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RENAL OSTEODYSTROPHY

THE PATHOPHYSIOLOGY OF DIVALENT CATION ABSORPTION

Pedro J. Vergne-Marini, M.D.

The development of chronic hemodialysis and transplantation as an accepted and available therapeutic modality has, over the last ten years, brought into the forefront a number of complications such as anemia, uremic pericarditis and renal osteodystrophy which, although known over the last 100 years, were of little therapeutic importance since death ensued a short time after the development of chronic renal failure (CRF). In 1883, Lucas (1) published a paper "On a Form of Late Rickets Associated with Albuminuria, Rickets of Adolescents" which has been quoted all too often as being the first monograph associating renal and bone disease, but Virchow (2), in 1855, described five cases of destructive bone disease associated with nephritis and ectopic calcification. In 1905 MacCallum (3) described the first case of a parathyroid tumor in association with chronic nephritis and in 1927 Parsons (4) observed the radiographical changes of osteomalacia and osteitis fibrosa. So, as far back as 1927 the clinical signs and symptoms of renal osteodystrophy were described and the correlation between the bone disorder and parathyroid hyperplasia was known and latter emphasized by Fuller Albright. Furthermore, the association of the above with vitamin D was first made by Liu and Chu (5) in 1943. A historical review of their paper is important since they made several key observations:

1. Lesions of the bone are varied, from slight osteoporosis to marked osteitis fibrosa cystica. Renal function was impaired to a variable degree.
2. Impaired renal PO_4 excretion and negative Ca^{++} balance.
3. Chronic acidosis and its effect on Ca^{++} intake.

4. Correction of Ca^{++} absorption by dihydrotachysterol and raised the question of inactivation of vitamin D by renal insufficiency.
5. Therapeutic plan including the above plus Ferric ammonium citrate which would facilitate Ca^{++} absorption by complexing with PO_4 as insoluble Ferric phosphate.

As can been seen in this brief historical review, by 1943 we had an understanding of the interrelationship of the different organs involved in the pathogenesis of renal osteodystrophy but a clear cut understanding of the pathophysiology of renal osteodystrophy did not develop until the last seven (7) years. For this reason, in this review, we will address ourselves to the management of renal osteodystrophy on the basis of recent advances in vitamin D metabolism and gastrointestinal divalent ion absorption.

Renal osteodystrophy may be defined as a chronic disorder of bone metabolism associated with renal failure in which increased reabsorption, diminished mineral deposition, and sclerosis of bone occur either simultaneously or in varying degrees. It is characterized by an elevated alkaline phosphatase from bone, slightly decreased serum calcium and increased serum phosphorus. The magnitude of these latter changes may be altered by aggressive therapy with phosphate binding antacids. Symptoms are present in about 10% of the patients even though radiologic evidence of osteitis fibrosa may be found in 50% of the cases. On the other hand, bone biopsy will readily have one or a mixture of the following clinical abnormalities in varying degrees: 1) osteitis fibrosa cystica; 2) osteomalacia; 3) osteoporosis; and 4) osteosclerosis. Osteomalacia will be the predominant lesion in about 10% of the hemodialysis

population but the exact incidence varies from area to area. Several factors have been implicated for the latter distribution such as: 1) type of water and calcium concentration; 2) dietary habits; 3) water treatment; and 4) awareness by the dialyzing physician.

Because of the infrequency with which osteoporosis (6) and osteosclerosis (7,8) are found in our dialysis population and our lack of understanding on the pathophysiology of the latter, these two entities will not be discussed any further. Osteitis fibrosa (9) can be seen in up to 90% of patients reaching end stage renal disease (ESRD). It represents the end result of a continuous and persistent effect of parathyroid hormone (PTH) on the bone. Under the stimulatory influence of PTH, osteons are removed by osteoclastic resorption and replaced by poorly mineralized lamellar bone, woven bone or merely fibrous tissue. In addition, increased osteoclastic resorption at endosteal surface unmatched by periosteal bone apposition progressively reduces cortical thickness with a marked increase in the trabecular surface covered by osteoid, most of which is covered with active osteoblast (9). The radiologic picture consists of subperiosteal reabsorption of the terminal phalanges of the fingers. The first change observed is that the contour of the terminal phalanx loses its sharpness, followed by the loss of continuity and later the classical scalloped erosions on the side of the phalanges which are usually situated at the radial border. As the disease progresses, there is gradual dissolution of the trabecular network most pronounced in the terminal phalanx, the terminal knob of which may disappear giving the appearance of clubbing (pseudoclubbing). There are multiple other radiological changes including reabsorp-

tion of the distal clavicles (8), "salt and pepper" appearance of the calvarium and brown tumors, but they are less important in that they appear after the previously described lesions.

Osteomalacia is seen in any condition which is characterized by vitamin D deficiency (10). The histological characteristics (10) are:

1. A large increase in the area occupied by osteoid.
2. The proportion of bone trabeculae covered by osteoid.
3. The gross reduction in the amount of the calcification front.

Some of this excess osteoid is calcified and very little is covered by active osteoblast. The interrelationship between vitamin D deficiency and the lesion of osteomalacia is not yet clearly elucidated. Several theories have been proposed but the one that is presently accepted is that mature collagen fiber can act as a nucleation center for the precipitation of calcium phosphates from super saturated solutions of calcium and phosphate salts. The spatial orientation of the collagen fibers within the organic bone being of extreme importance to the process of phase transformation and heterogeneous nucleation which normally initiates the deposition of micro crystalline material within and upon fibrillar bone matrix (11,12). This latter process appears to be regulated by $1,25(OH)_2D_3$. The radiologic findings are widening and saucerization of most of the epiphyses which also become deeper and irregular. The distal ends of the radius and ulna are the sites of earliest lesions. In the more advanced lesions there are gross dislocations of the shaft of the bones from the epiphyses, particularly at the wrist. The other lesions are secondary to bone softening and the appearance of

pseudofractures. Bricker (13), in 1969, proposed the intact nephron hypothesis from which a unifying concept of the interrelationship between vitamin D, PTH, GI malabsorption of calcium and bone disease could be developed.

