

# Phosphorus, Regulation of Plasma Calcium, and Secondary Hyperparathyroidism: A Hypothesis to Integrate a Historical and Modern Perspective

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Fifty years ago, Fuller Albright in his classic book, *Parathyroid Glands and Metabolic Bone Disease*, advanced the concept that phosphorus was critical for the modulation of calcium mobilization from bone and the regulation of plasma calcium (1). The basis for his conclusions were elegantly summarized in his book and were derived from his meticulously performed clinical studies during the previous 20 years in which prolonged calcium and phosphorus balance studies were obtained in patients with parathyroid disorders. In these studies, parathyroid extract was infused in healthy volunteers and in patients with primary hyperparathyroidism ( $1^0$  HPT) and hypoparathyroidism (2–5). Albright observed that the increase in serum calcium always followed the phosphaturic response. In a separate series of studies, the administration of vitamin D and AT10 (dihydroxycholesterol) and the infusion of calcium were evaluated in patients with hypoparathyroidism (6,7). In these studies, Albright observed that even in the absence of parathyroid hormone (PTH), an increase in serum calcium was associated with a decrease in serum phosphorus and increased urinary phosphorus excretion. As a result of these studies (2–7), Albright concluded that the primary action of PTH was on renal phosphorus excretion and that the resulting changes in serum calcium were not due to a direct effect of PTH on bone but rather were secondary to PTH-induced changes in serum phosphorus. Thus, according to Albright, the increased calcium mobilization from bone was an indirect effect of PTH due to its lowering of serum phosphorus (1). Although we do not believe or even suggest that PTH does not have a direct effect on bone, we do believe that Albright's observations about the central role of phosphorus on calcium mobilization from bone and plasma calcium regulation deserve much greater emphasis. In this article, we use available data from previous clinical and experimental studies to develop our hypothesis that phosphorus plays a critical role in the regulation of plasma calcium and PTH-mediated calcium mobilization from bone.

In his 1948 book (1), Albright concluded that PTH-enhanced renal excretion of phosphorus was the primary mechanism for increased calcium mobilization from bone for the following reasons. (1) The first consequence of PTH administration was to increase phosphorus excretion and all else followed subsequently. In more recent studies, it has been shown that after a PTH infusion, a rapid decrease in serum phosphorus and increase in urinary phosphorus are observed before any change in serum calcium (8). (2) Forced feeding of phosphorus to patients with  $1^0$  HPT lowered serum calcium and urinary calcium excretion; perhaps it should be added that today we also know that such an approach increases PTH levels, and still serum calcium decreases (9). (3) In patients with renal insufficiency and phosphorus retention, it was not possible to increase serum calcium with parathyroid extract. (4) Many patients with  $1^0$  HPT never develop bone disease. This suggested to Albright that the bone disease was a secondary complication (1).

These observations clearly show that Albright had thought in considerable depth about the mechanism of PTH action. In 1942, Collip, the first investigator to prepare biologically active parathyroid extract in 1925 (10) and who advanced the concept that PTH had a direct effect on bone, performed a study that strengthened Albright's belief in the primacy of phosphorus. A bilateral nephrectomy or ureteral ligation was performed in dogs to prevent the urinary excretion of phosphorus and any reduction in serum phosphorus. The study showed that the infusion of parathyroid extract failed to increase the serum calcium (11).

Although Albright believed that PTH-induced phosphorus excretion was responsible for calcium mobilization from bone, he also acknowledged in his book (1) that considerable evidence available from previous studies, including his own (12), suggested that PTH had a direct effect on bone. We believe that the concept advanced by Albright that phosphorus directly modifies calcium mobilization from bone has failed to receive sufficient attention. As so often happens, when the primacy of one concept gains ascendancy (direct effect of PTH on bone), other observations that were correct (effect on phosphorus on calcium mobilization from bone) are left to languish and fail to be adequately integrated into the framework of the accepted dogma. Although our emphasis will be on clinical and animal studies, it should also be noted that several excellent *in vitro* studies, one of which is shown in Figure 1, have convincingly

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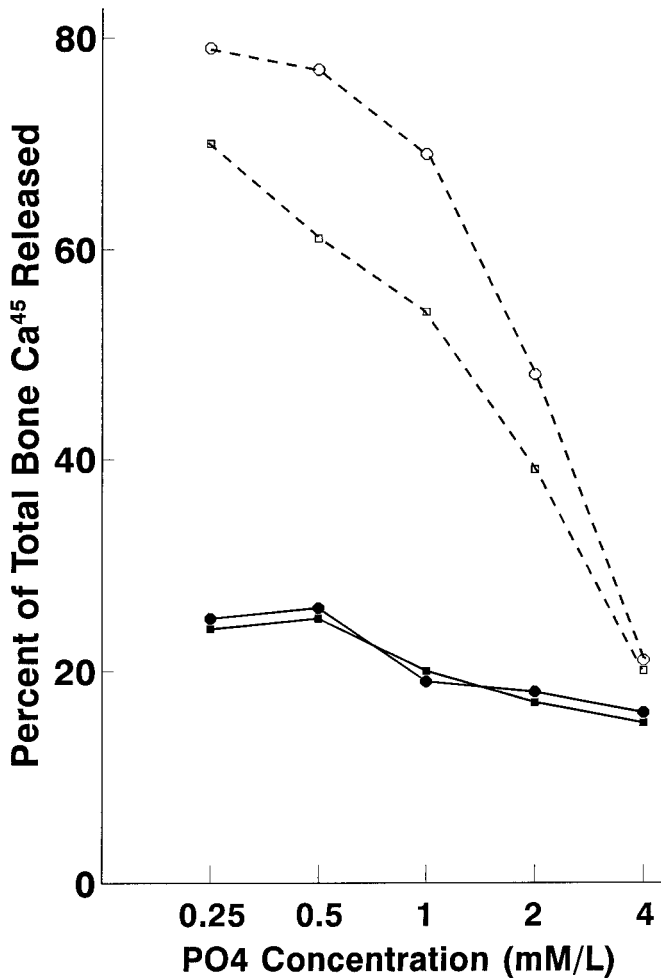


Figure 1. Results of an *in vitro* study demonstrating that parathyroid hormone (PTH) enhances calcium efflux from bone and that phosphate markedly reduces calcium efflux from bone both in the presence and absence of PTH. ○, PTH-live; □, control-live; ●, PTH-killed; ■, control-killed. From Raisz *et al.*, (13) and reprinted with permission from *Endocrinology*.

demonstrated that an increase in the medium concentration of phosphorus profoundly reduced calcium efflux from bone and dramatically reduced the calcemic action of PTH on bone (13,14). In these studies, a distinct effect of phosphorus was shown between a 1 mM and 2 mM phosphorus concentration, a range observed in humans and many animal species.

### Concept of the Equilibrium Operating Point (Set Point)

To show that phosphorus is a critical factor in the modulation of calcium mobilization from bone, we have used an approach to the PTH–calcium relationship that has been advocated by Parfitt (15,16). In this approach, the relationship between serum calcium and PTH is expressed as a function of each other and has been described as reciprocal causality in which the dependent and independent status are interchanged. Parfitt states that these functions can be of mathematical form, provided that they are monotonic and have slopes of opposite

sign so that they intersect at only one point, referred to as the equilibrium operating point (15–17). As shown in Figure 2, the equilibrium operating point or the set point (not to be confused with the secretory set point of the PTH–calcium curve) is the intersection of the two function curves formed when PTH modifies the serum calcium and the serum calcium modifies PTH. The former is obtained when different doses of PTH are infused and serum calcium is measured; in clinical studies, the inability to perform such studies has limited this approach. The latter function curve is obtained when PTH secretion is modified by changes in the serum calcium; this is the traditional PTH–calcium curve that has been performed in many animal and clinical studies (18–22). The approach advocated by Parfitt (15,16) and others (17) shows that the system for calcium homeostasis between the parathyroid gland, bone, and kidney should be viewed as an integrated, self-correcting system that is modified by several important factors, including phosphorus, calcitriol, and renal and bone function. These factors modify calcium as a function of PTH (curve 1). Our goal is to show that based on previous studies performed in both azotemic and nonazotemic humans and animals, phosphorus has a critical role in the modification of the bifunctional relationship between PTH and calcium.

