UPDATE ON

SECONDARY HYPERPARATHYROIDISM

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Introduction

Secondary hyperparathyroidism is a state of compensatory hypersecretion of PTH and may occur in any clinical condition in which there is a tendency toward hypocalcemia. Thus, secondary hyperparathyroidism has been classically described in chronic renal disease, rickets or osteomalacia, and intestinal malabsorption syndromes. More recently, it has become apparent that a subclass of patients with nephrolithiasis associated with a renal leak of calcium may also develop secondary hyperparathyroidism.[1,2] Other known causes for the development of secondary hyperparathyroidism include target organ resistance to the action of PTH (e.g. pseudohypoparathyroidism), an altered set-point for calcium-mediated PTH suppression (e.g. chronic renal disease), and the presence of humoral factors which may stimulate parathyroid growth or secretion (e.g. MEN syndromes). Persistent hypersecretion of PTH in these syndromes can produce all of the characteristics of hyperparathyroid bone disease, including osteopenia, osteitis fibrosa and osteosclerosis.

Recent information has shed new light on the control of PTH secretion with potential relevance to the management of secondary hyperparathyroidism in end stage renal disease. A role for secondary hyperparathyroidism has been proposed in the development of certain forms of hypertension and osteoporosis. Elevated PTH levels have been disclosed in normocalcemic subjects who are obese or black. Moreover, some new pathogenetic information has become available pertaining to the development of secondary hyperparathyroidism in the familial hypercalcemias and in patients taking Lithium for manic-depressive illness. In this review, we shall examine some of the recent gains in knowledge concerning secondary hyperparathyroidism, as well as their clinical implications.

Control of PTH Secretion

The factors affecting PTH secretion have been nicely reviewed by Ed Brown.[3] A partial listing of factors that modulate PTH release is shown in Table 1, but in this discussion we will focus on the role of calcium and vitamin D metabolites.

Table 1. Factors Modifying PTH Secretion*

Agent	Effect on Secretion
Cations	
Trivalent-Aluminum	↓
Divalent-Calcium	↓
- Magnesium	↓
Monovalent-Lithium	↑
Agents Affecting Transport of Divalent Cations	
Verapamil	↓
Ca Ionophores	↓
Hormones and Neurotransmitters	
β-Adrenergic Catecholamines	↑
α-Adrenergic Catecholamines	↓
Dopaminergic Catecholamines	↑
Histamine	↑
Calcitonin	↑
Somatostatin	↓
Cortisol	↑
Vitamin D Metabolites	↓
Miscellaneous	
Cyclic AMP	↑
Phosphodiesterase Inhibitors	↑

* Arrows indicate the effect on secretion of PTH of an increase in concentration of the agents listed.

Regulation of PTH Secretion by Calcium

Calcium is generally considered the principal factor regulating PTH release in vivo.[4] A decrease in serum ionized calcium as small as 0.1 to 0.2 mg/dl constitutes an important stimulus to secretion.[5,6] Recent studies have refined our understanding of calcium-regulated secretion and suggested that the sensitivity of the parathyroid glands to calcium may vary in both normal and abnormal parathyroid tissue. Early studies in vivo suggested that there was an inverse linear relationship between extracellular calcium concentration and PTH release.[5] Subsequently, it has become clear that there is, in fact, a

sigmoidal relationship between these parameters (Fig 1).[7-9]

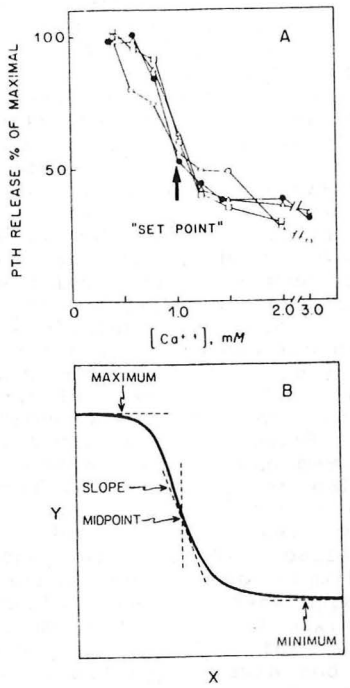

Fig. 1. A Sigmoidal relationship between immunoreactive PTH release and extracellular calcium in dispersed parathyroid cells from normal human parathyroid cells from normal human parathyroid glands [modified from *Brown* et al., [8]]. Set-point indicates the calcium concentration causing half of the maximal inhibition of PTH release. **B** Parameters describing a sigmoidal curve such as that in **A**. Maximum and minimum refer to the asymptotic values for the curve on the Y axis. Midpoint refers to the value on the X axis which yields a value for Y half way between the maximum and the minimum. Slope is the slope of the curve at the midpoint.

This sigmoidal curve may be defined by four parameters: the maximal and minimal values on the ordinate, the midpoint of the curve on the abscissa and the slope at the midpoint. The midpoint of the curve relating PTH release to calcium concentration, defined as the set-point, is the calcium concentration causing half of the maximal inhibition of secretion. There is reasonable uniformity in the values for set-point in man as well as in various experimental animals both in vivo and in vitro.[3] In studies with dispersed human or bovine parathyroid cells, and in vivo studies in man, PTH release was half-maximally inhibited at a calcium concentration of about 1.0 mM (8-9 mg/dl total calcium concentration). In man as well as in other species, the sigmoidal curve relating PTH secretion to extracellular calcium concentration is remarkably steep at its mid-point. Thus, maximal stimulation of PTH secretion is achieved with only slight hypocalcemia (~7-8 mg/dl); conversely, maximal (although not complete) inhibition is observed at 11-12 mg/dl. This system is, therefore,

poised to respond to very small changes in extracellular calcium concentration.

The maximum suppressibility of bioactive PTH release by calcium is not complete.[10] This failure to achieve complete suppressibility is of importance in normal and abnormal parathyroid physiology. For example, Gittes and Radde showed that transplantation of large numbers (20-80) of normal rat parathyroid glands to otherwise normal rats resulted in chronic hypercalcemia.[11] This may be considered an experimental model for the type of secondary hyperparathyroidism that occurs in chroni renal insufficiency, which also sometimes results in hypercalcemia.

While total immunoreactive PTH release may not be completely suppressed by hypercalcemia (generally reduced by about 80%), it is likely that the release of bioactive PTH is inhibited considerably more. Studies both in vivo[12] and in vitro[13] have demonstrated convincingly that parathyroid tissue directly releases fragments of PTH. The release of hormonal fragments is greater at high than at low extracellular calcium concentrations.[12,13] Thus, increased intraglandular degradation of PTH to inactive fragments may represent a mechanism by which the release of bioactive hormone is reduced at elevated extracellular calcium concentrations.[14] In vivo, nephrogenous cyclic AMP excretion is almost completely suppressed during calcium infusion.[15]

Certain conditions may alter the sensitivity of the parathyroid glands to extracellular calcium. For example, an increase in set-point for calcium has been observed in parathyroid tissue removed at the time of subtotal parathyroidectomy for severe secondary hyperparathyroidism in patients with chronic renal failure (Fig 2).[16] In other words, the sigmoidal curve is shifted to the right in patients with secondary hyperplasia and it takes a greater amount of calcium to induce half-maximal suppression of PTH secreton. The mean set-points (mM Ca) for normal subjects, patients with secondary parathyroid hyperplasia and for those with parathyroid adenomas were 0.99, 1.13 and 1.20, respectively. In contrast to the differences in set-point, there were no significant differences in the maximum rates of PTH release in the three groups.

Figure 2

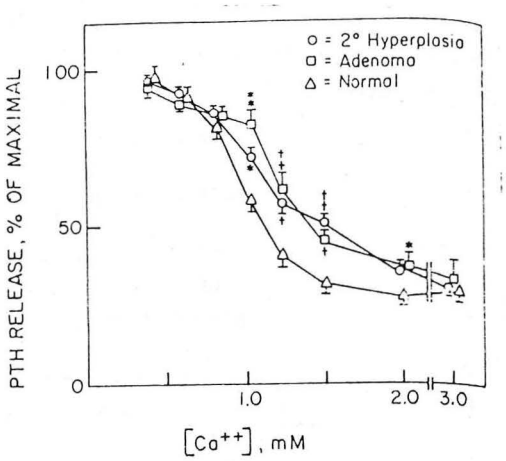

FIG. 2 Calcium-regulated PTH release in dispersed parathyroid cells from normal glands, adenomas, and glands with secondary hyperplasia.

