18d</td>
<td>2.16 ± 0.15</td>
</tr>
<tr>
<td>nephrogenous CAMP (nmol/100 ml GF)</td>
<td>1.83 ± 0.19d</td>
<td>1.18 ± 0.16</td>
</tr>
<tr>
<td>creatinine clearance (ml/min)</td>
<td>96 ± 6c</td>
<td>132 ± 5</td>
</tr>
</tbody>
</table>

aData are means ± SEM. iPTH, intact parathyroid hormone; FEPi, fractional excretion of phosphate; GF, glomerular filtrate. Reprinted from reference (32), with permission.

Elderly versus young men: bP < 0.01, cP < 0.001, dP < 0.05.

### Table 2. Parameters of the PTH–calcium curve before and after calcitriol treatment in responders and nonresponders to calcitriol treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Responders (n = 25)</th>
<th>Nonresponders (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal PTH (pg/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre</td>
<td>1172 ± 108</td>
<td>1899 ± 170b</td>
</tr>
<tr>
<td>post</td>
<td>599 ± 70c</td>
<td>2001 ± 312b</td>
</tr>
<tr>
<td>Basal PTH (pg/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre</td>
<td>586 ± 51</td>
<td>959 ± 80b</td>
</tr>
<tr>
<td>post</td>
<td>197 ± 26d</td>
<td>969 ± 85d</td>
</tr>
<tr>
<td>Basal/maximal PTH (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre</td>
<td>52 ± 3</td>
<td>52 ± 2</td>
</tr>
<tr>
<td>post</td>
<td>33 ± 3c</td>
<td>54 ± 3b</td>
</tr>
<tr>
<td>Set point of calcium (mM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre</td>
<td>1.08 ± 0.02</td>
<td>1.08 ± 0.03</td>
</tr>
<tr>
<td>post</td>
<td>1.13 ± 0.02c</td>
<td>1.13 ± 0.02c</td>
</tr>
</tbody>
</table>

aData are means ± SEM. Reprinted from reference (70), with permission.

bP < 0.01, responders versus nonresponders.

P < 0.01, pre- versus post-calcitriol.

dBasal PTH pre- versus post-calcitriol different or not different by definition.
citriol in Table 2); (2) patients who had moderate hyperparathyroidism and did respond to calcitriol treatment (basal PTH 586 ± 51 pg/ml, responders to calcitriol in Table 2); and (3) patients who had diabetes and mild hyperparathyroidism (basal PTH 117 ± 13 pg/ml) (129). In the last group, many patients had basal PTH values that were less than those recommended by Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines (58) but were classified as having mild hyperparathyroidism because PTH values were several times greater than those in normal individuals. In essence, the primary defect is not in the level of PTH but rather in the skeletal response to PTH. The results shown in patients with severe hyperparathyroidism (Figure 7A) and moderate hyperparathyroidism (Figure 7B) were before calcitriol was given. In patients with mild hyperparathyroidism (Figure 7C), ionized calcium values were not available for all patients, so total serum calcium values were used.

As shown in Figure 7, A and B, top, as the serum calcium concentration increased in both the severe and moderate hyperparathyroidism groups, there was a modest but significant increase in maximal PTH. As the serum calcium concentration increased, basal PTH values increased in the severe hyperparathyroidism group, whereas basal PTH values did not change in the moderate hyperparathyroidism group (Figure 7, A and B, middle). In the severe hyperparathyroidism group, the basal/maximal ratio did not decrease, and there was even a tendency for an increase in this ratio (Figure 7A, bottom). This result suggests that in the severe hyperparathyroidism group, basal PTH values were not suppressed by an increasing serum calcium concentration. When multiple regression analysis was performed to evaluate the severe hyperparathyroidism group (Table 3), the basal PTH value (dependent variable) was directly correlated with both the maximal PTH and the serum calcium concentration. Because the increase in basal PTH was associated with an increase in the serum calcium concentration, it suggests that PTH was driving the serum calcium concentration. Conversely, in the moderate hyperparathyroidism group, the basal/maximal PTH ratio decreased as the serum calcium concentration

![Figure 7](image.png)