### Serum Calcium and Phosphorus as a Function of PTH

In our recent study, different doses of PTH were infused in parathyroidectomized rats via subcutaneously implanted miniosmotic pumps (23). As shown in Figure 3, we determined

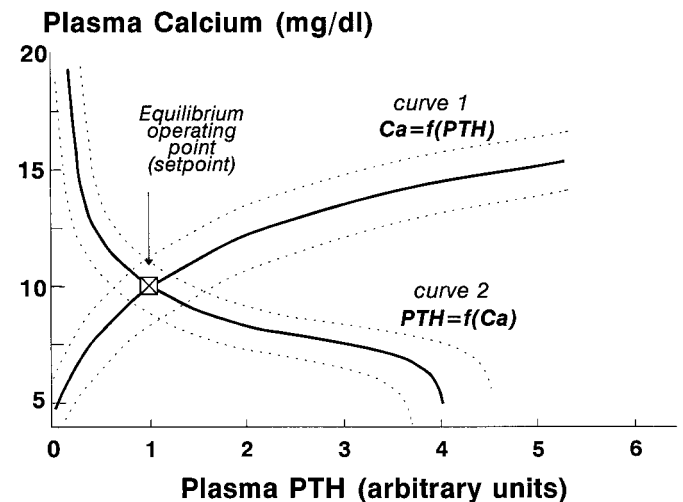
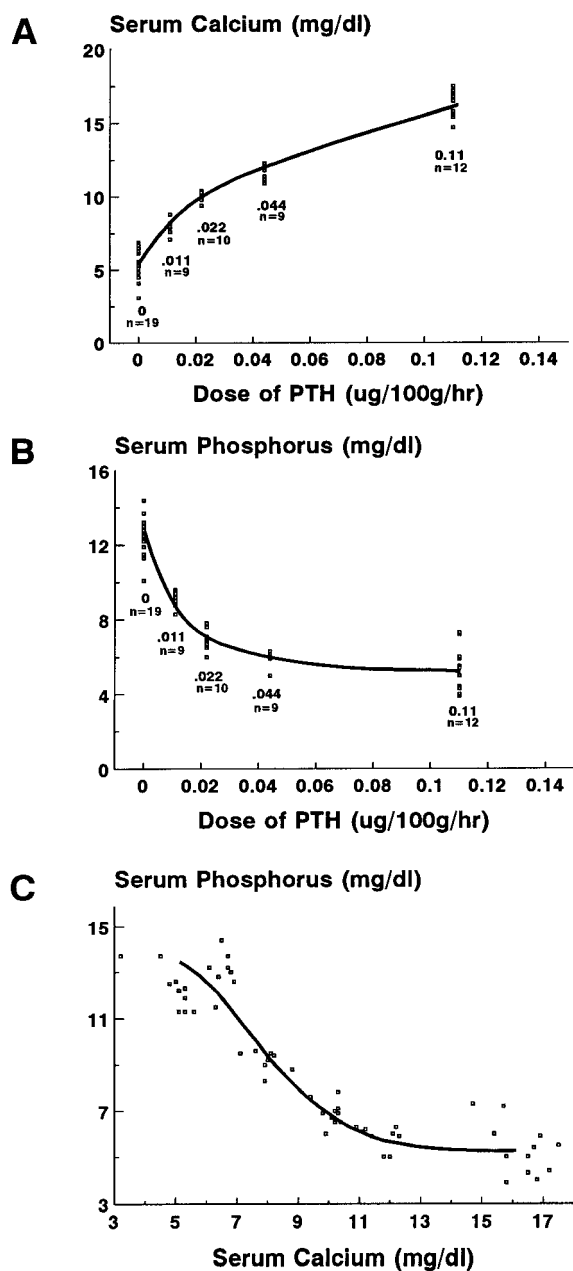


Figure 2. Adapted from Parfitt (15,16). The representation is that of reciprocal causality between calcium and PTH. In curve 1, calcium is a function of PTH, and in curve 2, PTH is a function of calcium. The intersection of the two function curves determines the equilibrium operating point or set point for the system. Plasma PTH is in arbitrary units, but we have modified the original figure by Parfitt so that the maximal PTH represents the approximate multiple seen in studies in healthy humans in which the basal and maximal intact PTH are approximately 25 and 100 pg/ml, respectively (Brent *et al.*, reference 18). Reprinted with permission from *Bone*.

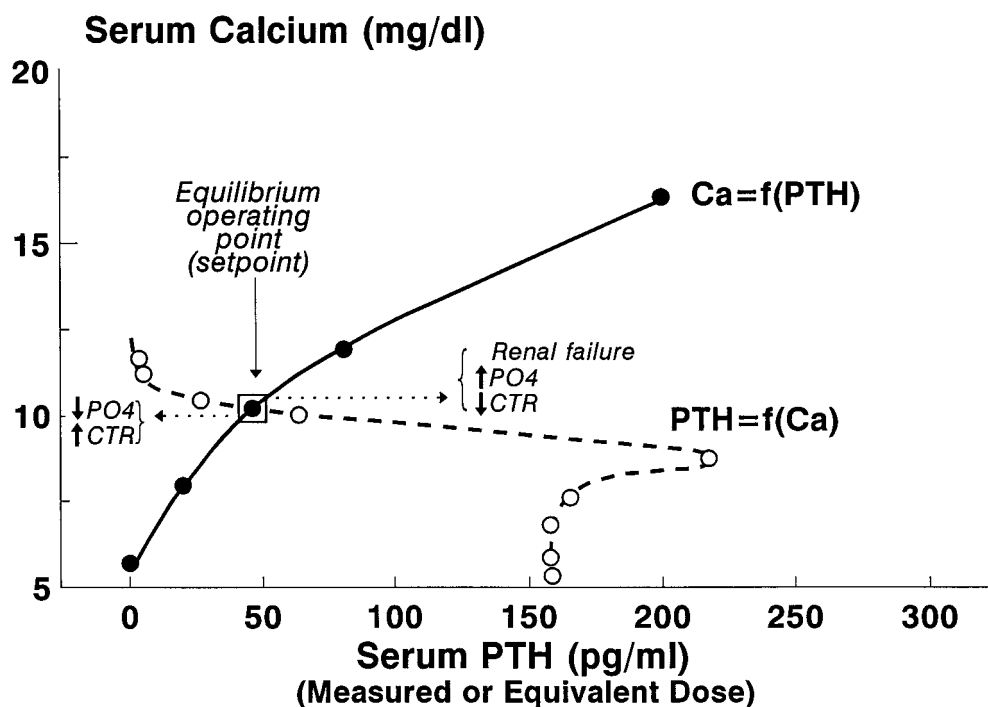


**Figure 3.** (A) The individual serum calcium values are shown for each dose of PTH that was infused for 48 h with a subcutaneously implanted miniosmotic pump. The line connecting the different PTH doses is based on the equation  $y = ax^{(bx^c)}$ , for which the coordinates are  $a = 4.8 \pm 0.26$ ,  $b = -2.49 \pm 0.11$ , and  $c = 0.68 \pm 0.03$ ;  $r^2 = 0.963$  and  $P < 0.001$ . (B) The individual serum phosphorus values are shown for each dose of PTH that was infused for 48 h with a subcutaneously implanted miniosmotic pump. The line connecting the different PTH doses is based on the equation,  $y = ax^{(bx^c)}$ , for which the coordinates are  $a = 15.87 \pm 1.07$ ,  $b = 1.828 \pm 0.17$ , and  $c = 0.576 \pm 0.05$ ;  $r^2 = 0.915$  and  $P < 0.001$ . (C) The individual serum calcium and phosphorus values obtained after a 48-h infusion of different PTH doses are shown for each rat. The line representing the relationship between serum calcium and phosphorus is based on the equation  $y = a + bx + cx^2$ , for which the coordinates are  $a = 21.5 \pm 1.13$ ,  $b = -2.01 \pm 0.23$ , and  $c = 6.14 \pm 0.01$ ,  $r^2 = 0.857$  and  $P < 0.001$ . From Berdud *et al.*, (23) and reprinted with permission from *Calcified Tissue International*.