These results indicated that parathyroid hypersecretion in the setting of renal insufficiency may be related to abnormal regulation of secretion of calcium at the cellular level, as well as to an increased mass of functioning parathyroid tissue. This defect was analogous to the abnormality previously reported in most cell preparations from parathyroid adenomas.[8] The mechanism for the altered set-point in patients with renal insufficiency remains uncertain. Possible explanations include chronic parathyroid stimulation from hypocalcemia; uremic toxins; and alterations in circulating metabolites of vitamin D (see below).

Calcium modulates PTH secretion in a number of ways (Table 2).

Table 2. Functions Modified by Calcium in Parathyroid Tissue

Function	Effect of High Calcium
Basal and Agonist-Stimulated Secretion	↓
Basal and Agonist-Stimulated Cyclic AMP	↓
Adenylate Cyclase Activity	↓
Phosphodiesterase Activity	↑
Cyclic AMP-Dependent Protein Kinase Activity	↓
PreproPTH mRNA Activity	↓
Degradation of PTH	↑

Early studies suggested that cyclic AMP played an important role in the regulation of PTH release by divalent cations and other factors. Abe and Sherwood found that the release of cyclic AMP and PTH from bovine parathyroid tissue slices were inhibited in parallel by elevated extracellular calcium concentrations.[17] Subsequent studies have shown that agents which stimulate intracellular cyclic AMP production cause PTH secretion, whereas agents which reduce parathyroid cell cyclic AMP content inhibit PTH secretion (Fig 3).[18] The effects of elevations of cyclic AMP in the parathyroid gland, as in other tissues, are mediated by changes in cyclic AMP-dependent protein kinase activity with attendant alterations in the phosphorylation of key cellular substrates involved in the secretory process. As indicated in Fig. 3, calcium may lower cellular cyclic AMP by inhibiting adenylate cyclase and/or by activating a calmodulin-activated phosphodiesterase. Calcium is also believed to have other direct inhibitory effects on the secretory process, independent of changes in cyclic AMP.

Fig. 3

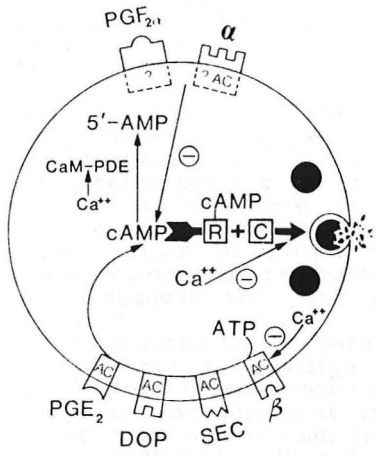

Fig. 3 Cyclic AMP metabolism and the control of PTH release. Receptors for PGF_2, dopamine (DOP), secretin (SEC) and β-adrenergic catecholamines (β) enhance cAMP accumulation in the parathyroid cell through activation of adenylate cyclase (AC). $PGF_{2\alpha}$ and α-adrenergic catecholamines (α) lower cAMP, perhaps by inhibiting adenylate cyclase (α-agonists). cAMP binds to the regulatory subunit (R) of cyclic AMP dependent protein kinase, liberating the now active catalytic subunit (C). The phosphorylation of key cellular substrates by C presumably activates the secretory process with release of secretory granules (indicated by the dark circles). Calcium might lower cellular cAMP by inhibiting adenylate cyclase and/or by activating a calmodulin-activated phosphodiesterase (CaM-PDE). It is likely, however, that calcium also has direct inhibitory effects on the secretory process, independent of changes in cAMP.

In addition to inhibiting PTH secretion, there is now evidence that a high serum calcium concentration, reversibly and specifically decreases preproPTH mRNA synthesis in cultured bovine parathyroid cells.[19] Moreover, a high calcium concentration has been found to promote increased intracellular degradation of PTH so that more inactive C-terminal fragments are released from the parathyroid glands.[14] It is of interest that a calcium-regulated peptidase has been indentified in porcine parathyroid tissue.[20]

Regulation of Parathyroid Gland Function by 1,25-$(OH)_2D$

PTH and 1,25-$(OH)_2D$ act together to regulate calcium homeostasis. PTH is trophic to 1,25-$(OH)_2D$ synthesis both directly and via its effect in lowering renal tubular phosphorus. Both hormones increase serum calcium concentration, which in turn decreases the secretion of PTH.

There is also accumulating evidence that 1,25-$(OH)_2D$ itself has a direct effect on PTH synthesis and secretion, analogous to the feedback of steroid hormones on pituitary peptide release. Parathyroid cells have stereospecific, high affinity receptors for 1,25-$(OH)_2D$[21,22] similar to the receptors found in the classic target sites for 1,25-$(OH)_2D$, namely intestine and bone.[23,24] Moreover, after intravenous administration of [^{3}H]-1,25-$(OH)_2D$ to chicks and rats, there is marked accumulation of radioactivity in the parathyroid nuclei.[25,26] These data suggest that the parathyroid gland is a target organ for 1,25-$(OH)_2D$.

Silver et al., using isolated bovine parathyroid cells in primary culture, showed in vitro that 1,25-$(OH)_2D$ reduced preproPTH mRNA levels by 50% at 48 hr.[27] This effect occurred at physiologic levels of 1,25-$(OH)_2D$ (10^{-11}M), was dose-dependent and reversible; and 1,25-$(OH)_2D$ was more potent in this regard than the less active vitamin D metabolites 24,25-$(OH)_2D$ and 25-(OH)D (Figs 4,5).

Fig. 4

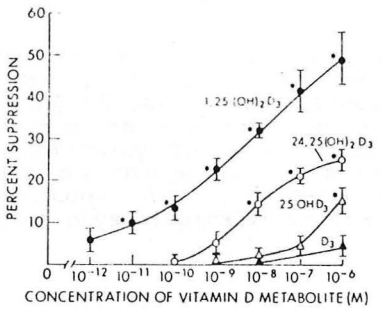

FIG. 4 Dose-response of vitamin D_3 and its metabolites on the percentage suppression of cellular preproPTH mRNA content is shown at 48 hr. ●, 1,25-$(OH)_2D_3$; ○, 24,25-$(OH)_2D_3$; △, 25-OH-D_3; and ▲, vitamin D_3. The results represent mean ± SEM in quadruplicate plates. *, $P < 0.01$ compared with control.

Fig. 5

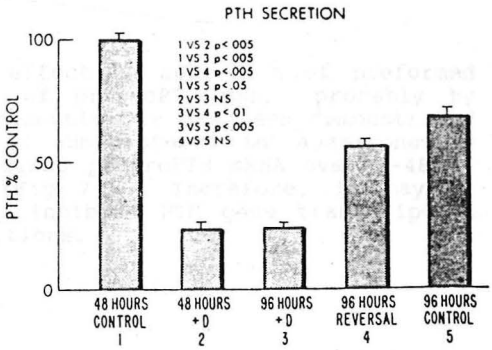

FIG. 5 PTH secretion from bovine parathyroid cells cultured for 48–96 h in the presence of and after removal of 10^{-7} M 1,25-$(OH)_2D_3$ (bars 2, 3, and 4) or in the presence of vehicle alone (controls; bars 1 and 5). Cells were cultured for 48 h in vehicle or 1,25-$(OH)_2D_3$ (bars 1 and 2), then levels of PTH secretion were determined using a C-terminal assay, as described in the text. Simultaneous cell incubations were continued for an additional 48 h in the presence of 1,25-$(OH)_2D_3$ (bar 3) or vehicle (bar 5). A set of cells that had been cultured for 48 h in 10^{-7} M 1,25-$(OH)_2D_3$ was then cultured 48 h in medium free of added 1,25-$(OH)_2D_3$ (bar 4) to test for recovery of PTH secretion after suppression by 1,25-$(OH)_2D_3$. Each condition was tested in quadruplicate in three such experiments. Values, expressed as a percentage of control levels, indicate the mean ± SEM. Results of tests of significance are shown.

Cantley et al. showed that this reduced preproPTH mRNA level correlated with a similar reduction in PTH secretion by the cells at the corresponding times, with no effect of $1,25\text{-}(OH)_2D$ on PTH secretion at shorter time intervals (Fig 6).[28]

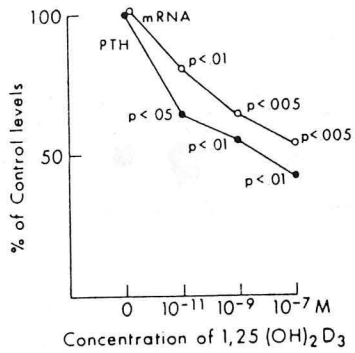

Fig 6 Suppression of pre-pro-PTH mRNA levels (O) and PTH secretion rates (●; N-terminal assay) after 48 h of culture in medium containing 10^{-11}, 10^{-9}, and 10^{-7} M $1,25\text{-}(OH)_2D_3$ or vehicle alone. Values of both parameters are expressed as a percentage of the vehicle-treated control value, defined as 100%. *P* values indicate the level of significance compared with controls.