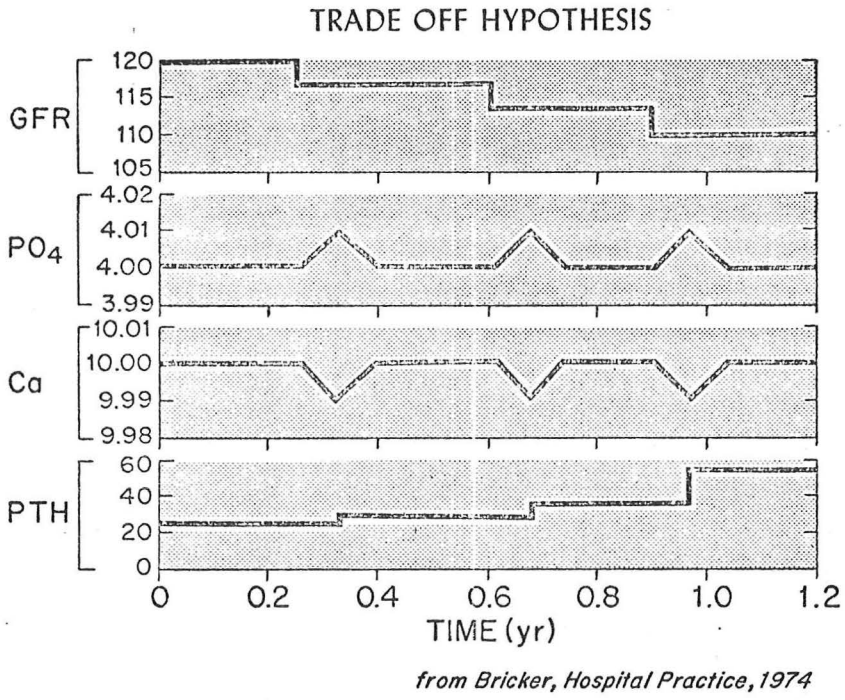


Figure 1

In summary, he proposed that the derangements in hormonal levels were the price to be paid for the maintenance of "a constant internal meliu". For example, with the loss of a functioning nephron a small amount of phosphate would be retained which would transiently decrease the ionized calcium, resulting in stimulation of the release of PTH with subsequent increase in phosphate excretion by the kidney, decrease in calcium excretion and increase

in calcium reabsorption from bone. The end result would be the maintenance of the homeostasis of calcium and phosphorus within normal limits but at increased levels of circulating PTH and an increase in the reabsorption of calcium from bone with the consequent development of "renal osteodystrophy". Not included in their original of the trade-off hypothesis would be the loss of the ability of the kidneys to hydroxylate $25(OH)D_3$ to $1,25(OH)_2D_3$ (15) which would decrease the intestinal calcium absorption as will be shown later, but which in addition, may be a protective since $1,25(OH)_2D_3$ is needed for PTH to have its full physiologic effect with regards to calcium reabsorption from the bone.