that the dose of 1-34 rat PTH required to maintain a normal serum calcium (Figure 3A) and phosphorus (Figure 3B) in rats on a normal diet (0.6% P, 0.6% Ca) was  $0.022 \mu\text{g}/100 \text{ g per h}$  (24,25); this PTH dose also produced a normal calcitriol level (25). Thus, this replacement PTH dose should be equivalent to a normal endogenous PTH level of approximately 40 pg/ml, which was measured in normal rats on the same diet. As in previous studies, we were not able to measure infused 1-34 rat PTH in the serum (26–29). However, the highest infused PTH dose of  $0.11 \mu\text{g}/100 \text{ g per h}$ , which is five times greater than the normal replacement dose, should be equivalent to an endogenous PTH level of approximately 200 pg/ml. This issue becomes important because it is the PTH dose that we have used in previous studies to evaluate the calcemic response to PTH in normal and azotemic rats (26–29). As we will show later, this infused dose of PTH provides important information on the calcemic efficiency of PTH in experimental conditions during which other variables such as phosphorus, calcitriol, and renal failure were controlled. Our study also showed that a reciprocal relationship existed between serum calcium and phosphorus over a wide range of values (Figure 3C). Moreover, at each PTH dose except for the highest,  $0.11 \mu\text{g}/100 \text{ g per h}$ , the calcium-phosphorus product was similar; at the highest PTH dose, the calcium-phosphorus product was greater because the increase in serum calcium was not matched by a commensurate fall in serum phosphorus. These observations were essentially identical to those reported almost 70 years ago by Fuller Albright (4). The constancy of this reciprocal relationship between serum calcium and phosphorus except for marked hypercalcemia, in which the failure to further decrease serum phosphorus seemed to retard further increases in serum calcium, suggested to Albright that a PTH-induced reduction in phosphorus was critical for the increase in serum calcium.

### Equilibrium Operating Point (Set Point) as Affected by Dietary Phosphorus and Renal Function: Experimental Studies

As a result of our PTH infusion studies in rats, we were able to develop the curve shown in Figure 2 in which calcium is a function of PTH (curve 1). This function curve was essentially generated in static conditions by measuring, on a constant diet, the serum calcium for different doses of infused PTH. However, in normal biologic conditions, this function curve should be viewed as a dynamic continuum that changes with the PTH level and the bone response to PTH. For the curve in which PTH is a function of the serum calcium (curve 2), we have used the results in normal rats, maintained on a normal diet (0.6% Ca, 0.6% P), kindly provided by Drs. Ewa Lewin and Klaus Olgaard (22); in these rats, the maximal PTH was 218 pg/ml. The intersection of these two curves represents the equilibrium operating point or the set point of the system (Figure 4). As shown in Figure 4, we would like to propose that both phosphorus deprivation, often reflected by hypophosphatemia, and an increase in serum calcitriol shift the set point (equilibrium operating point) to the left so that less PTH is needed to maintain the same serum calcium concentration. Conversely,

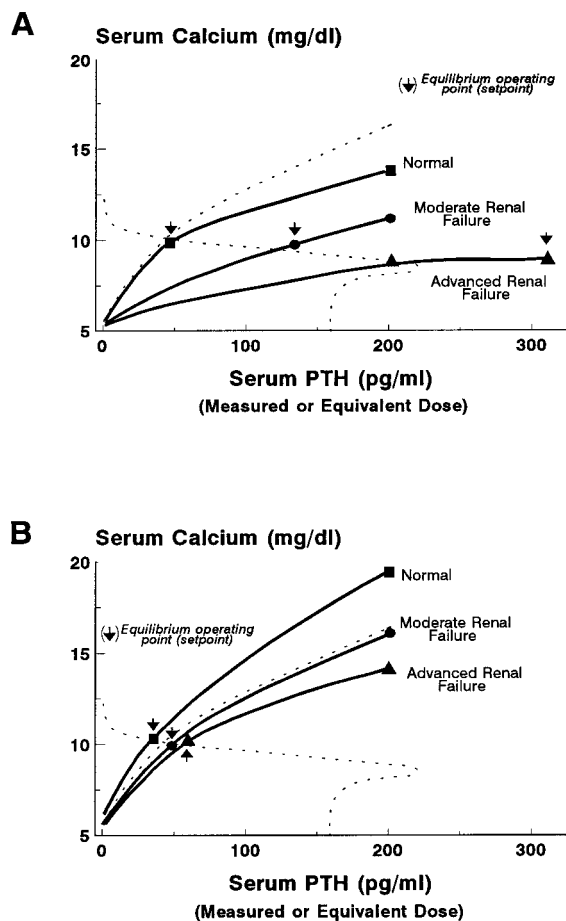


**Figure 4.** Two function curves, one in which calcium is a function of PTH and another in which PTH is a function of calcium. The first curve (calcium as a function of PTH; ●) was established in parathyroidectomized rats in which different doses of PTH were infused for 48 h. The second curve (PTH as a function of calcium; ○) was obtained in normal rats as a result of an ethyleneglycol-bis( $\beta$ -aminoethyl ether)- $N,N'$ -tetra-acetic acid infusion to lower serum calcium and a calcium infusion to increase serum calcium. The intersection of the two function curves represents the equilibrium operating point or set point for the system. Also shown are potential factors that can move the equilibrium operating point (set point) to the left (increased efficiency of PTH) and to the right (decreased efficiency of PTH). The legend for the x-axis indicates that PTH values were measured by RIA ( $PTH = f(Ca)$ ), or during the PTH infusion studies ( $Ca = f(PTH)$ ), the dose of PTH needed to normalize the serum calcium and phosphorus in parathyroidectomized rats was assigned a PTH value of 40 pg/ml because in parathyroid-intact rats on the same diet (P 0.6%, Ca 0.6%), the measured PTH value was 40 pg/ml. Thus, when the infused PTH dose was 5 times greater than the normal replacement dose, PTH was given a value of 200 pg/ml.

an increase in phosphorus retention as generally reflected by an increase in serum phosphorus, a decrease in serum calcitriol, and renal failure shift the set point to the right so that more PTH is needed to maintain the same serum calcium concentration. In the situations cited above, it should be emphasized that the serum calcium is changing as a function of PTH. Less information is available on whether PTH secretion actually changes as a function of serum calcium, but a high phosphorus concentration (30–33) and hypercalcemia (21) may change the PTH response to calcium.