Thus, in vitro $1,25\text{-}(OH)_2D$ has no effect on secretion of preformed hormone, but decreases the levels of preproPTH mRNA, probably by acting on DNA transcription. More recently, it has been demonstrated in vivo in the rat that $1,25\text{-}(OH)_2D$ administered intraperitoneally dramatically decreased parathyroid gland preproPTH mRNA over 3-48 hr with no change in serum calcium (Fig 7).[29] Therefore, it may be concluded that $1,25\text{-}(OH)_2D$ directly inhibits PTH gene transcription under physiologically relevant conditions.

Fig. 7

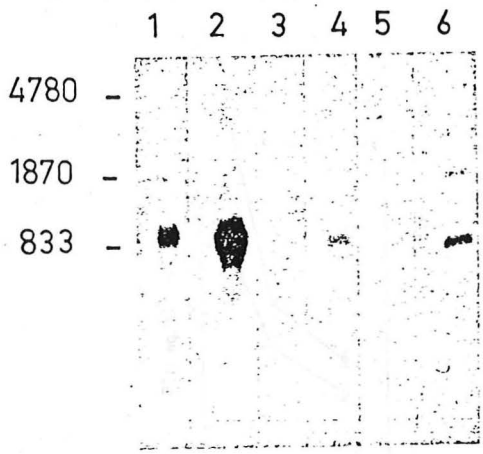

Figure 7 Gel blot analysis of total RNA from parathyroid-thyroid tissue after hybridization with ^{32}P nick-translated preproPTH cDNA. Lanes: *1*, parathyroid-thyroid tissue RNA from one control rat; *2*, parathyroid-thyroid tissue RNA from two control rats combined; *3*, parathyroid-thyroid tissue RNA from one rat 24 h after 100 pmol $1,25(OH)_2D_3$ i.p.; *4*, the combined parathyroid-thyroid tissue RNA from two rats 24 h after 100 pmol $1,25(OH)_2D_3$ i.p.; *5*, rat liver RNA; *6*, purified preproPTH cDNA fragment. RNA size in nucleotide base pairs is shown for ribosomal 18S and 28S RNAs.

It is likely that the ability of 1,25-$(OH)_2$D to inhibit PTH gene transcription is independent of calcium. The effect of 1,25-$(OH)_2$D in markedly decreasing preproPTH mRNA in isolated bovine parathyroid cells was certainly not a function of extracellular fluid calcium, which was maintained at 1.25 mM.[27] In the in vivo rat study, there was no increase in serum calcium when 1,25-$(OH)_2$D was administered. However, 1,25-$(OH)_2$D has been shown to affect the lipid composition of cell membranes and thereby increase transcellular calcium transport.[30] It is therefore possible that some of the effect of 1,25-$(OH)_2$D on preproPTH mRNA may be due to an ionophore effect of 1,25-$(OH)_2$D rather than its classic mode of action on the cell genome. Whatever the mechanism of the 1,25-$(OH)_2$D effect on PTH gene transcription, it is an effect of 1,25-$(OH)_2$D and not of alteration in serum calcium. Nevertheless, the presence of 1,25-$(OH)_2$D may modify the secretory response of parathyroid cells to varying levels of calcium (Fig 8).[28] In the presence of 1,25-$(OH)_2$D less PTH is secreted per parathyroid cell at any level of ambient calcium. In renal insufficiency, where there may be a deficiency of 1,25-$(OH)_2$D, one would anticipate more PTH release at any level of serum calcium, i.e. a shift of the

"sigmoidal" curve to the right. This may explain the increased set-point for calcium suppression of PTH release previously noted to occur in patients with chronic renal failure.[16]

Fig. 8

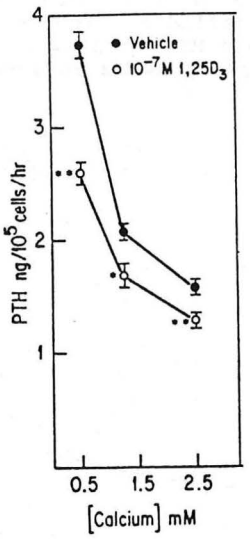

FIG. 8 Ability of bovine parathyroid cells cultured for 48 h in the presence of 10^{-7} M 1,25-$(OH)_2D_3$ (○) or vehicle alone (●) to respond acutely to changes in extracellular calcium (0.5, 1.25, and 2.5 mM) in a representative experiment. In the *left panel*, PTH secretion rates (nanograms per 10^5 cells/h; mean ± SEM; measured using our C-terminal assay) at each calcium level are shown for vitamin D-treated and control cells. At each calcium level, vitamin D-treated cells secreted less PTH than did controls ($P < 0.05$ or better). Cell numbers were not affected (average of 451,000 in vehicle-treated wells *vs.* 457,000 in vitamin D-treated wells; P = NS).

In summary, 1,25-$(OH)_2$D appears to be the major factor controlling PTH gene transcription and this is manifested by its effect in vivo on serum PTH levels. Calcium is the major determinant of parathyroid activity by its control of PTH secretion and catabolism. There is some evidence that calcium itself may also affect PTH gene transcription.[19] In addition, the parathyroid gland responds to chronically low levels of extracellular calcium by hypertrophy and proliferation of parathyroid cells with a tremendous increase in total PTH production. Whereas calcium is believed to be mostly involved with parathyroid cell replication and PTH secretion, the control of parathyroid transcription and hence PTH production by the individual parathyroid cells maybe determined more by 1,25-$(OH)_2$D.[29] Since 1,25-$(OH)_2$D itself decreases PTH synthesis and hence

serum PTH levels, it participates in a classic, short endocrinological feed-back loop.

Pathogenesis of Secondary Hyperparathyroidism in Chronic Renal Insufficiency

Secondary hyperparathyroidism with a markedly elevated serum concentration of PTH is a well-established complication of renal insufficiency.[31] The blood levels of PTH became elevated early in the course of renal insufficiency as shown in Fig. 9.

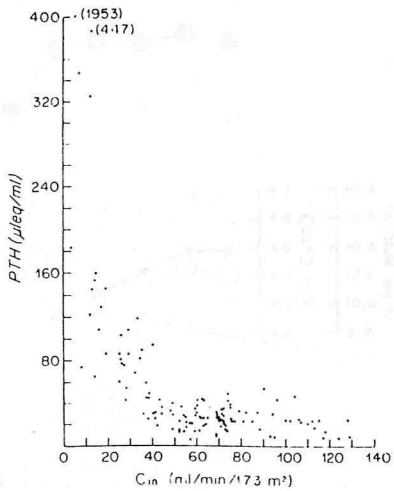

Figure 9 Relationship between serum immunoreactive PTH and the renal clearance of inulin in patients with varying levels of renal function. The immunoassay of PTH was done utilizing an antiserum believed to react with 1-84 PTH as well as with its mid-region and carboxyl terminal fragments. (From Arnaud, C. D.: Kidney Int. 4:89, 1973. Reprinted from *Kidney International* with permission.)

Several factors have been implicated in the pathogenesis of secondary hyperparathyroidism including:

(1) Phosphate retention with a rise in serum phosphate concentration and a resultant fall in serum calcium concentration. The role of phosphate retention has been emphasized by Slatopolsky and Bricker.[32] As the phosphate retention theory originated, it was postulated that a transient and even undetectable increase in serum phosphorus occurs early in renal failure with each small decrement in renal function. The transient hyperphosphatemia would temporarily lower the blood ionized calcium level, which would stimulate the secretion of PTH. Higher levels of PTH would reduce the tubule reabsorption of phosphorus and cause phosphaturia; both serum

phosphorus and calcium levels would return toward normal at the expense of a higher serum level of PTH.