EFFECTS OF PHOSPHATE ON I, 25 $(OH)_2$ D_3 PRODUCTION

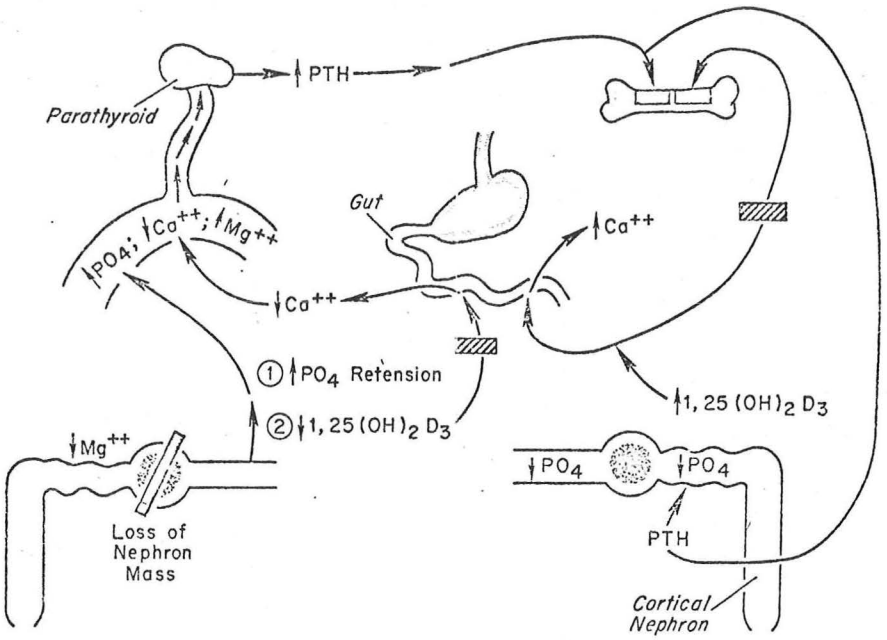


Figure 2

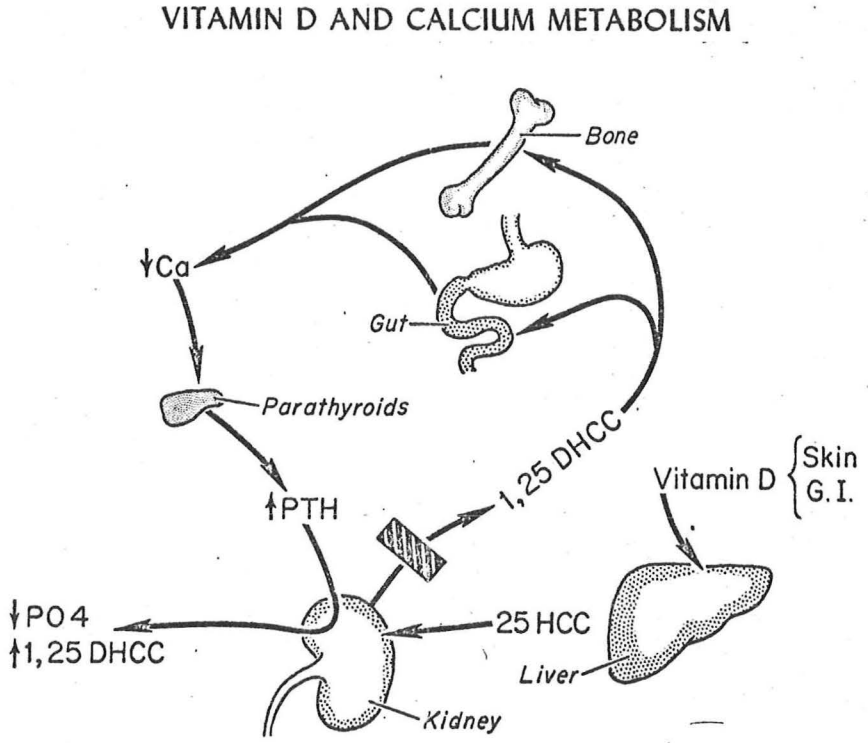


Figure 3

Vitamin D

In 1968 de Luca, by injecting tritiated vitamin D, showed that vitamin D_3 is converted to a polar metabolite, 25 dihydroxycholecalciferol ($25(OH)D_3$), in the liver as shown in Figure 3. Administration of $25(OH)D_3$ resulted in a lag period of 4-5 hours before the tritiated compound was recovered from chicken intestine vs 10-14 hours for vitamin D_3. It has been shown that the major circulating metabolite is hydroxylated by the microsomes of the liver (requiring O_2 and reduced pyridine nucleotide) and transported by an α_2-globulin to the kidneys. The synthesis of $25(OH)D_3$ further enabled the discovery of $1,25(OH)_2D_3$ in the intestine of chickens (16). Its onset of

action in promoting Ca^{++} absorption is more rapid and 100 times as potent as $25(OH)D_3$. The mitochondria of renal cortical cells of the proximal tubule was identified as the site of conversion of $25(OH)D_3$ to $1,25(OH)_2D_3$ (17). Furthermore, the biogenesis of $1,25(OH)_2D_3$ is feedback regulated by Ca^{++} as shown in Figure 4.