In previous studies, we have evaluated the effects of dietary phosphorus and calcitriol supplementation in normal rats and in rats with surgically induced renal failure (26–29). In Figure 5, the serum calcium and phosphorus values are shown for rats with normal renal function (creatinine  $\leq 0.4$  mg/dl), moderate renal failure (creatinine 0.5 to 0.6 mg/dl), and advanced renal failure (creatinine  $\geq 0.7$  mg/dl). These rats received either a high phosphorus diet (HPD, 1.2% P, 0.6% Ca) (Figure 5A) or a low phosphorus diet (LPD, 0.2% P, 0.6% Ca) (Figure 5B) for 14 d before a 48-h PTH infusion ( $0.11 \mu\text{g}/100 \text{ g body wt per d}$ ). As shown in Figure 3A, this infused dose of PTH is equivalent to an endogenous PTH level of approximately 200 pg/ml. Shown as a dotted line in Figure 5, A and B, is the

bifunctional PTH–calcium relationship for parathyroidectomized rats with normal renal function which were maintained on a normal diet (0.6% P, 0.6% Ca) and received doses of PTH that ranged from 0 to 5 times normal. After 14 d of the HPD, PTH values progressively increased as the magnitude of renal failure increased and were markedly different for similar serum calcium levels (Figure 5A). Thus, the set points (equilibrium operating points) were widely divergent. With the LPD (Figure 5B), PTH values only increased minimally with renal failure and were only marginally different for similar serum calcium values. Thus, despite the marked differences in renal function, the respective set points (equilibrium operating points) were tightly grouped. During the PTH infusion, the calcemic response to PTH or perhaps more precisely stated as the serum calcium value for a PTH concentration approximately five times normal, was much greater at every level of renal function in rats on the LPD than on the HPD (Figures 5A and 5B). It should also be noted that in normal rats that were maintained on the 0.6% P diet, the serum calcium level for a PTH infusion dose of  $0.11 \mu\text{g}/100 \text{ g per h}$  was greater than the normal rats in the HPD group (Figure 5A) and less than the normal rats in the LPD group (Figure 5B). Thus, these studies show that differences in dietary phosphorus clearly affect the set point and thus



**Figure 5.** (A) The effect that a high phosphorus (1.2%) diet has on the equilibrium operating point (set point) in normal rats and in rats with moderate and advanced renal failure. The use of a high phosphorus diet in renal failure resulted in a marked rightward displacement of the equilibrium operating point. The use of a high phosphorus diet in normal rats did not have much effect on the equilibrium operating point compared with normal rats on a normal phosphorus (0.6%) diet (dotted line), whereas the calcemic response to a 48-h infused dose of PTH, equivalent to approximately 200 pg/ml, was reduced in rats on a high *versus* a normal phosphorus diet. In renal failure, there was a progressive decrease in the calcemic response to a high-dose PTH infusion. The curve for PTH as a function of serum calcium performed in normal rats is represented as a dotted line. (B) The effect that a low phosphorus (0.2%) diet has on the equilibrium operating point (set point) in normal rats and in rats with moderate and advanced renal failure. The use of a low phosphorus diet in renal failure resulted in a minimal but significant rightward displacement of the equilibrium operating point. The use of a low phosphorus diet in normal rats tended to shift the equilibrium operating point to the left compared with normal rats on a normal phosphorus (0.6%) diet (dotted line), and the calcemic response to a 48-h infused dose of PTH equivalent to approximately 200 pg/ml was greater in rats on a low *versus* a normal phosphorus diet. In renal failure, there was a progressive decrease in the calcemic response to a high-dose PTH infusion, but the calcemic response to high-dose PTH was essentially the same in normal rats on a 0.6% phosphorus diet as in rats with moderate renal failure on a 0.2% phosphorus diet. The curve for PTH as a function of serum calcium performed in normal rats is represented as a dotted line. See the legend of Figure 4 for an explanation of measured and equivalent doses of PTH.

the ability of PTH to maintain a normal serum calcium in renal failure. Moreover, when calcium was a function of PTH during the PTH infusion, phosphorus loading impaired the calcemic action of PTH in both nonazotemic and azotemic rats.

The data in Figure 6, modified from our previous studies (26–29), show in detail how changes in dietary phosphorus affect the dynamics of the calcemic response to PTH in different stages of renal failure. The duration of the study diet, the definition of renal failure, and the low and high phosphorus diets were the same as stated in the previous paragraph. In normal rats, the serum PTH, calcium, and phosphorus values were not different between rats on a HPD or LPD (Figure 6A). Nevertheless, despite a similar serum phosphorus, the serum calcium was less after the 48-h PTH infusion in the rats on the HPD. When rats on a HPD were changed to a LPD during the PTH infusion, the serum calcium was not different than in the group maintained on the LPD. Thus, this study shows that the serum phosphorus concentration may not always reflect the phosphorus load in normal rats, and the phosphorus burden is actually responsible for calcium release from bone. When rats on a HPD were changed to a LPD for 48 h during the PTH infusion, the bone response to PTH was restored to normal presumably because the combination of a LPD and normal renal function allowed the excretion of any residual phosphorus that had accumulated before the PTH infusion.

The dynamics of the bifunctional relationship between PTH and calcium in moderate renal failure are shown in Figure 6B. At the end of the study diet, the set point was different between the LPD and HPD groups. Thus, a threefold greater PTH in the HPD group was needed to maintain a similar serum calcium, and the serum phosphorus was also greater despite the much greater PTH value. During the 48-h PTH infusion, serum phosphorus values increased with the HPD and, as a result, serum calcium was much less for a similar PTH value. When rats on a HPD were changed to a LPD during the PTH infusion, the postinfusion serum phosphorus was not different from that of the group maintained on a LPD; nevertheless, the post-PTH infusion serum calcium for similar PTH values was intermediate between the HPD and LPD groups. This result was different than in rats with normal renal function, which received a HPD and were changed to a LPD during the PTH infusion. Thus, it is likely that the presence of renal failure did not allow the complete excretion of the previously accumulated phosphorus load. These results demonstrate the important concept that phosphorus affects the calcemic efficiency of PTH, and while the serum phosphorus often reflects the phosphorus load, dynamic situations develop in which the serum phosphorus may not indicate the phosphorus load presumably because renal excretion of phosphorus may be more efficient than bone removal. It should be noted that a similar situation has been shown to develop during hemodialysis in which the rapid fall in serum phosphorus during dialysis is not an indicator of the total phosphorus burden since a rapid equilibration follows dialysis, during which serum phosphorus values again increase (34).