Considerable evidence supports an important role for phosphate retention in producing secondary hyperparathyroidism. Reiss et al. showed that an oral load of phosphate, providing 1.0 g of elemental phosphorus, led to an increase in serum phosphorus, a fall in ionized calcium level, and an increase in serum PTH in normal subjects (Fig 10).[33]

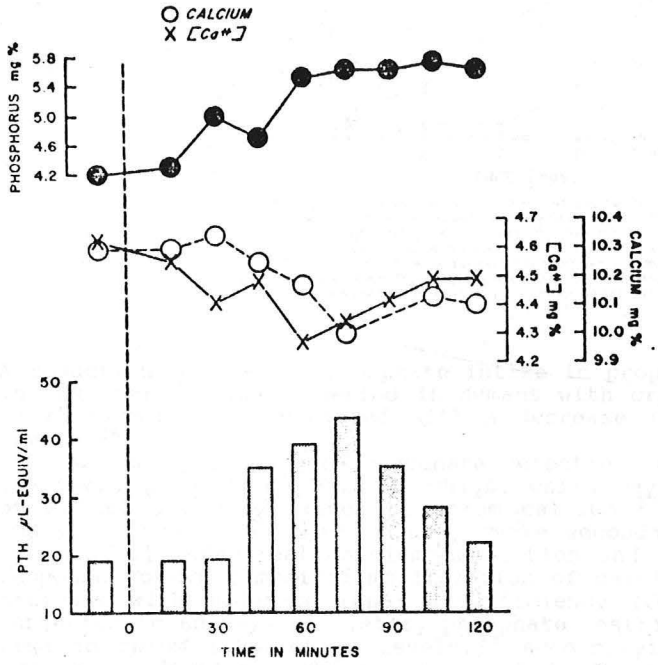

Figure 10 *Effect of oral phosphate on serum PTH, total calcium, ionized calcium and phosphorus in a normal man. Normal ranges: PTH, 10 to 60 μl Eq/ml; total calcium, 9.0 to 10.5 mg/100 mi; ionized calcium, 4.08 to 4.80 mg/100 ml; phosphorus, 3.0 to 4.5 mg/100 ml. From Reiss et al. [20]. By permission of The Rockefeller University Press.*

Studies in experimental renal failure have shown that the restriction of dietary phosphate in proportion to the decrease in GFR can prevent the development of secondary hyperparathyroidism in azotemic dogs followed for 2 months,[34] and subsequent studies showed a substantial reduction of serum PTH levels in animals with renal failure treated with proportional phosphate restriction for 2 years (Fig 11).[35]

Fig. 11

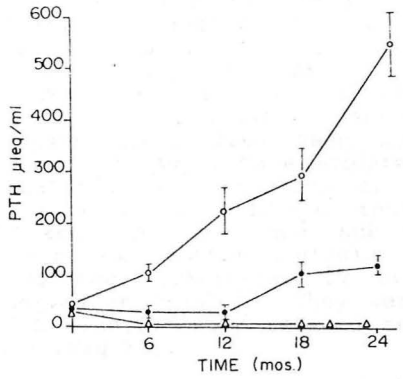

Figure 11 Serial values of immunoreactive parathyroid hormone (mean ± SE) in dogs with chronic renal insufficiency. The dogs received either a normal constant phosphate intake (○), a phosphate intake reduced in proportion to the decrease in glomerular filtration rate (●), or a proportional reduction in phosphate intake and 25-(OH)D_3, 20 µg twice/week (Δ), for two years. (Modified from Rutherford, W. E., et al.: J. Clin. Invest. 60:332, 1977.)

A reduction of dietary phosphate intake in proportion to the decrease in GFR over a 2-month period in humans with creatinine clearances of 50-90 ml/min was associated with a decrease in serum PTH to normal levels.[36]

Another problem with phosphate retention is that it may decrease the renal production of 1,25-$(OH)_2$D, which may permit more secretion of PTH at any given level of serum calcium.[37] A reduction in 1,25-$(OH)_2$D concentration would also provoke secondary hyperparathyroidism by reducing intestinal calcium absorption and impairing the calcemic response to PTH (impaired mobilization of calcium from bone). When 4 patients with moderate renal insufficiency (Ccr 55-66 mg/min) were subjected to 60 days of dietery phosphate restriction, there was a 44% rise in serum 1,25-$(OH)_2$D levels.[37] Accompanying this rise in 1,25-$(OH)_2$D production, there was marked improvement of intestinal absorption of calcium, calcemic response to PTH, serum ionized calcium concentration and PTH levels. Thus, a critical role was assigned to a disturbance in vitamin D metabolism in the genesis of hyperparathyroidism of renal failure.[37]

(2) Diminished synthesis of 1,25-$(OH)_2$D.

In adults with chronic renal insufficiency and GFR below 40-50 ml/min, blood levels of 1,25-$(OH)_2$D have been reported to be lower than controls, and plasma concentrations vary in direct proportion to the estimate of GFR.[31] On the other hand, patients with GFR above 50-60 ml/min have generally exhibited normal levels of 1,25-$(OH)_2$D, depending on dietary phosphate intake. With inadequate production of 1,25-$(OH)_2$D, reduced intestinal absorption of calcium and resistance of the skeleton to the calcemic action of PTH would contribute to the

reduced level of ionized calcium in the blood, thereby stimulating the secretion of PTH and leading to secondary hyperparathyroidism.

Growing evidence suggests that low levels of $1,25\text{-}(OH)_2D$ may also play a role in the altered synthesis and secretion of PTH.[27-29] Since $1,25\text{-}(OH)_2D$ has been shown to play a role in the feedback suppression of PTH secretion, a deficiency of $1,25\text{-}(OH)_2D$ might reduce the sensitivity of the parathyroid glands to suppression by an increment in the level of blood calcium. This altered set-point may contribute to the secondary hyperparathyroidism seen in uremia.[38] Several clinical studies address this issue. To elucidate whether $1,25\text{-}(OH)_2D$ directly feedback regulates the secretion of PTH, Madsen et al. studied 10 patients with acute oliguric renal failure.[39] Serum ionized calcium was kept constant and subnormal by continuous peritoneal dialysis with low calcium dialysis fluid. Five patients were treated with .25 mcg $1,25\text{-}(OH)_2D$ IV every 6 hr, while 5 comparable patients served as controls. They were able to show that intravenous $1,25\text{-}(OH)_2D$ significantly reduced serum PTH without any change in serum calcium (Fig 12).

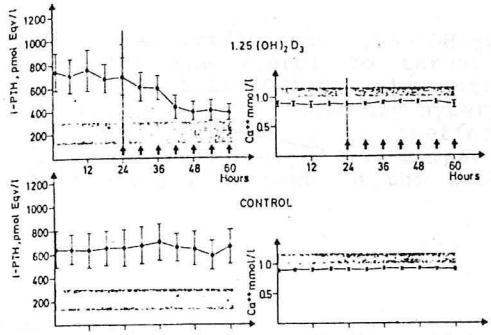

FIG. 12 Ca^{++} and immunoreactive PTH (iPTH) (mean ± SEM) during low calcium peritoneal dialysis. The *arrows* indicate iv injection of 0.25 μg $1,25\text{-}(OH)_2D_3$. ▭, The normal range of Ca^{++} and iPTH. *Upper panel*, $1,25\text{-}(OH)_2D_3$ group; *lower panel*, control group.

Slatopolsky et al. showed that in chronic renal failure patients on thrice weekly hemodialysis, intravenous $1,25\text{-}(OH)_2D$ given after dialysis markedly suppressed serum PTH levels (by 70%) whereas raising the serum calcium to a comparable level by oral calcium supplements only decreased PTH by 25% (Fig 13).[40] Therefore, even where there is an increased parathyroid mass with altered set-point, as in chronic renal failure, $1,25\text{-}(OH)_2D$ is an important factor in controlling serum PTH levels.

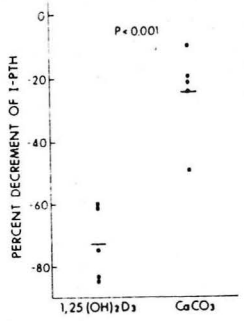

Figure 13 The effects of intravenous $1,25(OH)_2D_3$ or calcium carbonate on i-PTH in five patients. A 73.5±5.08% decrease in the levels of i-PTH was observed during intravenous $1,25(OH)_2D_3$ administration. The administration of calcium carbonate decreased the levels of i-PTH by only 25±6.65% ($P < 0.001$).

These human studies used intravenous 1,25-$(OH)_2$D, which would provide a greater delivery of the sterol to target organs such as the parathyroid, than oral 1,25-$(OH)_2$D. Administration of oral 1,25-$(OH)_2$D results in suppression of secondary hyperparathyroidism only if hypercalcemia occurs--otherwise it is ineffective (Fig 14).[40] In contrast, intravenous 1,25-$(OH)_2$D at comparable dosage is very effective in suppressing PTH, even in the absence of hypercalcemia (Fig 15).40

Fig 14

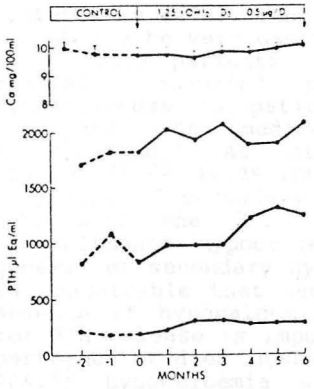

Figure 14 Long-term effects of $1.25(OH)_2D_3$ given orally (0.5 µg/d) on serum calcium and serum i-PTH in three patients maintained on chronic hemodialysis.