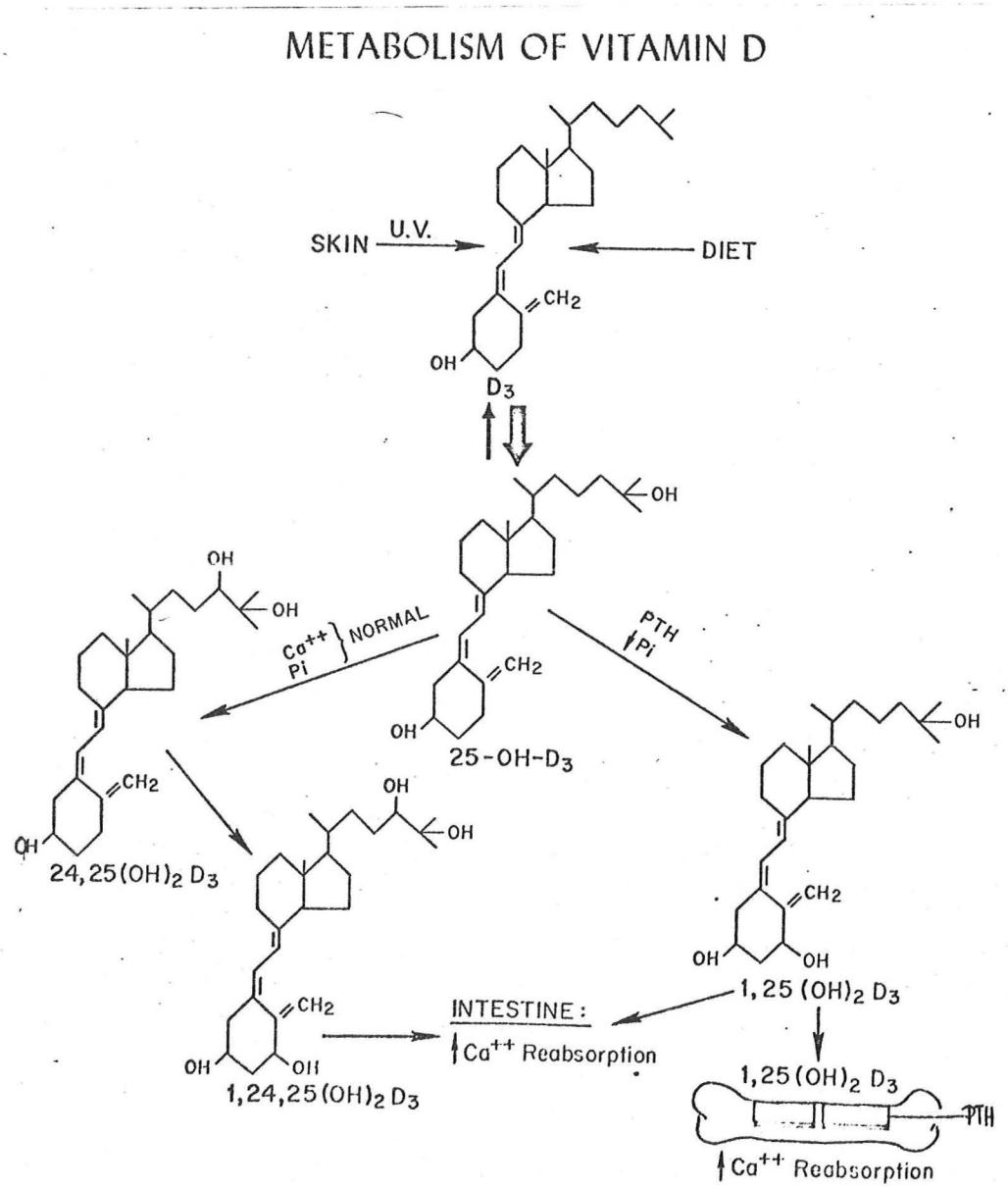


Figure 4

It is postulated that this can be accomplished by PTH, responding to hypocalcemia, which then stimulates the conversion of $25(OH)D_3$ to $1,25(OH)_2D_3$ instead of $24,25(OH)_2D_3$ (14) or other polar metabolites whose physiologic role is unknown at present. Hypophosphatemia has also been shown in thyroparathroidectomized animals (18) to result in an increase in the circulating levels of $1,25(OH)_2D_3$. The mechanism by which parathyroid hormone increased the production of $1,25(OH)_2D_3$ in normal has been suggested by some investigators to be secondary to its effect at the renal tubule which decreases phosphate reabsorption and alters intracellular phosphate levels as shown previously. This latter hypothesis requires further clarification. It therefore seems reasonable to postulate that a decrease in renal mass (Bricker's) causes a decrease in $1,25(OH)_2D_3$ and malabsorption of Ca^{++} at the small bowel.

Wasserman and Haussler (19,20) have shown that $1,25(OH)_2D_3$ regulates the synthesis of Ca^{++} binding protein and a specific brush border Ca^{++} dependent ATPase, which is consistent with <u>in vitro</u> and <u>in vivo</u> experiments which show that calcium transport involves two steps: 1) uptake at the mucosal surface (suggested to be a process of facilitated diffusion which is carrier mediated); and 2) transfer toward the serosal surface which appears to be the rate limiting step. The metabolic pathways of vitamin D are shown in Figure 4. Please note the $24,25(OH)_2D_3$ can be converted to $1,24,25(OH)_2D_3$ whose physiologic role is unknown at the present time but may be one of a reservoir since when hydroxylated at the 1 position it has comparable activity to $1,25(OH)_2D_3$.

The levels of $1,25(OH)_2D_3$* in our normal population are 3.2±1.0 ng/100 ml versus 0.3±0.4 ng/100 ml in our anephrics. After treatment with $1\alpha(OH)D_3$

*Measured by radioimmunoassay of Haussler, M.R.

2 μg daily for 7 days, the levels of 1α $25(OH)_2D_3$ were increased to 11.6±0.5 ng/100 ml. This data is compatible with previously published results but also shows that the ^{25}hydroxylation of $1\alpha(OH)D_3$ at the liver does not appear to be regulated by the circulating levels of the latter and the possibility of vitamin D intoxication appears to be greater.

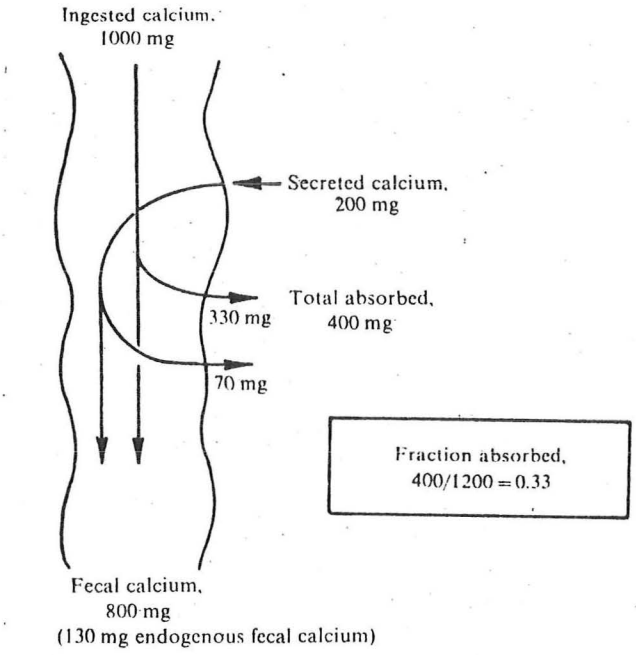


Figure 5

Calcium Balance

As can be seen in Figure 5, the normal individual, and not the usual patient with renal failure, has an average daily intake of calcium of approximately 1000 mg (21), if he ingests a diet containing a small amount of dairy products. About 800 mg of calcium appears in the stool; however, on the average, 130 mg of this does not come from the diet but rather is secreted into the gut by the lining epithelial cells (and is known as endogeneous fecal calcium). Therefore, of the 1000 mg ingested, about 670 mg of

it appears in the stool and 330 mg are absorbed. Thus, in an average American diet, about 30-40% of dietary calcium is absorbed. This percentage absorbed, however, is not a fixed number. There exists the phenomenon of adaptation, which adjusts the fraction absorbed to the changes in total intake. Thus, when intake is low the fraction absorbed increases and when intake exceeds 1000 mg/day the fraction absorbed decreases. This provides a very wise mechanism for keeping the absolute amount absorbed relatively constant over wide fluctuations in intake, so that neither calcium deficiency when total intake is low nor calcium overload when intake is high, is likely to occur. The precise mechanism by which this adjustment in fractional absorption is made is not clear, but most recent evidence suggests that it is mediated by variations in production of vitamin D ($1,25(OH)_2D_3$) by the body, since vitamin D is known to alter the ability of the gut to absorb calcium. The precise mechanism by which vitamin D increases calcium absorption by the gut will be discussed subsequently. Suffice it to say that, apparently, variations in endogenous $1,25(OH)_2D_3$ levels adjust the fraction of calcium absorbed to changes in the total intake. Thus, if one measures GI absorption of calcium, the fraction absorbed itself is not meaningful unless one also knows what the previous level of dietary calcium intake has been.