The groups in advanced renal failure show that phosphorus

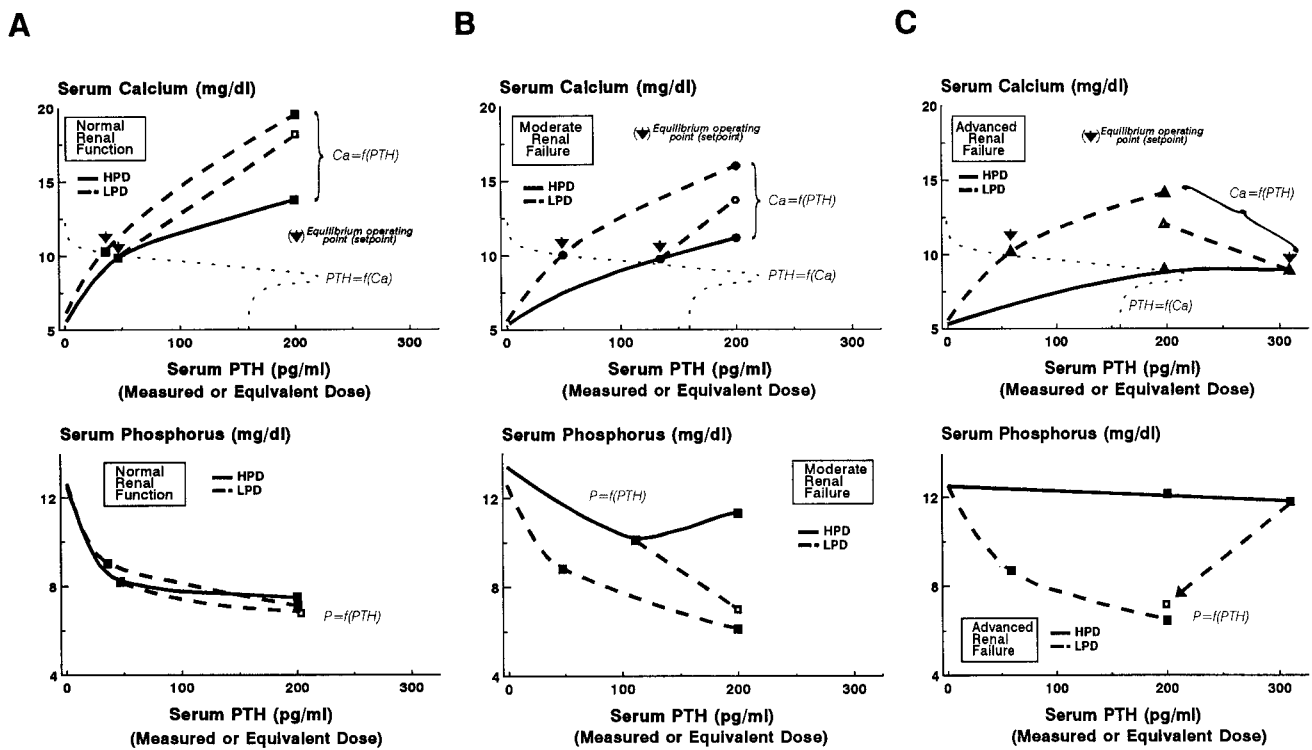


Figure 6. Serum calcium (top) and phosphorus (bottom) values for normal renal function (A), moderate renal failure (B), and advanced renal failure (C) for rats maintained on high (1.2%, solid line) and low (0.2%, dashed line) phosphorus diets are shown. A subgroup of rats on a high phosphorus diet (HPD) was changed to a low phosphorus diet (LPD) immediately before the 48-h high dose (0.11  $\mu\text{g}/100\text{ g per h}$ ) PTH infusion, which has been shown to be 5 times the normal PTH level (40 pg/ml). PTH as a function of serum calcium is shown as a dotted line; this evaluation was only performed in rats with normal renal function and is shown as a point of reference. See the legend of Figure 4 for an explanation of measured and equivalent doses of PTH.

Table 1. Effect of chronic phosphorus loading on serum and urinary calcium and phosphorus values and intact PTH values<sup>a</sup>

Category	Serum Values			Urine Values			
	Ca <sup>2+</sup> (mM)	PO <sub>4</sub> (mM)	PTH (pg/ml)	PO <sub>4</sub> (mM/24 h)	PO <sub>4</sub> Clearance (ml/min)	Ca (mM/24 h)	FE <sub>Ca</sub> (%)
Control	1.33 ± 0.03	0.91 ± 0.17	24.4 ± 4.5	43 ± 3	35 ± 10	7.40 ± 0.44	1.8 ± 0.4
Phosphate loading							
day 1	1.29 ± 0.03 <sup>b</sup>	1.20 ± 0.15 <sup>b</sup>	58.3 ± 18.7 <sup>c</sup>	213 ± 7 <sup>c</sup>	129 ± 24 <sup>c</sup>	3.38 ± 0.30 <sup>c</sup>	0.8 ± 0.2 <sup>c</sup>
days 5 to 7	1.34 ± 0.02	0.77 ± 0.10	61.7 ± 13.0 <sup>c</sup>	240 ± 9 <sup>c</sup>	229 ± 35 <sup>c</sup>	3.92 ± 0.33 <sup>c</sup>	0.9 ± 0.3 <sup>c</sup>
Recovery							
day 1	1.38 ± 0.02	0.56 ± 0.12 <sup>c</sup>	26.5 ± 4.2	75 ± 5	90 ± 32	5.73 ± 0.36	1.4 ± 0.3
days 4 to 6	1.35 ± 0.02	0.81 ± 0.20	23.8 ± 4.5	44 ± 5	40 ± 13	8.72 ± 0.68	1.9 ± 0.3

<sup>a</sup> Reprinted with permission from *The American Journal of Physiology* (35). Results are given as mean ± SEM. PTH, parathyroid hormone.

<sup>b</sup>  $P < 0.05$  for comparison with previous steady-state period (control or phosphate loading).

<sup>c</sup>  $P < 0.01$  for comparison with previous steady-state period (control or phosphate loading).

loading markedly impairs the calcemic efficiency of PTH (Figure 6C). During the study diet, marked differences in the equilibrium operating point, PTH, and phosphorus values were observed between the LPD and HPD groups. Thus, with the HPD, a sixfold greater PTH value than with the LPD was not able to maintain a normal serum calcium. Similarly, despite a sixfold greater PTH, the serum phosphorus was much greater

in the HPD group. When rats were maintained on a HPD during the PTH infusion, neither serum calcium nor serum phosphorus changed; the degree to which the exogenous infusion of PTH suppressed endogenous PTH in these rats is not known. When the HPD group was changed to a LPD during the PTH infusion, the postinfusion serum calcium was intermediate between the LPD and HPD groups, even though the post-

Table 2. Demographic and biochemical data of mineral metabolism in healthy young and old men<sup>a</sup>

Parameter	Old Men (n = 9)	Young Men (n = 13)
Age (yr)	74 ± 2	39 ± 1
Body weight (kg)	84 ± 2	78 ± 2
Blood		
creatinine (mg/dl)	0.96 ± 0.04	0.92 ± 0.03
ionized calcium (mg/dl)	4.84 ± 0.04	4.84 ± 0.03
phosphorus (mg/dl)	2.7 ± 0.1 <sup>b</sup>	3.6 ± 0.1
intact PTH (pg/ml)	42 ± 4 <sup>b</sup>	23 ± 4
calcitriol (pg/ml)	37 ± 2	31 ± 2
25-OHD (ng/ml)	20 ± 2	22 ± 1
PTH <sub>max</sub> (pg/ml)	158 ± 22	137 ± 11
basal/maximal PTH (%) <sup>c</sup>	23	16
Urine		
creatinine clearance (ml/min)	96 ± 6 <sup>b</sup>	132 ± 5
calcium (mg/24 h)	190 ± 25	174 ± 19
phosphorus (mg/24 h)	1071 ± 66	1144 ± 55
FE <sub>Pi</sub> (%)	28.2 ± 1.4 <sup>b</sup>	16.8 ± 1.2
NcAMP (nmol/100 ml GF)	1.83 ± 0.19 <sup>d</sup>	1.18 ± 0.16

<sup>a</sup> Reprinted with permission from *The American Journal of Physiology* (20). Results are given as mean ± SEM. FE<sub>Pi</sub>, fractional excretion of phosphorus; NcAMP, nephrogenous cAMP; GF, glomerular filtrate.

<sup>b</sup>  $P < 0.01$  versus young men.

<sup>c</sup> Calculated from the mean value of the intact and maximal PTH; individual values are not available.

<sup>d</sup>  $P < 0.05$  versus young men.

PTH infusion serum phosphorus was not different from the LPD group. These results again show that with renal failure, more than 48 h is required to establish an equilibrium and completely excrete the previously accumulated phosphorus load. It should also be stated that because of the decreased ability to excrete phosphorus during advanced renal failure, the phosphorus load that accumulated during the study diet was also presumably greater than in the nonazotemic rats. In summary, during phosphorus loading more PTH was needed to maintain a normal serum calcium and when PTH was infused, the serum calcium was less for similarly high PTH levels.