Fig 15

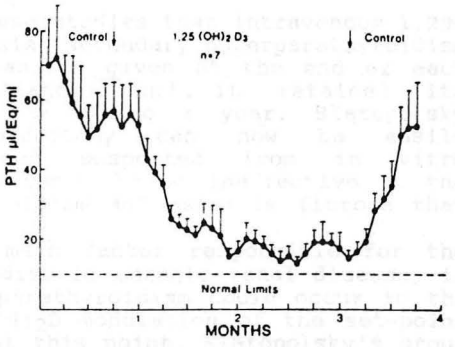

Figure 15 Sequential changes in serum i-PTH in patients with mild hyperparathyroidism before, during and after treatment with $1.25(OH)_2D_3$. An 86% decrease in the levels of i-PTH was observed during intravenous $1.25(OH)_2D_3$ administration.

The reason that intravenous administration of 1,25-$(OH)_2D$ appears to be so much more effective relates to recent findings indicating substantial degradation of 1,25-$(OH)_2D$ in the intestine.[41] Therefore, it is possible that while oral administration of the vitamin D metabolite increases intestinal calcium absorption, the delivery of 1,25-$(OH)_2D$ to peripheral target organs may be limited. Serum levels of 1,25-$(OH)_2D$ in a representative patient after the administration of 1 mcg of 1,25-$(OH)_2D$ given intravenously or orally are shown in Fig 16.

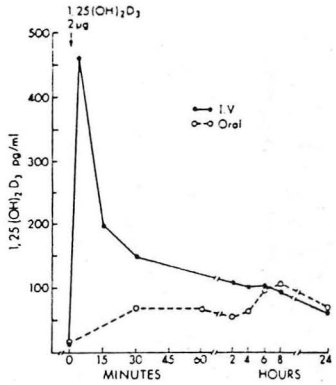

Figure 16 Serum levels of 1.25$(OH)_2D_3$ in a representative patient after the administration of 2.0 µg of 1.25$(OH)_2D_3$ given intravenously (● —— ●) or orally (o - - - o).

Slatopolsky et al. concluded from these studies that intravenous 1,25-$(OH)_2D$ may be very useful in suppressing secondary hyperparathyroidism in dialysis patients. It could be easily given at the end of each dialysis, assuring patient compliance, and it retained its effectiveness in patients studied for up to a year. Slatopolsky concluded, "A medical parathyroidectomy can now be easily accomplished." As might have been suspected from in vitro studies,[27,29] 24,25-$(OH)_2D$ has been shown to be ineffective in the treatment of secondary hyperparathyroidism and osteitis fibrosa that occur with renal failure.[31]

Although hypocalcemia is the main factor responsible for the genesis of secondary hyperparathyroidism in chronic renal disease, it is conceivable that secondary hyperparathyroidism could occur in the absence of hypocalcemia, if 1,25-$(OH)_2D$ modulation of the set-point for PTH release is important. To test this point, Slatopolsky's group performed studies in dogs in which GFR was surgically reduced by about 70%.[42] Hypocalcemia was prevented in these uremic dogs by the

administration of a high calcium diet. Despite a moderate increase in ionized calcium, PTH increased from 64±8 to 118±21 pg/ml, as serum 1,25-$(OH)_2$D decreased from 25±4 to 12±4 pg/ml (Fig 17). Treatment with 1,25-$(OH)_2$D at a dosage which did not alter serum ionized calcium, prevented the rise in PTH (Fig 18). One may conclude that low levels of 1,25-$(OH)_2$D, independent of a fall in serum calcium, may contribute to altered regulation of PTH secretion by calcium in renal insufficiency.[42]

Fig 17

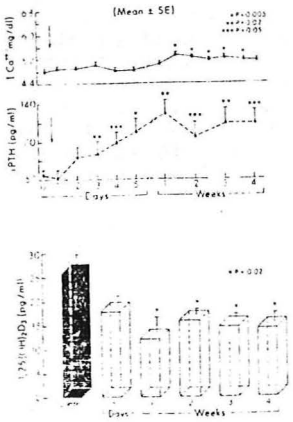

Figure 17 Serum-ionized calcium, amino iPTH levels, and serum $1,25(OH)_2D_3$ before and after the induction of renal insufficiency (*arrow*) in a group of six dogs from protocol I. ICa, ionized calcium.

Fig 18

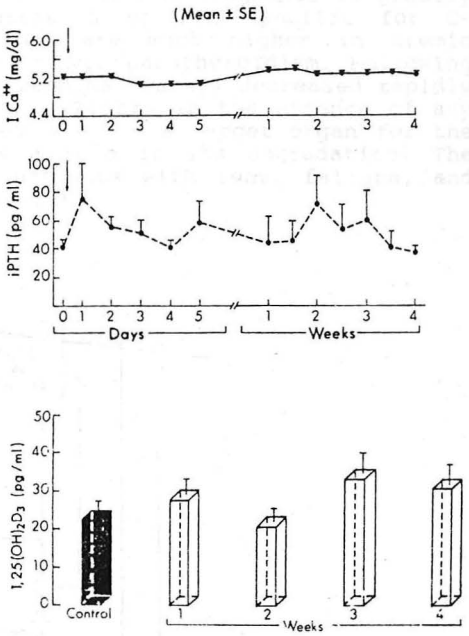

Figure 18 Serum-ionized calcium, amino iPTH levels, and serum $1,25(OH)_2D_3$ in a group of six dogs from protocol III who received 75–100 ng of $1,25(OH)_2D_3$ twice daily before and after renal insufficiency (*arrow*). ICa, ionized calcium.

(3) Abnormal set-point for calcium regulated PTH secretion.

The increased set-point noted in hyperplastic parathyroid glands from patients with renal insufficiency has been explained partly on the basis of 1,25-$(OH)_2$D deficiency. In addition, Bellorin-Font et al. have demonstrated that the adenylate cyclase of hyperplastic glands is less susceptible to inhibition by calcium.[43] Under normal conditions, this adenylate cyclase requires 0.22-0.28 mM ionized

calcium for 50% inhibition, whereas comparable inhibition of the enzyme from hyperplastic parathyroid glands was seen at 0.70 to 1.00 mM ionized calcium. Thus, it is possible that this alteration in the regulation of the adenylate cyclase plays an additional role in the abnormal secretion of PTH seen in uremia.

(4) Role of reduced clearance and degradaton of PTH.

A diagram of the renal handling of parathyroid hormone is shown in Fig. 19. The kidney plays an important role in the degradaton of PTH, and decreased degradation of PTH could be a factor contributing to the pathogenesis of hyperparathyroidism in renal failure. Because the kidney may be the only organ removing the C-terminal fragments of PTH from the circulation, the level of C-terminal fragments is greatly increased in renal failure. Measurements of PTH specific for C-terminal fragments reveal values that are much higher in uremic patients than in patients with primary hyperparathyroidism. Following renal transplantation, plasma PTH (C-terminal assay) decreased rapidly to 20% of the preoperative value within 24 hrs in the absence of any change in serum calcium.[45] The kidney also is a target organ for the intact 1-84 PTH molecule and plays a role in its degradation. The clearance of PTH 1-84 is slowed in patients with renal failure, and this may result in higher serum levels.[31]

Fig. 19

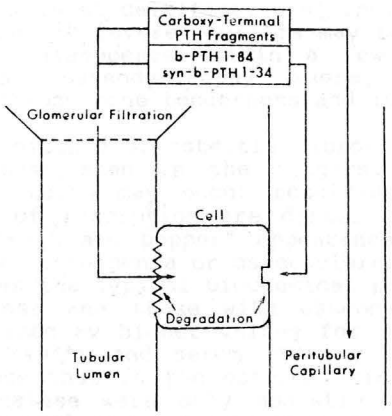

Figure 19 Schematic representation of the renal uptake of parathyroid hormone (PTH) illustrating degradation of the carboxy-terminal and mid-region fragments of PTH via glomerular filtration alone, whereas clearance of PTH 1-84 and PTH 1-34 occurs via both glomerular filtration and uptake from the peritubular capillaries. (Modified from Martin, K. J., et al.: J. Clin. Invest. 60:808, 1977.)