**Figure 7.** PTH response to the predialysis serum calcium concentration in hemodialysis patients with severe (A), moderate (B), and mild (C) hyperparathyroidism. In hemodialysis patients with severe hyperparathyroidism (A; nonresponders to calcitriol treatment shown in Table 2), both maximal and basal PTH increased as the iCa concentration increased, whereas the basal/maximal PTH ratio did not change. In hemodialysis patients with moderate hyperparathyroidism (B; responders to calcitriol treatment shown in Table 2), the maximal PTH value increased as the iCa concentration increased, but there was no correlation between basal PTH and iCa; however, an inverse correlation was present between the basal/maximal PTH ratio and iCa, suggesting that an increasing serum calcium concentration decreased basal PTH levels. In patients with mild hyperparathyroidism (C), all of whom had diabetes and needed a basal PTH value <300 pg/ml for inclusion in the study, an inverse correlation was present between both basal PTH and the basal/maximal PTH ratio and the serum calcium concentration. It should also be noted that the y axis scale for basal and maximal PTH is less than in A and B. Data are means ± SEM. A and B are reprinted from *Kidney International*; C was produced from data available in reference (129).
concentration increased (Figure 7B, bottom). This result suggests that the increase in serum calcium was acting to suppress PTH secretion. This interpretation is supported by the result of the multiple regression analysis shown in Table 3, in which basal PTH, besides correlating with the maximal PTH, was inversely related to the serum calcium concentration. The latter result suggests that an increasing serum calcium concentration acted to suppress basal PTH values.

Finally, to define better the characteristics of PTH secretion in dialysis patients with even lower PTH values, we included our results in patients with mild hyperparathyroidism (129). As shown in Figure 7C, top, the correlation between maximal PTH and serum calcium was NS. For both basal PTH and the basal/maximal PTH ratio, there was an inverse correlation with the serum calcium concentration (Figure 7C, middle and bottom). Moreover, an inspection of Figure 7C, top, suggests the possibility of two separate populations. A smaller group with a higher maximal PTH in which the maximal PTH value seems to increase as the serum calcium concentration increases is similar to responses seen in Figure 7, A and B. In the other larger group, the maximal PTH seems to decrease as the serum calcium concentration increases. The suppression of both the basal PTH value and the ratio of basal/maximal PTH as the serum calcium concentration increased shown in Figure 7C, middle and bottom, suggests that PTH secretion was even more sensitive to increases in the serum calcium than in the group with moderate hyperparathyroidism shown in Figure 7B. Moreover, the multiple regression analysis for the group of patients with mild hyperparathyroidism (Table 3) shows the presence of an inverse relationship between basal PTH and the serum calcium concentration that is even greater than the correlation between basal and maximal PTH. Thus, as was seen in patients with moderate hyperparathyroidism, an increasing serum calcium concentration acts to suppress basal PTH values in patients with mild hyperparathyroidism.

Our analysis suggests that in dialysis patients, there is a hierarchy of sensitivity of PTH to the serum calcium concentration that becomes progressively less as the magnitude of hyperparathyroidism increases. In many ways, the concept of a hierarchy of physiologic responses of PTH to the serum calcium concentration is similar to the pathologic changes of parathyroid gland hyperplasia in CKD in which the development of diffuse hyperplasia is followed by that of nodular hyperplasia (130). Moreover, the transition from the former to the latter is characterized by a progressive decrease in the calcium-sensing receptor (131) and the vitamin D receptor (132), both of which could respectively contribute to the reduced sensitivity of PTH secretion to increases in the serum calcium concentration and to calcitriol treatment (68,70).