### Different Causes of Secondary Hyperparathyroidism and the Potential Role of Phosphorus

We have provided a detailed explanation of our experimental studies because we believe that an understanding of the approach in which the equilibrium operating point is evaluated provides new insights into the results of many previous clinical and animal studies. Although in human studies it may not be possible to determine calcium as a function of PTH by performing a series of PTH infusions, the placement of calcium on the ordinate and PTH on the abscissa facilitates the direct comparison of the PTH value for a serum calcium value and clearly shows the set point (equilibrium operating point) for the integrated system for calcium regulation. As we will show, we believe that several factors determine the calcemic efficiency of PTH. The most important of these are the serum phosphorus or, more correctly, the phosphorus burden, serum calcitriol, and renal failure. As we have shown in our experimental

studies in which it was possible to evaluate the serum calcium as a function of PTH, changes in serum phosphorus play an important role in determining the calcemic efficiency of PTH. Moreover, as will be shown, we wish to emphasize that in renal failure, a normal serum phosphorus with an elevated PTH level should be considered as an “inappropriate normal” serum phosphorus, because in the presence of a high PTH, the serum phosphorus should be low. We believe that this decrease in phosphorus makes the bone more responsive to the calcemic action of PTH. In the examples below, we will attempt to convince the reader that in virtually all conditions in which PTH is stimulated, a reduction in serum phosphorus enhances the calcemic action of PTH. In renal failure, when an increased PTH level is no longer able to lower the serum phosphorus, the calcemic response to PTH is reduced even by a “normal” serum phosphorus.

In our evaluation of secondary hyperparathyroidism (2<sup>0</sup> HPT), we will examine how the handling of phosphorus is different in renal failure than vitamin D deficiency, another well known form of 2<sup>0</sup> HPT. Furthermore, we suggest that aging may be a form of 2<sup>0</sup> HPT and will discuss how the handling of phosphorus in the elderly differs from a younger population. It should be emphasized that in the different forms of 2<sup>0</sup> HPT that will be discussed, there is no calcium gradient for PTH to overcome. As opposed to 1<sup>0</sup> HPT, in which the calcemic action of PTH is operating in an hypercalcemic environment, the serum calcium is normal or even low in the 2<sup>0</sup> HPT of vitamin D deficiency, renal failure, and aging. Furthermore, except for renal failure, the calcium–phosphorus product decreases since an increased PTH reduces serum phosphorus.

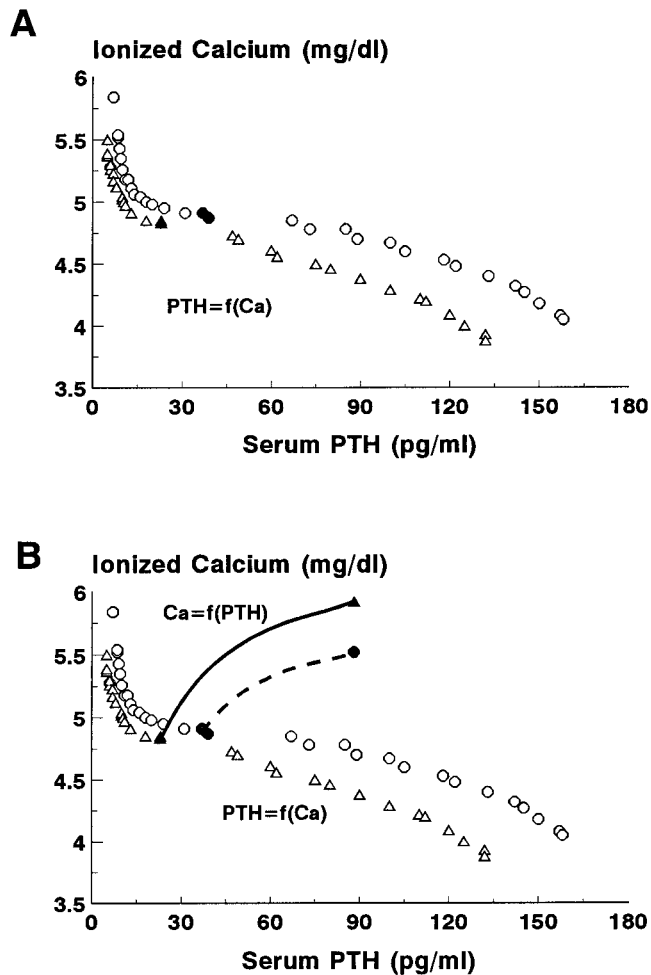


Figure 7. The figure is adapted from the studies of Portale *et al.* (20) and Halloran *et al.* (47), in which a PTH–calcium curve was performed in young and old men. As observed in Panel A for essentially the same serum calcium value at baseline, the PTH level was approximately twofold greater in the old men. The two basal PTH values, which are essentially identical for each group, were obtained before the ethylenediaminetetra-acetic acid and calcium infusions. In Panel B, a 24-h PTH infusion was performed at a dose shown in a previous study to increase baseline PTH by fourfold in normal volunteers (Cosman *et al.*, reference 48).  $\Delta$ , young men;  $\circ$ , old men;  $\blacktriangle$ , basal-young men;  $\bullet$ , basal-old men. Reprinted with permission from *The American Journal of Physiology*.

Thus, this situation with a low-to-normal serum calcium and a lower than normal calcium–phosphorus product could conceivably result in a more favorable environment for calcium efflux from bone. This possibility is supported by the *in vitro* study of Ramp and McNeil (14), in which a high calcium concentration reduced PTH-induced calcium efflux from bone. Similarly, as has been shown *in vivo* by Berdud *et al.* (23), the relationship between PTH and calcium is curvilinear, but has a steeper slope between serum calcium values from 5 to 10 mg/dl than for values greater than 10 mg/dl. This indicates a greater efficiency of PTH in the low-to-normal range of serum calcium than for hypercalcemia (Figure 3A).

Before focusing on phosphate handling in the different

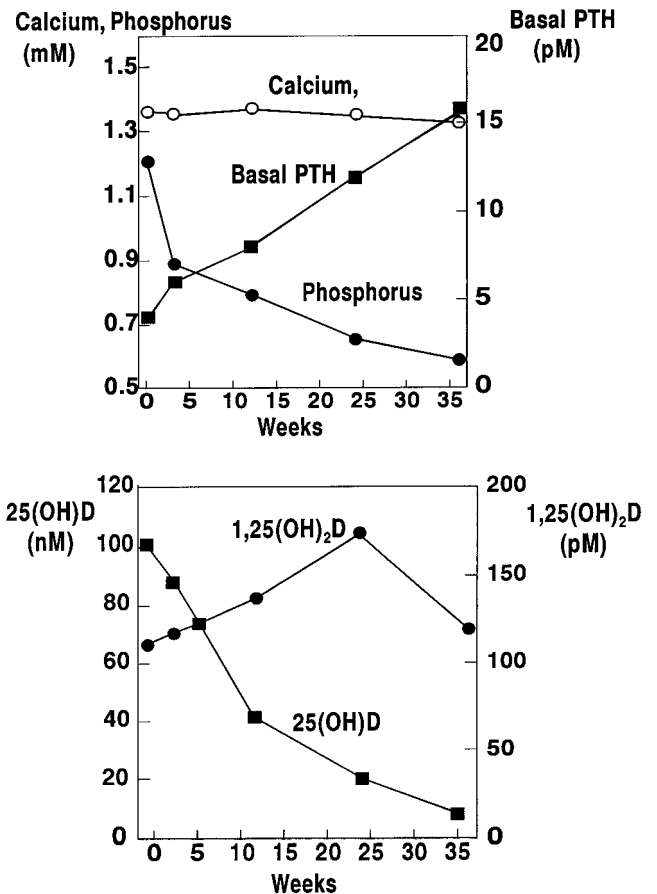


Figure 8. Shown are the ionized calcium, phosphorus, and basal PTH values (top panel) and 25(OH)D and 1,25(OH)<sub>2</sub>D values (bottom panel) during the first 36 wk of a study in which dogs were placed on a calcium- and vitamin D-deficient diet for 91 wk. Note the progressive increase in serum PTH and the marked decrease in serum phosphorus, while the serum calcium tends to remain stable. In addition, during the first 24 wk, 1,25(OH)<sub>2</sub>D levels increase even though 25(OH)D values are decreasing. Adapted from Cloutier *et al.*, (49) and reprinted with permission from *The Journal of Bone and Mineral Research*.