As we all know, the total body content of calcium, as well as bone content of calcium is dependent not only on the amount of calcium absorbed from the diet, but also upon the amount of calcium excreted. I have already mentioned the endogenous fecal calcium, that is that amount secreted into

the GI tract, is a relatively fixed number but previously reported as being a significant contributor to the negative calcium balance in CRF (22). The other major excretory route is the kidney which on the average excretes 150-250 mg/day, and also has the ability to vary excretion over a wide range to accommodate changes in intake and absorption. Thus, so long as that absorbed from the diet equals that excreted into the gut plus that excreted in the urine, the individual is in perfect calcium balance, with neither net accumulation of calcium in the body, and consequently in bone, nor net loss of calcium from skeletal stores. However, changes in either excretion or absorption, or both, could lead to either net calcium retention or loss. The factors which control urinary calcium excretion are numerous (23) but the two most important ones are (a) the glomerular filtration rate and (b) parathyroid hormone. A fall in GFR leads to a reduction in calcium excretion, all other factors being equal. Parathyroid hormone acts to increase the tubular reabsorption of calcium and thus diminishes urinary excretion. Therefore, to some extent, changes in the amount of PTH secreted can regulate the urinary excretion of calcium.

Phosphorus Balance:

The average daily intake of phosphorous in a normal man is about 800-900 mg. The fraction absorbed varies in a way similar to that described for calcium. With an average intake, however, absorption is about 70% of intake (23).

The major excretory route is via renal excretion. Under normal circumstances, urinary phosphate excretion approximately equals dietary absorp-

tion, again achieving overall balance. The factors which alter the urinary excretion of phosphorous are also numerous (23), but again the major factors are:

A. The plasma level X GFR.

B. Tubular reabsorption of phosphorous which can be altered by PTH.

Finally it should be mentioned that the plasma values of phosphate and calcium bear a more-or-less reciprocal relationship to each other. That is, if the plasma calcium tends to rise, the plasma phosphorous tends to fall and vice versa. This is related to their limited solubility in human plasma at pH 7.4 . In fact when the product of the serum calcium times the serum phosphorous exceeds a value of about 70, metastatic calcification of calcium phosphate tends to occur in the soft tissues (24) with the production of degenerative changes in the myocardium and in the conducting system with the development of severe fatal arrhythmias within 3-6 months (25).

Now lets look at the same control mechanisms for phosphorous. Again, if intake is sharply curtailed, the gut somehow adjusts fractional absorption so that a higher percentage of the reduced intake is absorbed. This tends to minimize the effect of a reduced intake, nonetheless, serum phosphate would tend to fall somewhat. As I have just mentioned, since there tends to be a reciprocal relationship between serum phosphorous and calcium values, the fall in phosphorous would be associated with a rise in the plasma calcium value. This would tend to suppress the secretion of the parathyroid hormone, and the result would be an <u>increase</u> in the tubular reabsorption of phosphate, since

PTH tends to decrease tubular reabsorption of phosphate and PTH secretion is being suppressed by the reciprocal rise in calcium. Thus, once again, a decrease in phosphate intake is adjusted to by both an increase in the fraction absorbed by the GI tract and a decrease in the urinary excretion. Finally, if phosphate intake were to increase massively, the opposite events in the GI tract, plasma, and kidneys would occur.

Calcium Absorption in Chronic Renal Disease:

It has been well recognized since the balance studies of Liu and Chu (5), and later confirmed by de Warderner , that patients with renal failure were in negative calcium balance since if 237 mg of calcium were given in the diet approximately 276 mg were recovered in the stool and it was not until the intake of dietary calcium was increased to approximately 943 mg that a positive calcium balance (26) was obtained. Over the last several months we have studied the kinetics of calcium absorption in the jejunum and ileum and the response of these two segments to $1\alpha(OH)D_3$ an analogue of $1,25(OH)_2D_3$ so as to determine the fluxes of calcium, and the correctability of the defect with a vitamin D_3 derivative since this defect contributes to the development of renal osteodystrophy. As can be seen in Figure 6, jejunal calcium absorption is markedly depressed in patients with chronic renal failure when compared to normal volunteers (22).