Effect of Sustained Hypocalcemia on PTH Secretion in Hemodialysis Patients
In hemodialysis patients, the question often asked is whether the existing serum calcium concentration is modifying the dynamics of PTH secretion. We studied the effect of the serum calcium concentration on the dynamics of PTH secretion in a group of hemodialysis patients with basal PTH values >500 pg/ml (Figure 8) (73,133). Patients were divided into two groups on the basis of whether the predialysis serum calcium was less than or greater than 9 mg/dl. Whereas the basal PTH value was not different between the two groups, the maximal PTH value in the hypocalcemic group was less (P < 0.01) than that in the normocalcemic group (Figure 8A). The ratio of basal/maximal PTH was greater (P < 0.01) in the hypocalcemic group (Figure 8B). The reason for the similar basal PTH value in the two groups was that hypocalcemia stimulated PTH secretion in the hypocalcemic group. The lesser maximal PTH value in the hypocalcemic group suggests that (1) the magnitude of hyperparathyroidism was less in this group; (2) the response to calcitriol treatment for similar high basal PTH values would be better in the hypocalcemic group than in its normocalcemic counterpart (134); and (3) the better response to calcitriol treatment in hypocalcemic patients is not only because of a lesser degree of hyperparathyroidism but also from the correction of hypocalcemia.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Magnitude of Hyperparathyroidism</th>
<th>Severe</th>
<th>Moderate</th>
<th>Mild</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH (pg/ml)</td>
<td>(Nonresponders to Calcitriol) Basal PTH</td>
<td>959 ± 80</td>
<td>586 ± 51</td>
<td>117 ± 13</td>
</tr>
<tr>
<td>Dependent variable Basal PTH</td>
<td>Basal PTH</td>
<td>Basal PTH</td>
<td>Basal PTH</td>
<td></td>
</tr>
<tr>
<td>Independent variables</td>
<td></td>
<td>(Patients with Diabetes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>basal calcium</td>
<td>2.8 (P = 0.01)</td>
<td>-2.9 (P = 0.008)</td>
<td>-4.0 (P &lt; 0.001)</td>
<td></td>
</tr>
<tr>
<td>maximal PTH</td>
<td>6.5 (P &lt; 0.001)</td>
<td>7.3 (P &lt; 0.001)</td>
<td>3.6 (P = 0.001)</td>
<td></td>
</tr>
<tr>
<td>r²</td>
<td>0.78</td>
<td>0.71</td>
<td>0.54</td>
<td></td>
</tr>
</tbody>
</table>

Studies of parathyroid function were performed in hemodialysis patients with moderate and severe hyperparathyroidism before treatment with calcitriol (70) and in hemodialysis patients with diabetes and mild hyperparathyroidism (129).
Increase in Basal/Maximal PTH Ratio in Hemodialysis Patients

In studies of PTH secretion in dialysis patients, we have consistently found that in the absence of marked hypocalcemia, the basal/maximal PTH ratio generally varies between 40 and 60% (26,69,70,72,129,134–136). A similar increase in the basal/maximal PTH ratio has also been reported in patients with stages 3 and 4 CKD (18,33). In renal failure, the increase in measurable large amino-terminal fragments of which 7-84 PTH is the prototype could conceivably increase the basal/maximal PTH ratio when a first-generation iPTH assay is used; however, even with the use of the second-generation iPTH assay, which does not measure 7-84 PTH, the ratio of basal to maximal PTH in dialysis patients still approaches values that are seen with the first-generation iPTH assay (24,26).

If maximal PTH values are representative of parathyroid gland mass or at least the functional gland mass that is capable of secreting PTH, then the increase in the basal/maximal PTH ratio would suggest that basal PTH can be maintained at high values without a proportional increase in the actual or functional parathyroid gland mass. For example, if the maximal PTH value is 1000 pg/ml, then a normal basal/maximal PTH ratio of 25% would mean that the basal PTH value is 250 pg/ml; however, a basal/maximal PTH ratio of 50% would result in a basal PTH value of 500 pg/ml without a corresponding increase in parathyroid gland mass. The downside of this adaptation is that the reserve PTH response to hypocalcemia would be diminished.

Shift of the PTH–Calcium Curve in Hemodialysis Patients

In normal humans, the serum calcium concentration is tightly controlled (137). In contrast, the serum calcium concentration can be readily modified in hemodialysis patients either by changing the dialysate calcium concentration (135,136,138) or by treatment with calcitriol or its analogs (70,134,135,139–142). In these studies, it was shown that PTH secretion adapts to the existing serum calcium concentration. Because PTH secretion adapts to the existing serum calcium concentration, the hypothesis that we had advanced in the early 1990s that the set point of calcium reflects the magnitude of hyperparathyroidism in hemodialysis patients (72) has less validity than originally suggested. Such a concept originated from the relationship shown in curve 1 of Figure 1, which shows PTH to be the primary modifier of the serum calcium concentration. The calcemic effect of high PTH values is readily appreciated when hypercalcemia is present in hemodialysis patients with severe hyperparathyroidism (Figure 7A) (67,143,144) At the time our hypothesis was advanced, such a concept was in agreement with published in vitro data that had shown that parathyroid glands that were obtained from patients with primary and secondary hyperparathyroidism had a higher set point of calcium than did normal parathyroid glands (145,146); however, as a result of subsequent studies of hyperparathyroidism in hemodialysis patients in whom the set point of calcium increased even though calcitriol treatment decreased PTH values, it became apparent that besides the magnitude of hyperparathyroidism, the adaptation of PTH secretion to the existing serum calcium concentration affected the set point of calcium for PTH secretion.