forms of <sup>2</sup><sub>0</sub> HPT, it would seem appropriate to show how the healthy young adult adapts to a phosphate load. In an excellent study by Krapf *et al.* in young male volunteers, intravenous phosphate was continuously infused for 7 d (35). As shown in Table 1, on day 1 of the phosphate infusion, PTH levels increased by 140%, serum phosphorus increased by 32%, and ionized calcium decreased despite the marked increase in PTH. By days 5 to 7 of the infusion, PTH remained at a similar increased level (150% greater than baseline), but ionized calcium was restored to normal probably because serum phosphorus had decreased to 16% below preinfusion values; during the same time, urinary phosphorus excretion had increased by sixfold from preinfusion values. Thus, for a similarly elevated PTH value, the ionized calcium was low when the serum phosphorus was high (day 1) and normal when the serum phosphorus was low (days 5 to 7). Moreover, on the first day after the phosphate infusion was stopped, serum PTH had



returned to normal, whereas serum phosphorus decreased further (39% below preinfusion values) and ionized calcium tended to be greater than preinfusion levels. This study illustrates that the young healthy adult can adapt to a phosphate load by markedly increasing urinary phosphorus excretion. Thus, despite the continuous exposure to a large phosphate load, calcium homeostasis was maintained by a modest increase in PTH levels and a decrease in serum phosphorus levels.

### Secondary Hyperparathyroidism in Aging: Potential Role of Phosphorus

Portale and associates recently reported results of studies of parathyroid function and mineral metabolism in healthy young and old men (20). As shown in Table 2, serum PTH values were greater ( $42 \pm 4$  versus  $23 \pm 4$  pg/ml,  $P < 0.01$ ) and serum phosphorus values decreased by 25% ( $2.7 \pm 0.1$  versus  $3.6 \pm 0.1$  mg/dl,  $P < 0.001$ ) in the old men, whereas serum calcitriol values were not different. In previous studies, the increase in PTH observed with aging has been shown to be associated with a decrease in serum phosphorus in men but not women (36–40). Because estrogen is known to enhance renal phosphorus excretion and decrease the efflux of phosphorus from bone (41–44), the decrease in estrogen during aging may be important for this difference.

As shown in Figure 7A, we have replotted the results of the study by Portale *et al.* (20) in the form of the bifunctional relationship between PTH and calcium with serum calcium on the ordinate and PTH on the abscissa. Thus, as is readily observed, to maintain the same serum calcium more PTH is needed in the elderly men. Moreover, it is our belief that the lower serum phosphorus in the elderly men ( $2.7$  versus  $3.6$  mg/dl) functions to enhance the calcemic action of PTH. We also believe that if the serum phosphorus were  $3.6$  mg/dl, the

same as in the young men, skeletal resistance to PTH would have been further increased and, in essence, result in a situation analogous to that observed in renal failure in which despite a high PTH level, serum phosphorus does not decrease or the decrease is inappropriate. Serum calcitriol levels were similar between the two groups. Thus, we believe that skeletal resistance to PTH develops during aging perhaps due to a lower GFR, but it may also be a result of differences in bone quality; the latter may be due to denser bones with less bone water and miscible calcium available for calcium efflux from bone (45,46). The increased PTH results in a lowering of the serum phosphorus, which then functions to improve the calcemic action of PTH.

The information provided by the study shown in Figure 7A is further enhanced when combined with another study by the same investigators performed in the same groups of patients, in which the calcemic response to infused PTH was compared between the healthy young and old men (20). To combine the results of both studies and show a form of presentation similar to that in our animal studies in which PTH and calcium were shown as a bifunctional relationship requires a minor mathematical calculation. The dose of infused human synthetic 1-34 PTH used for the 24-h infusion was  $0.5$  U/kg per h (47). This same PTH dose was used in an earlier study and increased PTH levels approximately fourfold in healthy young women (48). Thus, in Figure 7B, we plotted the final infused PTH level to be fourfold greater than normal in the young men. As was shown in Figure 7A (same serum calcium for a higher PTH in the old men), skeletal resistance was also observed during the PTH infusion since both the rate of increase and the final serum calcium for a similar PTH was less in the old than the young men ( $P < 0.05$ ). This result was observed even though the serum phosphorus remained significantly lower in the old men throughout the 24-h PTH infusion (47). This latter result would

Table 3. Mineral metabolism in male patients with different stages of renal failure<sup>a</sup>

Parameter	Control (n = 9)	RP1 <sup>b</sup> (n = 6)	RP2 <sup>c</sup> (n = 13)	RP3 <sup>d</sup> (n = 8)
Age (yr)	40.3 ± 11.1	39.5 ± 19.2	41.0 ± 12.1	47.0 ± 13.6
Creatinine clearance (ml/min)	125.1 ± 23	110.3 ± 29	63.1 ± 18.5 <sup>e,f</sup>	25.6 ± 13 <sup>e-g</sup>
Ionized calcium (mM)	1.27 ± 0.03	1.26 ± 0.04	1.27 ± 0.06	1.26 ± 0.03
Phosphorus (mM)	1.11 ± 0.10	0.98 ± 0.23	0.98 ± 0.24	1.10 ± 0.25
Intact PTH (pg/ml)	26.2 ± 12.7	22.0 ± 5.2	39.0 ± 13.2 <sup>e</sup>	142.1 ± 79.4 <sup>e-g</sup>
Calcitriol (pg/ml)	39.9 ± 9.7	35.2 ± 7.2	27.2 ± 12.0 <sup>e,f</sup>	14.0 ± 7.3 <sup>e-g</sup>
25-OHD (ng/ml)	23.6 ± 9.3	21.3 ± 6.1	24.9 ± 10.5	19.3 ± 11.7
Maximal PTH (pg/ml)	87.4 ± 28.8	80.2 ± 18	138 ± 25.7 <sup>e,f</sup>	312 ± 29.3 <sup>e-g</sup>
Minimal PTH (pg/ml)	8.5 ± 3.4	12.5 ± 7.8	16.2 ± 12.2	29.3 ± 15.3 <sup>e-g</sup>
Basal/maximal PTH (%)	27 ± 12	28 ± 7	29 ± 9	46 ± 17 <sup>e-g</sup>

<sup>a</sup> Reprinted with permission from *Kidney International* (57). Results are given as mean ± SD.

<sup>b</sup> RP1 = GFR >70 ml/min.

<sup>c</sup> RP2 = GFR between 30 and 70 ml/min.

<sup>d</sup> RP3 = GFR <30 ml/min.

<sup>e</sup>  $P < 0.05$  versus C.

<sup>f</sup>  $P < 0.05$  versus RP1.

<sup>g</sup>  $P < 0.05$  versus RP2.

be expected to enhance the calcemic action of PTH on bone. These results suggest to us as perhaps they would have to Fuller Albright, that the low serum phosphorus was not simply a consequence of the mild hyperparathyroidism as was suggested by the authors, but rather it also functions as an important mechanism to improve the bone response to PTH.

### *Secondary Hyperparathyroidism in Vitamin D Deficiency: Potential Role of Phosphorus*

In an important study of vitamin D deficiency, Cloutier *et al.* studied mineral metabolism and the PTH–calcium curve at regular intervals in dogs maintained on a vitamin D- and calcium-deficient diet for 91 wk (49). Shown in Figure 8 are the values for ionized calcium, phosphorus, PTH, 25(OH)D, and calcitriol during the first 36 wk of the study. At 3, 12, and 24 wk of the vitamin D- and calcium-deficient diet, PTH values increased to 1.5, 2, and 3 times normal, respectively; serum calcium values did not change; and there was a trend for serum calcitriol values to increase despite a decrease in 25(OH)D values. Serum phosphorus values decreased significantly from 1.25 mM at baseline to values of 0.92, 0.81, and 0.67 mM at 3, 12, and 24 wk, respectively; these changes represented decreases of 26, 35, and 46% respectively. At 36 wk, ionized calcium values decreased minimally as PTH rose to values approximately 4 times normal. Serum calcitriol values returned to normal at 36 wk as 25(OH)D values continued to decline. The serum phosphorus value at 36 wk was 0.61 mM, which represented a 51% decrease from baseline. Thus, the 50 to 400% increases in PTH from 3 to 36 wk of the vitamin D- and calcium-deficient diet were associated with progressive decreases in serum phosphorus from 26% at 3 wk to 51% at 36 wk. We suggest that as shown earlier in our experimental studies (Figures 5 and 6), this decrease in serum phosphorus functioned to enhance the calcemic action of PTH and maintain a normal serum calcium. The corollary of this axiom would be that if serum phosphorus did not decrease or the decrease was minimal, both of which happen in early-to-moderate renal failure, resistance to PTH would develop, resulting in greater increases in PTH and changes in PTH dynamics.