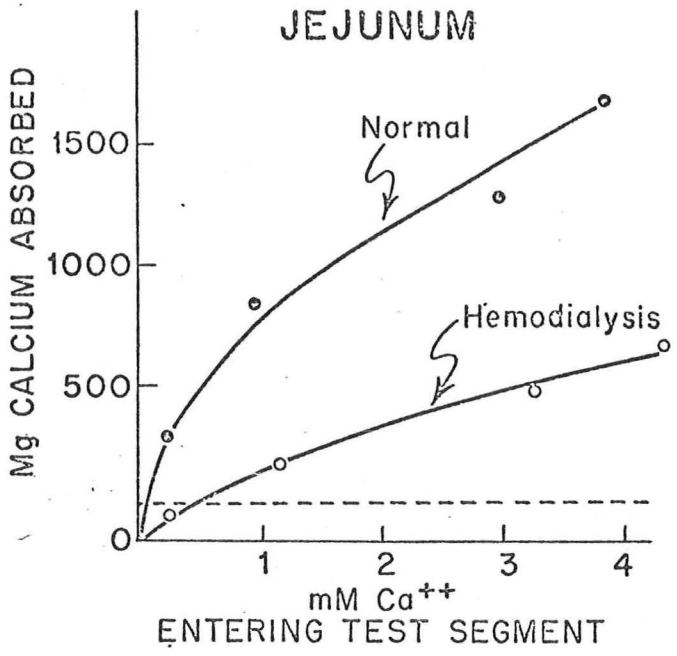


Figure 6

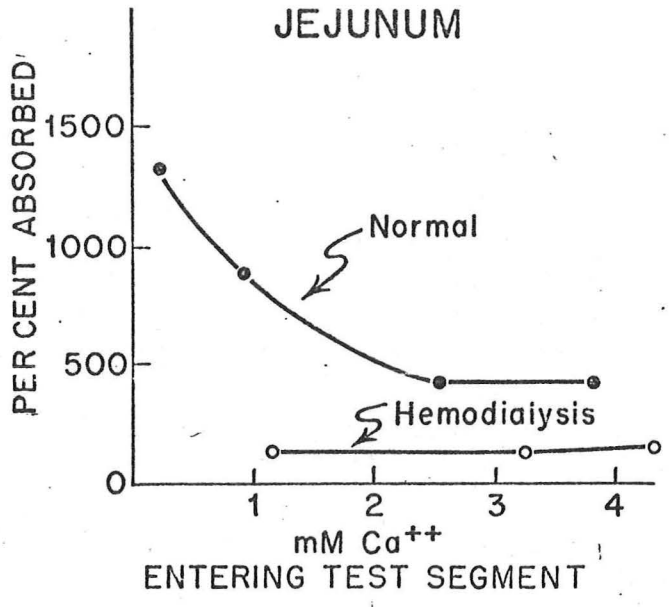


Figure 7

As can be seen in Figure 7, the percent of calcium absorbed from a solution entering the jejunum by the triple lumen perfusion technique is markedly reduced in patients with CRF. This type of experimental data didn't allow us to study the kinetics of calcium absorption so they were repeated utilizing ^{47}Ca. As can be demonstrated in Figure 8, absorption of ^{47}Ca is markedly decreased 40 versus 110 mMoles after treatment with $1\alpha(OH)D_3$.

STUDIES WITH ^{47}Ca IN JEJUNUM

FLUX RATIOS		
OBSERVED	3.7±1.4	6.12±1.3
CALCULATED*	3.2±0.3	2.53±.26
	P.N.S.	P < .025

* Ussing's equation

Figure 8

Furthermore, calcium secretion into the jejunum is unchanged, suggesting that calcium secretion into the GI tract may not be a significant contributory factor in the development of negative calcium balance in chronic renal failure. In addition, if the observed and calculated flux of calcium by Ussing's equation (28) are compared, there is no significant difference (P=NS) suggesting only passive transport down an electrochemical gradient. Therapy with $1\alpha(OH)D_3$

revealed that the observed flux ratio was significantly greater ($P<.025$) than the calculated ratio suggesting an active transport system. Figure 9 compares the intraluminal calcium absorption at varying concentration of calcium gluconate between patients before and after treatment with $1\alpha(OH)D_3$ with normal control volunteers. As can be seen, the defect in calcium absorption is almost totally corrected in the jejunum.

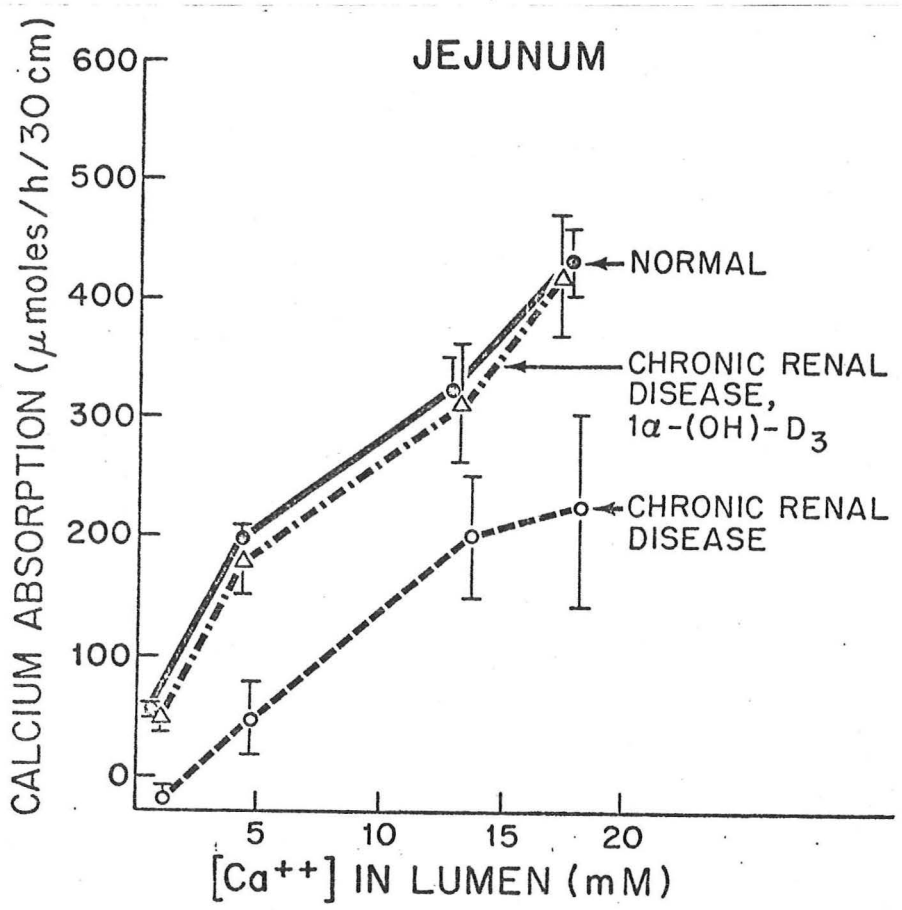


Figure 9

In contrast to the jejunum, indirect methods such as arm counting after oral ingestion of isotopic calcium have suggested that ileal hyperabsorption (29) of calcium compensates for duodenal and jejunal malabsorption of calcium in patients with chronic renal disease. Figure 10 compares the net calcium absorption in the jejunum and ileum in normal subjects and patients with CRF before and after therapy with $1\alpha(OH)D_3$.