Assessment and Management of Secondary Hyperparathyroidism in Renal Insufficiency

It is often difficult to assess on clinical grounds whether a patient has renal osteodystrophy comprised mainly of osteitis fibrosa vs. osteomalacia. The table prepared by Dr. Pak for his March 1981, Grand Rounds on this subject remains applicable (Table 3).[46]

Table 3.

	Renal Osteodystrophy		
	Osteitis Fibrosa	Osteomalacia	Mixed
Bone pain	+	+	+
Muscle weakness	+	++	+
Fracture	+	+	+
Extraskeletal calcification	+	-	+
Pruritis	+	-	+
Bone tenderness	-	+	+

Patients with predominantly secondary hyperparathyroidism have as their characteristic bone lesion osteitis fibrosa. Bone histomorphometry typically reveals an active resorption surface covered with a large number of osteoclasts and extensive fibrosis, abnormalities which correlate with parathyroid gland weight and serum PTH levels.[47] These patients tend to have a high Ca x P product (>70 mg/dl) which may result in extraskeletal calcifications, including conjunctival and corneal calcifications.[48] Severe pruritis may be present, which often improves or totally disappears within a few days of parathyroidectomy.[49] In renal osteodystrophy where osteomalacia is the predominant presentation, bone tenderness and muscle weakness are more prominent.

The radiologic picture of osteitis fibrosa consists of subperiosteal resorption, best seen in the fingers, where dissolution of terminal phalangeal tufts may occur resulting in "pseudoclubbing." Other common sites of resorption are distal clavicles. Less common presentations are "salt and pepper" appearance of the calvarium and brown tumors. Either osteopenia or osteosclerosis may be present.

Table 4 compares the typical biochemical presentation of patients with osteitis fibrosa and those with osteomalacia.[50] The osteitis group was characterized by higher values for serum phosphorus, alkaline phosphatase activity and serum PTH (by both C-terminal and N-terminal assay). Note that in the osteomalacia group, N-terminal PTH and alkaline phosphatase were only modestly elevated above normal. Serum calcium was normal and not significantly different between the two groups.

Table 4. Renal Osteodystrophy

	Osteitis Fibrosa	Osteomalacia	Normal Range
Serum Ca, mg/dl	9.48±0.15 SE	9.71±0.25	8.9-10.1
Serum P, mg/dl*	4.85±0.25	3.79±0.38	3.2±4.3
Alkaline phosphatase, IU*	94.5±18.9	31.3±5.0	26±7 (SD)
Magnesium, mg/dl*	2.89±0.09	3.30±1.7	1.7-2.1
iPTH (C-term), µl eq/ml**	1586±239	278±44	<40
PTH (intact), pg eq/ml*	1444±361	293±35	255±46 (SD)

*p<0.05, **p<0.01 between patient groups

Specific measures for the prevention and management of secondary hyperparathyroidism of renal insufficiency are outlined in Table 5.[31] Some more recent concepts will be highlighted.

Table 5 Guidelines for Management of Renal Osteodystrophy

Control of Serum Phosphorus (3.0 to 5.5 mg/dl)
Restrict dietary phosphorus intake to 0.7 to 1.0 gm/day
Individualize dosage of phosphate binders and ingest with meals: aluminum hydroxide, aluminum carbonate, or calcium carbonate; use minimum dose of aluminum-containing compounds
Avoid hypophosphatemia
Avoid aluminum excess

Adequate Calcium Intake
Give oral calcium supplements providing 1 gm/day, when serum P is controlled
Dialysate Ca should be 6.0 to 6.5 mg/dl (3.0 to 3.25 mEq/liter)

Use of Vitamin D Sterols
Indications for treatment: Adequate control of serum P and:
Hypocalcemia
Overt secondary hyperparathyroidism (high iPTH and high alkaline phosphatase and bone erosions) with serum Ca < 11.0 to 11.5 mg/dl
Osteomalacia particularly with secondary hyperparathyroidism
Advanced renal failure in children
Concomitant anticonvulsant therapy
Proximal myopathy
Prophylaxis in dialysis patients (cost-benefit ratio not established)
Types and Approximate Daily Doses
Vitamin D_2 or D_3: 10,000 to 200,000 IU (0.25 to 5.0 mg/day)
Dihydrotachysterol: 0.25 to 2.0 mg/day
Calcifediol (25-$(OH)D_3$): 25 to 100 µg/day
Calcitriol (1,25-$(OH)_2D_3$): 0.25 to 1.0 µg/day; intravenous calcitriol more effective: 0.5 to 3.0 µg thrice weekly

Parathyroidectomy
Indications: Evidence of secondary hyperparathyroidism (X-ray erosions, biopsy osteitis fibrosa, and adequately elevated iPTH), exclusion of aluminum-related bone disease plus any of the following:
Persistent hypercalcemia (serum Ca > 11.5 to 12.0 mg/dl)
Progressive or symptomatic extraskeletal calcification (particularly with serum Ca × P product > 75 (both in mg/dl)
Pruritus not responsive to other treatment
Calciphylaxis (ischemic ulcers and necrosis)
Symptomatic and persistent hypercalcemia after renal transplantation

Use of Calcium Salts as Phosphate-Binder

Phosphate retention is a major factor contributing to the development of secondary hyperparathyroidism in uremia, and reduction in dietary phosphorus intake in proportion to the decrease in GFR can largely prevent secondary hyperparathyroidism. Moreover, high serum phosphate levels contribute to the development of soft tissue calcifications. Up until recently, the only available approach to restricting phosphate was to prescribe low-phosphate diets and aluminum-containing antacids which bind phosphorus in the intestinal tract. It is now known however, that small amounts of orally administered aluminum can be absorbed, and in the presence of renal insufficiency, result in increased plasma and tissue aluminum content.[51] Accumulation of aluminum in bone may cause osteomalacia.[52] Recently, calcium carbonate has been reported to successfully lower serum phosphorus levels and raise serum calcium levels in a group of patients maintained on dialysis (Fig 20).[53]

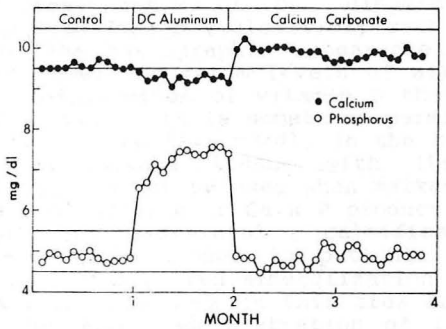

Figure 20 Mean Serum Calcium and Phosphorus Levels in 20 Patients during the Three Phases of the Four-Month Study.

For some patients, this agent may be a satisfactory substitute for traditional phosphate binders that contain aluminum. The required dose of calcium carbonate varies from patient to patient and often reaches 5-10 gm/day. It must be taken with meals. If a patient has severe hyperphosphatemia (a serum phosphorus of 7-15 mg/dl) it is advisable to lower the serum phosphorus level with antacids (to 5-7 mg/dl) before calcium carbonate therapy begins, to avoid the induction of extra-skeletal calcification. Calcium carbonate is not as effective as the aluminum containing antacids and in some patients both agents may have to be given, although at reduced dosage. In addition to the risk of metastatic calcification which will require further investigation, hypercalcemia may ensue, particularly if the patient is on treatment with $1,25\text{-}(OH)_2D$. Obviously, patients treated with calcium carbonate as a phosphate binder would have to be followed very carefully. At this institution, calcium citrate which is more soluble

and may therefore bind more phosphate is under investigation. Presently, other safe and effective phosphate-binding agents are not available. There have been preliminary reports of the use of a complex polymer of uronic acid that has been complexed with calcium; these reports suggest that it is as effective in phosphate binding as aluminum gels.[54] However, further long-term trials will be needed to evaluate its efficacy and safety.

Use of Vitamin D Sterols

Despite dietary phosphate restriction, the use of phosphate binders, the choice of an appropriate level of calcium in dialysate, and intake of adequate dietary calcium, a significant number of uremic patients still develop features of osteitis fibrosa. Knowledge of the kidney's role in producing $1,25\text{-}(OH)_2D$ has created interest in the use of active vitamin D sterols in such patients. When uremic patients have evidence of overt secondary hyperparathyroidism (e.g. bone erosions, high PTH levels, and increased alkaline phosphatase), adequate treatment with a vitamin D sterol often leads to improvement. Thus, pharmacological doses of D_2, dihydrotachysterol, 25-(OH)D (calcifidiol) and $1,25\text{-}(OH)_2D$ (calcitriol) each have been reported to improve symptoms, the radiographic appearance of bone and skeletal histology, and to lower the serum levels of alkaline phosphatase and PTH.[31] The major complication of vitamin D therapy is hypercalcemia, but with close monitoring, it is sometimes permissable to allow serum calcium to rise to 11.0 to 11.5 mg/dl, in the hope of suppressing the large mass of parathyroid tissue with its altered set-point. Vitamin D sterols should not be used when marked hyperphosphatemia is present, because the increase in Ca x P product can predispose to the development of extra-skeletal calcification.[55] Significant hypercalcemia may appear sooner in patients with aluminum-induced osteomalacia because of impaired mineralization of bone.[56]

The most exciting new work in this area has been the demonstration that the intravenous administration of $1,25\text{-}(OH)_2D$ may have a marked effect to suppress serum PTH concentrations.[39,40,42] Evidence has been reviewed earlier supporting a direct effect of $1,25\text{-}(OH)_2D$ on the parathyroid glands in addition to its effect to raise the serum calcium concentration (Fig 21).