### *Secondary Hyperparathyroidism in Renal Failure: Potential Role of Phosphorus*

We decided to discuss renal failure last because it is perhaps the most complex and difficult to analyze since the important variables such as PTH, calcium, phosphorus, and calcitriol are all continuously evolving and simultaneously changing. Furthermore, each is interrelated and directly affected by renal failure. Nevertheless, certain trends are present which suggest to us that in early renal failure, a modest reduction in serum phosphorus and calcitriol values, which are maintained at normal levels by PTH stimulation, result in a situation similar to that in the old men discussed earlier and tend to maintain a modest degree of 2<sup>0</sup> HPT. It should also be remembered that a series of elegant studies performed in the 1960s by Bricker, Slatopolsky, and colleagues led to the trade-off hypothesis, which maintained that in early renal failure a modest increase

in serum phosphorus required a higher PTH to lower the serum phosphorus and maintain a normal serum calcium (50–53). However, in subsequent studies this hypothesis was questioned because an increase in serum phosphorus was not observed in early renal failure and, moreover, some studies of phosphate loading showed that phosphorus excretion was even enhanced in early renal failure (54–56). We believe that the hypothesis proposed by Bricker, Slatopolsky, and colleagues and the latter observations are both conceptually correct. The principal difference is that the magnitude of phosphorus excretion and the lowering of the serum phosphorus are not appropriate for the magnitude of hyperparathyroidism present in renal failure. In those studies of phosphate loading, the serum phosphorus level was not different or only minimally lower than normal in patients with early renal failure even though PTH values were more than twice normal for a similar serum phosphorus (55–57). Moreover, in the healthy old men and in the vitamin D- and calcium-deficient dogs, the magnitude of hypophosphatemia for a similarly increased PTH level was consistently greater than observed in renal failure. Thus, we believe that as renal failure evolves, the magnitude of phosphorus excretion for a specific increase in PTH is progressively reduced. Even though the serum phosphorus may be mildly decreased in early-to-moderate renal failure, the serum phosphorus level, although mildly decreased, is inappropriately high for the degree of hyperparathyroidism, and this inappropriately high serum phosphorus level together with renal failure combine to induce skeletal resistance to PTH. Such was the sequence in our study in rats maintained on a normal diet (0.6% P, 0.6% Ca) for 14 d after three different degrees of renal failure were induced surgically (29). At all levels of renal failure, serum calcium, phosphorus, and calcitriol values were not different from those in rats with normal renal function. However, to maintain these “normal” values, a progressive increase in PTH was needed until at the highest serum creatinine, a greater than threefold increase in PTH was needed. We believe that the failure to lower the serum phosphorus as PTH increased reduced the calcemic action of PTH and contributed to the exacerbation of the 2<sup>0</sup> HPT. Subsequently, as renal failure progresses to a degree in which hyperphosphatemia and a reduction in serum calcitriol are observed, even greater skeletal resistance to PTH develops.

In early renal failure, PTH levels increase and serum phosphorus values may decrease, but it is our premise that due to the renal failure the decrease in serum phosphorus is not appropriate for the level of PTH. It would seem that the failure to appropriately lower the serum phosphorus contributes to the skeletal resistance to PTH. To evaluate our premise, we have analyzed the data contained in two recent studies in which detailed information of patients with different degrees of renal failure was available. In the study by Messa *et al.* (57), results of ionized calcium, phosphorus, PTH, and calcitriol, in addition to the results of dynamic testing of parathyroid function (PTH–calcium curve), are shown in Table 3. These studies were performed in control subjects and male patients with mild (RP1), moderate (RP2), and advanced renal failure (RP3); respective creatinine clearances were 125 ± 23 (control sub-

jects),  $110 \pm 29$  (RP1),  $63 \pm 18$  (RP2), and  $26 \pm 13$  (RP3) ml/min. In the early renal failure group (RP1) with a creatinine clearance that was not significantly different from the control group, all of the values were similar to those in the control group. It is important to note that the ionized calcium values were not different in the four groups. In the RP2 group with a 50% reduction in the creatinine clearance, a 50% increase in PTH levels was needed to maintain a normal serum calcium; serum phosphorus values tended to be lower but were not significantly different from controls. As opposed to the earlier cited study in the vitamin D-deficient dogs (49) in which a 50% increase in PTH was associated with a 26% decrease in serum phosphorus or in the study comparing healthy young and old men (20) in which a 82% increase in PTH was associated with a 25% reduction in serum phosphorus, the decrease in serum phosphorus was only 12% in the RP2 group. Similarly, in the study by Martinez *et al.* in patients with early renal failure, PTH values 50% greater than normal were needed to maintain a normal serum ionized calcium; despite the increase in PTH, the decrease in serum phosphorus was only 13% (56). We believe that even in early renal failure, the decrease in serum phosphorus is less than appropriate for the high PTH level, and the failure to further lower serum phosphorus increases skeletal resistance and results in a need for even higher PTH levels. Furthermore, as shown in the RP3 group (Table 3), as renal failure progresses, an even higher level of PTH (>5 times normal) is needed to maintain a normal serum calcium, and despite the marked increase in PTH, the serum phosphorus is normal. Thus, it is our premise that the “normal” serum phosphorus is inappropriate, exacerbates the skeletal resistance to PTH, and thus contributes to the progression of 2<sup>0</sup> HPT.

## Conclusion

Fifty years ago in his classic book, Fuller Albright summarized why he believed that serum phosphorus was critical for calcium regulation. Although Albright was incorrect in his belief that the calcemic action of PTH on bone was an indirect effect mediated by PTH-induced changes in serum phosphorus, many investigators have since shown that phosphorus directly affects the calcemic action of PTH on bone. However, to a large extent, these observations have failed to be adequately integrated into the model of PTH regulation of calcium. Through the use of a dynamic model of regulation first suggested by Yates (17) and later modified by Parfitt (15,16) to apply to calcium regulation, we have attempted to show: (1) how phosphorus affects the dynamics of calcium regulation by PTH and (2) how phosphorus loading exacerbates the development of 2<sup>0</sup> HPT in renal failure. We have advanced the concept that during the development of 2<sup>0</sup> HPT, a reduction in serum phosphorus in response to an elevation in PTH enhances the calcemic response to PTH. Furthermore, we have also presented evidence to show that as opposed to nonazotemic forms of 2<sup>0</sup> HPT, the decrease in serum phosphorus in the 2<sup>0</sup> HPT of renal failure does not appear to be appropriate for the degree of PTH elevation. Finally, we have emphasized that in renal failure, a normal serum phosphorus with an elevated PTH should not be considered appropriate, and the failure to de-

crease serum phosphorus reduces the calcemic response to PTH and enhances the progression of 2<sup>0</sup> HPT. Thus, additional studies are needed to determine the stage of renal failure at which it might be beneficial to begin dietary phosphorus restriction and/or phosphorus binders to compensate for the failure of PTH to appropriately enhance the renal excretion of phosphorus and to reduce the serum phosphorus concentration.

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