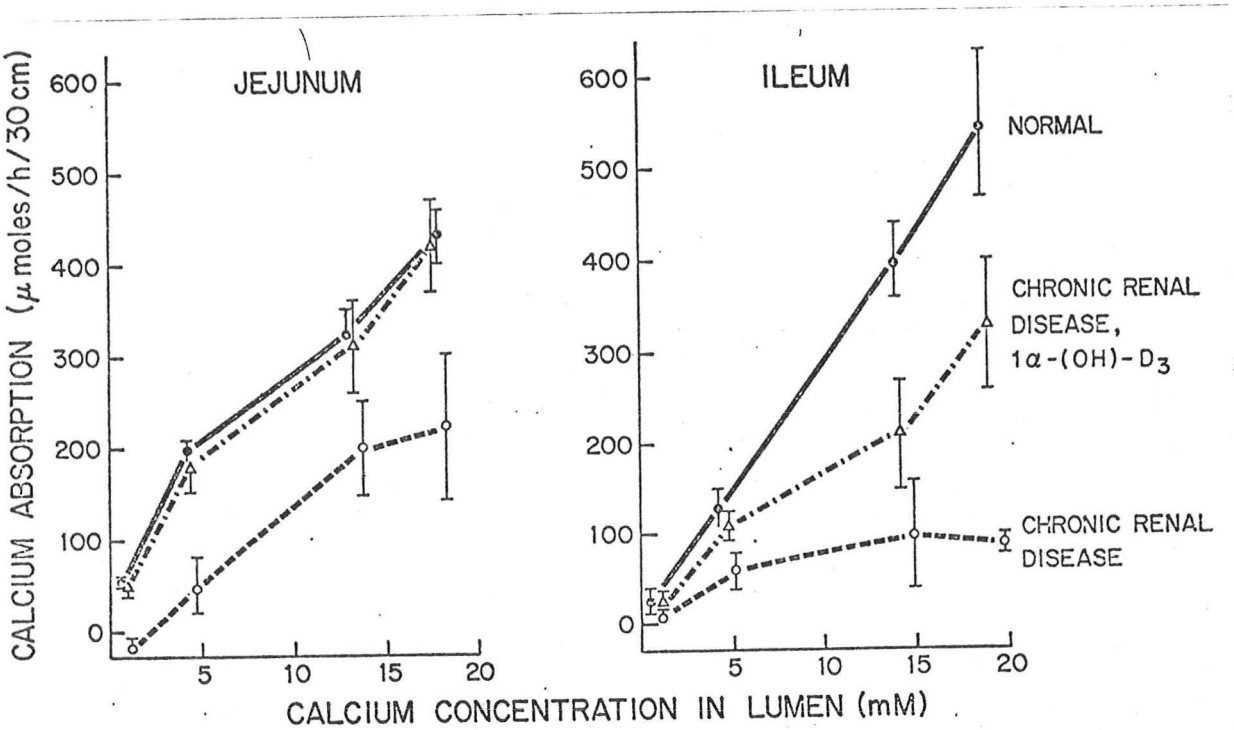


Figure 10

It can be seen that in the ileum the patients increased the net rate of calcium absorption at each of the four luminal concentrations but that they continued to absorb calcium at a slower rate than our normal controls. As seen in Figure 11, the effect of treatment on calcium flux ratios as measured with ^{47}Ca showed that before therapy the patients had an observed flux ratio which

was not significantly different than the flux ratio calculated for passive diffusion by utilizing Ussing's equation. However, after 1 week of $1\alpha(OH)D_3$ the observed flux ratio was significantly higher than the calcualted flux ratio for passive calcium diffusion, indicating that therapy with $1\alpha(OH)D_3$ the observed flux ratio was significantly higher than the calculated flux ratio for passive calcium diffusion, indicating that therapy with $1\alpha(OH)D_3$ had partially restored active calcium absorption in the ileum of patients with chronic renal disease. The reason for the partial correction in the net absorption in this segment of the small bowel are not clear to us.

STUDIES WITH ^{47}Ca IN ILEUM OF PATIENTS WITH RENAL DISEASE

	Before 1α HCC	After 1α HCC
Observed flux ratio	1.3±1.7	2.3±0.6
Calculated flux ratio*	0.9±0.3	0.9±0.2
P	>0.3	<0.05

*Ussing's equation

Figure 11

In summary, our studies suggest that:

A. In the jejunum
   1. The defect in Ca^{++} absorption appears to be specific and corrected by $1\alpha(OH)D_3$.
   2. Decreased net reabsorption, and not increased secretion causes the negative calcium balance.

B. In the ileum
   1. The latter is capable of high rates of calcium absorption approximately equal to that in the jejunum.
   2. Ileal calcium absorption in normal subjects appears to be

mediated by an active process but one which is nonsaturable up to 20 mM/L

3. Calcium absorption is markedly depressed in the ileum of patients with CRF without evidence of compensatory hyperabsorption. This is caused by a marked reduction in absorption without evidence of increased secretion.
4. Ileal malabsorption probably contributes to the negative calcium balance in patients with renal disease.

Summarizing the presently available experimental data, it appears safe to conclude that a progressive loss of functioning nephrons causes increased phosphate retention and increased secretion of PTH. There is a concomitant decrease in circulating $1,25(OH)_2D_3$ with a decrease in the active transport of calcium from the small bowel with further decreases of ionized calcium which amplifies the secretion of PTH causing the typical lesion of hyperparathyroidism in bone. Whereas, on the other hand, patients that because of relative lack of vitamin D_3 such as those in countries with lower amounts of sunlight or where vitamin D is not added to the dietary products, should be more prone to develop osteomalacia secondary to a relative deficit in circulating $1,25(OH)D_3$ with decrease in deposition of calcium on new formed osteoid. The other area which, in a review of this nature, has to be covered, is basically speculative since very little data at the presnt time is available. This is the effects of magnesium on the secretion of PTH since not only is the data scanty, it is totally contradictory. On one hand it has been suggested, as shown in Figure 12, that hypermagnesemia suppresses the secretion of PTH (30) whereas on the other hypomagnesemia (31) has been suggested to have a similar effect as shown in Figure 13.