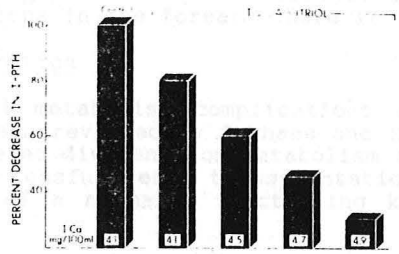

Figure 21 Mean values for serum iPTH and ionized calcium concentrations (I Ca) in 20 dialysis patients given calcitriol intravenously, 0.5 to 4.0 µg three times weekly. Serum iPTH decreased before there was any change in blood ionized calcium level. Modified from Slatopolsky, E., et al, J. Clin. Invest. 74:2136, 1984.

The role of 1,25-$(OH)_2D$ treatment in the prophyllaxis of skeletal disease for patients undergoing dialysis or those with mild renal failure has not yet been established. It has been suggested that renal function may decrease in patients during treatment with 1,25-$(OH)_2D$[57], although this may be related to either hypercalcemia or phosphate retention. Further studies are needed to establish the prophyllactic role of 1,25-$(OH)_2D$ in renal failure.

Considerations Regarding Parathyroidectomy (Table 5)

Despite medical attempts at parathyroid suppression as noted above, certain features of secondary hyperparathyroidism may necessitate parathyroid surgery. The features that may necessitate parathyroid surgery include: (1) persistant hypercalcemia, particularly when symptomatic, (2) intractable pruritus that does not respond to dialysis or other medical treatment, (3) progressive extraskeletal calcifications that occur in conjuction with a Ca x P product that is consistently greater than 75 to 80, despite appropriate attempts at phosphate restriction, (4) severe and progressive skeletal pain or fractures, and (5) the appearance of calciphylaxis (ischemic lesions of soft tissue and skin and vascular calcifications).[58]

It is important to be certain that parathyroid surgery is absolutely necessary before proceeding because there are several drawbacks. In addition to the risk of hypoparathyroidism, it has been demonstrated in careful bone histomorphometric studies that increased PTH secretion is an important factor of bone formation in dialyzed patients and that excessive reduction of the PTH secretion leads to "inactive bone."[59] In other words, after parathyroidectomy, there is a dramatic drop in resorption surfaces and osteoclast number which is coupled to a sharp reduction in bone formation rate. There have been several reports of decreased mineralization and osteomalacia appearing after total or subtotal parathyroidectomy.[60,61] Moreover, aluminum-related osteomalacia may actually worsen after parathyroidectomy.[62] Thus, when a patient notes worsening of bone pain and fractures following parathyroidectomy, aluminum-related bone disease must be excluded.

When parathyroid removal must be done, it is generally advisable to perform total parathyroidectomy with transplantation of a small fraction of the excised parathyroid cells into the forearm. The principal advantage is that if recurrence of parathyroid hyperplasia occurs, it develops in the forearm where it is readily accessible.

Renal Transplantation

The mineral metabolism complications of kidney transplantation have recently been reviewed by Sakhaee and Helderman.[63] Although many features of altered divalent ion metabolism and renal bone disease are corrected by successful renal transplantation, other problems appear. With insertion of a normally functioning kidney, the production of

1,25-$(OH)_2D$ can begin and high levels of PTH may decrease , albeit not quite to normal levels (Fig 22).[64]

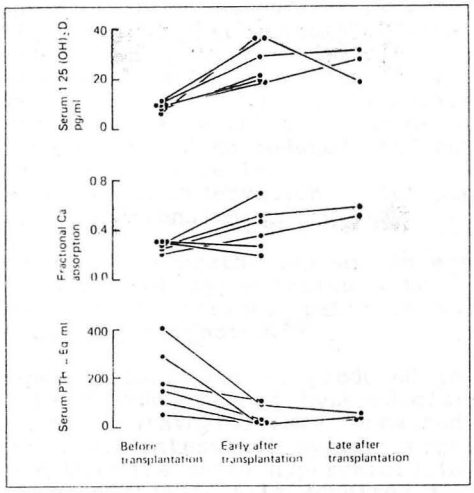

Fig. 22 Effect of renal transplantation on serum concentrations of 1,25(OH)-D, PTH and fractional intestinal Ca absorption in patients with end-stage renal disease. Each line represents a study in a separate patient. The shaded area denotes the normal range.

Part of the reason that some degree of secondary hyperparathyroidism persists post-renal transplant may relate to steroid therapy with concomittant hypercalciuria and subnormal intestinal calcium absorption. Moreover, the hyperplastic parathyroid glands are generally responsive to normal feedback, but at a higher blood calcium level. With resumption of the kidneys ability to excrete phosphorus and produce 1,25-$(OH)_2D$ and with improved skeletal responsiveness to the calcemic action of PTH,[64] serum calcium levels increase and the parathyroid glands may begin to involute. However, hypercalcemia with increased PTH levels and low serum phosphate may persist for years after transplantation.[65] If the hypercalcemia is symptomatic, treatment with phosphate is generally effective. The incidence of hypercalcemia, hypophosphatemia and increased renal clearance of phosphate may be 15 to 35% in transplant recipients.[31] If serum Ca rises to greater than 12 mg/dl in association with deterioration of renal graft function or if calciphylaxis occurs, then subtotal parathyroidectomy would be indicated.

Successful renal transplantation generally leads to gradual and steady improvement in renal osteodystrophy.[66] Osteomalacia has resolved in 81% of patients after one year. Osteitis fibrosa generally improves at a slow rate, and it did not disappear completely even years after transplantation, in accord with persistent mild secondary hyperparathyroidism.

Evidence Linking Secondary Hyperparathyroidism to Hypertension

There is emerging evidence that calcium metabolism may be disturbed in patients with essential hypertension. One appealing scheme proposed by Strazzullo suggests that renal sodium retention and ECF expansion causes renal hypercalciuria.[67] The resulting secondary hyperparathyroidism may cause hypertension by facilitating calcium influx into vascular smooth muscle, thereby causing vasoconstriction. In this scheme, both sodium restriction and calcium supplements should be protective since PTH would be reduced, and hence less calcium would enter vascular smooth muscle cells.

There are a number of observations which support the above scheme in certain types of hypertension:

1. Persons with hyperparathyroidism, in absence of renal damage, show a higher incidence of hypertension with a 20% remittance after parathyroidectomy.[68] In contrast, patients with hypoparathyroidism generally do not have hypertension.[69]

2. Renal hypercalciuria may be produced in normal subjects by a high sodium intake.[70] The induced hypercalciuria has been shown to cause secondary hyperparathyroidism, enhanced synthesis of 1,25-$(OH)_2D$ and compensatory intestinal hyperabsorption of calcium. It is therefore possible that the renal hypercalciuria described in patients with essential hypertension[67,71] is acquired from renal sodium retention and ECF volume expansion. The resulting PTH excess may then promote calcium influx and cause smooth muscle contraction. The studies of Bello et al. favor this possibility since they noted that a population of patients with hypercalciuria and renal lithiasis had an enhanced incidence of hypertension which was mostly of the low-renin type.[72] However, in our own series of patients with recurrent nephrolithiasis, hypertension was encountered in less than 20% of patients with renal hypercalciuria, a figure not substantially different from 16% for the prevalance of hypertension in the general population.

3. Berthelot et al.[73] have found that the evolution of DOCA hypertension in the rat is accompanied by a fall in plasma total and ionized calcium, a rise in serum PTH levels, and an increase in urinary cyclic AMP excretion. Parathyroidectomy prevented the development of hypertension.