In most studies in hemodialysis patients that have shown a change in the set point of calcium, the shift of the PTH–calcium curve was to the right as a result of a sustained increase in the serum calcium concentration from calcitriol treatment or the

---

**Figure 8.** Effect of predialysis hypocalcemia on the dynamics of PTH secretion. PTH–calcium curves were performed in hemodialysis patients with hypocalcemia (<9 mg/dl) and normocalcemia (>9 mg/dl) to determine how the dynamics of PTH secretion was influenced by predialysis hypocalcemia. For determination of maximal PTH, hypocalcemia was induced with a low-calcium dialysate (1 mEq/L). For determination of the minimal PTH, hypercalcemia was induced with a high-calcium dialysate (4 mEq/L). (A) The predialysis (basal) PTH value was similar in patients with hypocalcemia and in normocalcemic patients. Even though the predialysis (basal) PTH value was similar in the two groups, both the maximal PTH and the minimal PTH were less in the hypocalcemic group. (B) The maximal PTH was changed to 100%, and basal and minimal PTH are shown as percentage of the maximal PTH. The higher basal-to-maximal PTH ratio shows that the relative degree of PTH stimulation was greater in the hypocalcemic group. Results were published previously in references 73 and 133. Reprinted with permission from the American Society of Nephrology.
use of a high-calcium dialysate (70,134,135,139–141). When the increase in the set point of calcium was associated with a decrease in both basal and maximal PTH values, the decrease in basal PTH was more than that in maximal PTH as is shown by the decrease in the basal/maximal PTH ratio in Table 2 (70,134,135,139–141). This result shows that basal PTH secretion is sensitive to the increase in the serum calcium concentration. Conversely, the PTH–calcium curve can shift to the right after calcitriol treatment without a decrease in basal and maximal PTH (Table 2), but such a shift does show an adaptation of PTH secretion to the higher serum calcium concentration (70,139).

In two studies in hemodialysis patients, a lowering of the serum calcium concentration by the use of a low-calcium dialysate (136) or withdrawal of calcitriol treatment (134) resulted in a decrease in the set point of calcium and a left shift of the PTH–calcium curve. In these studies, the increase in the basal/maximal PTH ratio suggests a sensitivity of basal PTH values to the reduced serum calcium concentration.

**Hysteresis in Hemodialysis Patients**

Our previous study (104) that showed hysteresis in hemodialysis patients is of interest because the patients had a wide range of predialysis ionized calcium values from 3.5 to 5.5 mg/dl. Besides the widely recognized hysteretic response of PTH when the induction of hypocalcemia was started from a normal serum calcium concentration, it was possible to study PTH hysteresis in patients with hypocalcemia and mild hypercalcemia before the serum calcium concentration was intentionally lowered with a low-calcium dialysate. As shown in Figure 9, A and B, when the serum calcium concentration before dialysis was normal or slightly increased, hysteresis of PTH secretion was readily evident; however, when hypocalcemia was present before dialysis, the hysteretic loop for PTH decreased progressively as the magnitude of hypocalcemia increased (Figure 9, C and D). Also of interest was that the intersection of the two PTH curves (induction and recovery) was at a serum calcium value similar to the predialysis serum calcium value (Figure 9). The correlation between the predialysis serum calcium value and

![Figure 9. Hysteresis of the PTH response to the induction of and recovery from hypocalcemia in hemodialysis patients with different predialysis serum calcium values. (A through D) PTH hysteresis in patients with mild hypercalcemia (A), normocalcemia (B), mild hypocalcemia (C), and moderate hypocalcemia (D). As the predialysis serum calcium concentration progressively decreased, the degree of PTH hysteresis (difference between the two curves) also decreased. The decrease in hysteretic loop was because the basal PTH as a percentage of maximal PTH increased with hypocalcemia and the intersection of the two PTH curves occurred near the predialysis serum calcium concentration, which is the iCa value at the basal PTH shown in each panel. Data are means ± SEM. Results were published previously in reference 104. Reprinted with permission from the American Society of Nephrology.](image-url)
the serum calcium value at the intersection of the two PTH–calcium curves was $r = 0.87$ ($P < 0.001$).

Shown in Figure 10 are the composites of the four PTH–calcium curves that were obtained during the induction of hypo- and hypercalcemia and the four PTH–calcium curves that were obtained during the recovery from hypocalcemia. Four distinct and separate PTH–calcium curves were seen during the induction of hypo- and hypercalcemia (Figure 10A); however, during the recovery from hypocalcemia, the four PTH–calcium curves were remarkably similar (Figure 10B).

The finding of four distinct and separate PTH curves during the induction of hypo- and hypercalcemia is supported by other studies that showed that PTH secretion adapts to the existing serum calcium concentration (see the Shift of the PTH–Calcium Curve in Hemodialysis Patients section). The similar path of PTH recovery among the four groups after the induction of hypocalcemia suggests that constancy is present, although it could be argued that in the two hypocalcemic groups, lowering the ionized calcium concentration to values $<3.5$ mg/dl might have produced a different response.

That the path of PTH recovery intersects the induction PTH curve at a serum calcium concentration similar to that of the predialysis serum calcium value can be explained by two characteristics of PTH secretion. First, PTH secretion adapts to the existing serum calcium value, and, therefore, in hypocalcemia, the entire PTH–calcium curve shifts to the left. Second, even though the PTH–calcium curve shifts to the left in hypocalcemia, the shift is not entirely parallel. Hypocalcemia proportionally increases the basal PTH with respect to the maximal PTH so that the basal/maximal PTH ratio increases (see the Effect of Vitamin D Deficiency and Repletion and Effect of Sustained Hypocalcemia on PTH Secretion in Hemodialysis Patients sections). The consequence of the shift of the PTH–calcium curve to the left and the increase in the basal/maximal PTH ratio is that the path of PTH recovery will intersect the induction PTH–calcium curve at a lower serum calcium concentration and a higher PTH value when shown as a percentage of maximal PTH (Figure 9, C and D). Finally, Bas et al. (87) showed that, similar to the findings in hypocalcemia, hysteresis in sustained hypercalcemia depends on the degree of hypercalcemia: When hypercalcemia was severe, the subsequent PTH response during recovery was attenuated and hysteresis was not evident.

Conclusions

The relationship between PTH and serum calcium is bifunctional: PTH regulates the serum calcium concentration while the serum calcium concentration regulates PTH secretion. In acute studies, acid-base disorders were shown to modify PTH values independent of the serum calcium concentration. Although the traditional definition of maximal PTH is the PTH response to hypocalcemia, several factors were shown to increase or decrease acutely the maximal PTH response to hypocalcemia. Also, to a lesser extent, the maximal PTH response to hypocalcemia was shown to be affected by the rate of serum calcium decrease.

Besides CKD, vitamin D deficiency and old age are causes of secondary hyperparathyroidism. In a study of the development and treatment of vitamin D deficiency performed in dogs, the recovery from vitamin D deficiency was particularly intriguing because basal PTH values rapidly returned to normal with treatment of the vitamin D deficiency, whereas maximal PTH values stayed elevated even 19 mo after vitamin D repletion. For achievement of a normal basal PTH level while maximal PTH remained increased, the PTH–calcium curve, which had shifted to the left in vitamin D deficiency, had to stay shifted to

![Figure 10](https://example.com/figure10.png)

**Figure 10.** PTH response to the induction of and recovery from hypocalcemia in hemodialysis patients starting from different iCa concentrations. (A) The PTH response to the induction of hypocalcemia is shown starting from four different predialysis serum calcium concentrations. The basal PTH as a percentage of maximal PTH increased progressively as the magnitude of hypocalcemia increased. (B) The PTH response to the recovery from hypocalcemia is shown to be similar in the four groups. Data are means ± SEM. Results were published previously in reference 104. Reprinted with permission from the American Society of Nephrology.
the left during the 19 mo of vitamin D repletion. Old age is another cause of secondary hyperparathyroidism, and in this state, resistance to the calcemic action of PTH seems to play a major role.