4. A number of studies have indicated a decrease in serum ionized calcium in the hypertensive patient.[74,75] However, the overlap between normals and hypertensives is substantial. Resnick et al. have noted a decrease in ionized calcium with an accompanying increase in serum PTH and 1,25-$(OH)_2D$, primarily in patients with low-renin hypertension.[76] Secondary hyperparathyroidism was particularly prominent in patients with primary aldosteronism.[77] Total and ionized calcium rose in these patients upon removal of the aldosterone-producing adenoma. Secondary hyperparathyroidism appears to be maintained chronically in the presence of sodium overload. Patients with primary aldosteronism in the steady state are obviously sodium over-loaded, but they have urinary sodium equal to dietary sodium because of the phenomenon of mineralocorticoid escape. The marked elevations of PTH in these patients suggests that sodium over-load by itself, not simply

an increase in urinary sodium excretion, appears to be capable of sustaining secondary hyperparathyroidism.

5. Several lines of evidence suggest that this secondary hyperparathyroidism may tend to enhance any underlying hypertensive process. As mentioned above, parathyroidectomy reduces the level of DOCA hypertension.[73] Parathyroid hormone is known to enhance calcium influx into a variety of cells. For example, Wallach et al. noted that PTH increased flux of calcium into myocardium by 680% and into aorta by 46%.[78] Although not without challenge, a PTH-mediated increase in calcium transport into vascular smooth muscle would stimulate vasoconstriction and increase peripheral resistance.

6. The plasma from patients with essential hypertension contains a substance (not yet identified) that increases the cytosolic calcium concentration in platelets.[79] Cytosolic calcium is a trigger for vascular smooth muscle contraction, and if the plasma factor acts on these cells as it acts on platelets, it may be responsible for the increased peripheral vascular resistance associated with hypertension.

7. Resnick et al. observed that calcium supplementation lowered the blood pressure best in patients with low-renin hypertension.[80] More recently, Grobbee and Hofman observed that calcium supplementation was most effective in those hypertensive patients with high plasma PTH and/or low serum total calcium.[81] These observations may begin to shed light on why only a subset of patients with essential hypertension appear to respond to calcium supplements.[82]

To further assess these pathophysiologic relationships between calcium homeostasis and hypertension, we have initiated a collaborative study with Dr. Bryan Holland's group at UTMB-Galveston. The long-term goal of the proposed studies is to increase our understanding about which types of hypertensive patients are likely to have a blood pressure fall with dietary calcium supplementation. We postulate that hypertensive patients with chronic sodium overload have enhanced urinary calcium excretion, which causes a secondary hyperparathyroidism that amplifies the basic hypertensive process. The following specific aims are designed to evaluate this postulate and will involve comparisons of the following groups of patients:

a. Primary aldosteronism (bilateral hyperplasia) - 10 patients
b. Low-renin hypertension - 10 white, 10 black patients
c. Normal-renin hypertension - 20 white, 20 black patients
d. Normal subjects - 10 black, 10 white

(1). To compare the regulation of calcium homeostasis in these patients during low-sodium and high-sodium diets in order to determine which types of hypertensive patients are more likely to develop secondary hyperparathyroidism and if there are other fundamental abnormalities in calcium homeostasis.

(2). To compare the changes in calcium homeostasis in these patients during calcium supplementation and determine if calcium supplementation alone can reverse secondary hyperparathyroidism or if sodium balance must also be normalized.

(3). To compare the blood pressure response to calcium supplementation in patients with and without secondary hyperparathyroidism.

The ability of the Galveston group to carefully assess the renin-aldosterone axis in these hypertensive patients plus our own ability to detect subtle abnormalities in calcium metabolism during controlled diets should provide useful additional information.

Relationship of Secondary Hyperparathyroidism to Osteoporosis

Riggs and Melton[83] have suggested that osteoporosis occurs as two distinct syndromes, outlined in Table 6.

Table 6.
Pathogenesis of osteoporosis in the elderly

(a) Type I (involutional)
- (i) ↓ estrogen → ↑ PTH-mediated osteoclastic resorption → ↑ serum Ca → ↓ PTH secretion → ↓ 1,25-$(OH)_2D$ → ↓ intestinal Ca absorption
- (ii) Spinal involvement, distal radius
- (iii) Typically <65 years
- (iv) Female >> male

(b) Type II (senile)
- (i) Aging → ↓ 1,25-$(OH)_2D$ → ↓ Ca absorption → ↑ PTH
- (ii) Predilection for femoral neck fracture
- (iii) Typically > 65 years
- (iv) Female > male

For type II osteoporosis, there may be two major causes--impaired bone formation and secondary hyperparathyroidism. The age-related increase in parathyroid function occurs concomitantly with and probably results from the age-related decrease in calcium absorption. This latter phenomenon has been attributed to impaired metabolism of 25-(OH)D to 1,25-$(OH)_2D$ by the aging kidney.[84] The impaired adaptation of the PTH-vitamin D axis in these elderly patients may be exacerbated during periods of reduced calcium intake[84] or excessive sodium ingestion (because of enhanced sodium-induced calciuresis).[85]

An apparently unique presentation of osteoporosis was encountered in 8 postmenopausal women (mean age, 57 yr).[86] These women had a "renal leak" form of osteoporosis, characterized by increased fasting and 24-hr urine calcium excretion, normocalcemia, increased parathyroid activity with "high turnover" bone, but they did not have any compensatory increase in serum 1,25-$(OH)_2D$ or intestinal calcium absorption. Treatment with thiazide reversed the secondary hyperparathyroidism and reduced bone resorptive surfaces.[86]

Recent Insights into Other Forms of Secondary Hyperparathyroidism

A. Occurrence in obese and black subjects[87,88]

Perhaps because of the common denominator of increased strain on the skeleton produced by obesity or a greater muscle mass, obese individuals and members of the black race have an altered mineral metabolism. Obesity is associated with secondary hyperparathyroidism and increased urinary cyclic AMP levels, with parathyroid

function returning to normal following weight loss. In addition, obese white subjects have a significantly higher serum 1,25-$(OH)_2D$ and significantly lower serum 25-(OH)D and urinary calcium than age-matched non-obese white individuals. Serum ionized calcium and phosphate in the two groups are the same. The secondary hyperparathyroidism which is believed to result from a modified skeletal response to PTH or perhaps owing to increased calcium entry into bone, is the cause for the increased serum 1,25-$(OH)_2D$ concentration and decreased urinary calcium. The low serum 25-(OH)D that occurs in obese subjects is attributed to feedback inhibition of hepatic production of 25-(OH)D by 1,25-$(OH)_2D$. Blacks are known to have an increased skeletal mass and decreased urinary calcium as compared with values in whites. The greater skeletal mass in blacks has been attributed to a greater muscle mass. The PTH-vitamin D axis and urinary calcium excretion in blacks is altered exactly as in obese white individuals. Increased strain on the skeleton imposed by the greater muscle mass may be the initiating event. The biochemical changes by which physical forces seem to cause an apparent "resistance" of the skeleton to PTH are not known.

B. Parathyroid Mitogenic Activity in Patients with MEN I[89]

Familial multiple endocrine neoplasia type I (MEN I) is characterized by hyperfunction of parathyroid, pancreatic islet, and anterior pituitary cells. It is inherited as an autosomal dominant trait. Among the patients who express the gene for the disorder, 95% have primary hyperparathyroidism, whereas less than a third have either gastrinoma or prolactinoma. The recurrence rate of the hyperparathyroidism is approximately 50% within 10 years after subtotal parathyroidectomy. The cause of the abnormal activation (proliferation and secretion) of endocrine cells in MEN I is not known. Recently, Brand et al. using cultured bovine parathyroid cells found that plasma from patients with MEN I had parathyroid mitogenic activity which was 2400% over the control plasma value (by ^3H-thymidine incorporation).[89] Plasma from MEN I patients also stimulated the proliferation of bovine parathyroid cells in culture, whereas plasma from normal subjects inhibited it. Parathyroid mitogenic activity in plasma from patients with MEN I was greater than that in plasma from patients with various other disorders, including sporadic primary hyperparathyroidism (adenoma, hyperplasia or cancer), sporadic primary hypergastrinemia, sporadic pituitary tumor, FHH, and MEN II. The mitogenic activity persisted for up to 4 years post-total parathyroidectomy. The plasma also had far more mitogenic activity in cultures of parathyroid cells than did optimal concentratons of known growth factors or of any parathyroid secretagogue. This mitogenic activity was believed to be a humoral factor with molecular weight 50,000.

C. Hyperparathyroidism in Manic-Depressive Patients on Lithium

An elevation in set-point has been seen in vitro following exposure of dispersed bovine parathyroid cells to extracellular lithium.[90] Since patients with manic-depressive disease receiving lithium therapeutically may develop mild hypercalcemia and/or elevated PTH,[91,92] it is possible that lithium produces similar changes in set-point in vivo.

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