In hemodialysis patients, the basal (predialysis) PTH value is generally used to define the magnitude of hyperparathyroidism; however, the basal PTH value was shown to be modified by the existing serum calcium concentration. In hemodialysis patients with hypocalcemia, basal PTH was increased as a percentage of the maximal secretory capacity (maximal PTH). An increasing serum calcium concentration in hemodialysis patients with mild and moderate hyperparathyroidism was shown to reduce basal PTH values, indicating a sensitivity of PTH to serum calcium. Conversely, in hemodialysis patients with severe hyperparathyroidism, high PTH values act to drive the serum calcium concentration, and an increasing serum calcium concentration did not suppress PTH. In contrast to normal humans, in whom the serum calcium concentration is tightly regulated except in certain situations such as treatment with lithium or estrogen, in dialysis patients, the existing serum calcium concentration can be readily modified by treatment with either active vitamin D compounds or a low- or high-calcium dialysate concentration. When a sustained change in the serum calcium concentration is induced, the entire PTH–calcium curve, as represented by the set point of calcium for PTH secretion, shifts in the same direction as the new serum calcium concentration.

The phenomenon of hysteresis, in which for the same serum calcium concentration the PTH value is different during the induction of and recovery from hypocalcemia and also from hypercalcemia, was discussed in detail because it provides important insights into the physiology of PTH secretion. It is our hypothesis that hysteresis results from an unexplained capacity of the parathyroid gland to sense not only a directional change in the serum calcium concentration but also an acceleration and deceleration in the rate of change in serum calcium. Moreover, in our opinion, PTH hysteresis is important for preventing an overcorrection of the serum calcium concentration during the recovery from hypocalcemia and from hypercalcemia. Finally, it is established that hypocalcemia, the PTH hysteresis response during the recovery from hypocalcemia intersected the PTH value at approximately the same point at which serum calcium was decreased from its original hypocalcemic starting point. As such, it seems to suggest that there was an imprinting of the existing serum calcium value on PTH secretion. Last, the intraglandular degradation of iPTH and the production of large truncated amino terminal fragments (non–1-84 PTH) and C-PTH fragments are modified by changes in the serum calcium concentration and also by the presence of renal failure. Moreover, factors such as calcitriol treatment and partial parathyroidectomy may also alter the intraglandular degradation of iPTH. Whether the hysteresis of PTH secretion produced by directional changes in serum calcium results from the modification of the intraglandular degradation of iPTH and the production PTH fragments remains to be determined. Besides affecting the secretion of iPTH, the production of PTH fragments has been shown to affect the peripheral action of iPTH most notably by decreasing its calcemic action.

During the past two decades, much has been learned about the characteristics of PTH secretion. The seminal discovery of the calcium-sensing receptor and increased knowledge about the intracellular transcription and processing of PTH have provided us with a greater understanding of the factors that control PTH synthesis and secretion, but much remains to be learned, especially about the mechanisms of how PTH secretion adapts to (1) the existing serum calcium concentration, (2) directional changes in serum calcium together with those of acceleration and deceleration in the rate of change in serum calcium, and (3) a high maximal PTH value during the recovery from vitamin D deficiency by a left shift of the PTH–calcium curve.

Acknowledgments

M.R. received grant support from the Fondo de Investigacion Sanitaria of Spain (PI 041328) and from the Junta de Andalucia (106/03). E.A.-T. received grant support from the Ministry of Education and Science of Spain (grant SAF 2005-0144).

Disclosures

M.R. has research grants from Amgen, is a member of the Advisory Board of Amgen and Shire, and has received honorarium from Amgen and Shire. E.A.-T. is a co-investigator on a research grant from Amgen held by M.R.

References

1. Parfitt AM: Bone and plasma calcium homeostasis. Bone 8[Suppl 1]: S1–S8, 1987
centrations in rats by acting on a receptor different from the PTH/PTH-related peptide receptor. *Endocrinology* 142: 1386–1392, 2001


43. Li F, Muhlbaier RC: Food fractionation is a powerful tool to increase bone mass in growing rats and to decrease bone mass in aged rats: Modulation of the effect of dietary phosphate. *J Bone Miner Res* 14: 1457–1465, 1999


69. Dunlay R, Rodriguez M, Felsenfeld A, Llach F: Direct inhibitory effect of calcitriol on parathyroid function (sig-


129. Felsenfeld AJ: Considerations for the treatment of second-