EFFECTS OF HYPERMAGNESEMIA ON PTH SECRETION

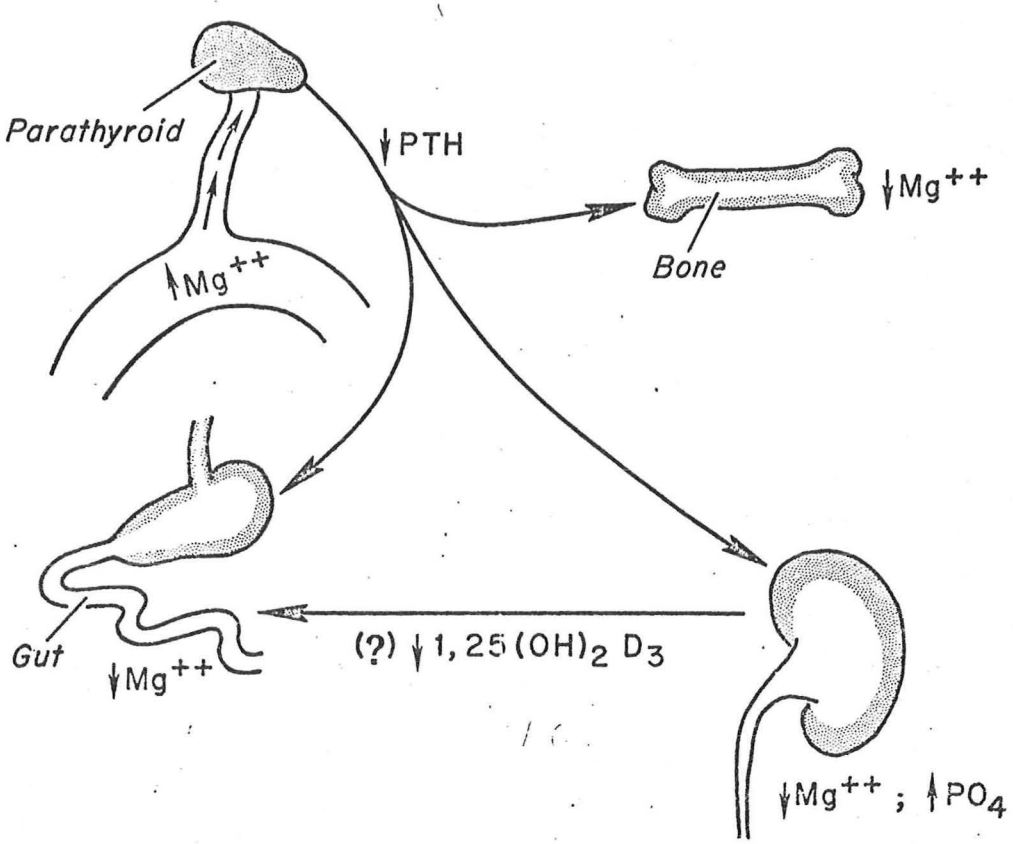
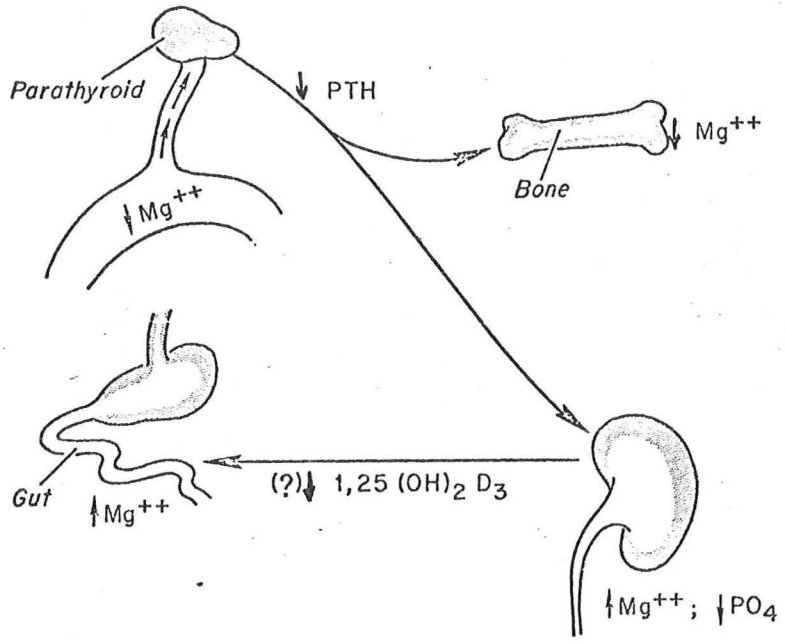


Figure 12

EFFECTS OF HYPOMAGNESEMIA ON PTH SECRETION



It is imperative that this question be answered since the manipulation of magnesium levels could be utilized as a possible tool to suppress PTH secretion. It is probable that hypermagnesemia in the 4-5 mg range would probably not be deleterious and out patients have a mean magnesium level of 2.53 (N=2.0) which could conceivably mean a 50% increase in magnesium levels. Our studies by utilizing the triple lumen perfusion technique (32) and using test solutions containing various combinations of Ca^{++} and Mg^{++} showed that Ca^{++} had little or no influence on Mg^{++} absorption even though Mg^{++} minimally depressed Ca^{++} absorption.

One interesting result of our experiments, as seen in Figure 14, is that Mg^{++} absorption is reduced in the jejunum of patients with chronic renal disease. This cannot be attributed to a generalized depression of intestinal function in renal disease patients, since their absorption of water, electrolytes and D-xylose was normal.

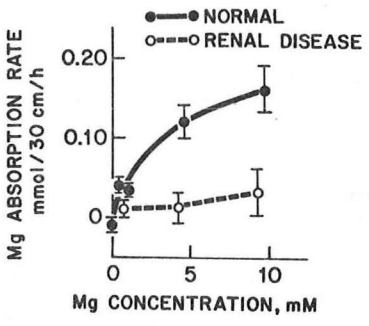


Figure 14

It is well known that patients with chronic renal disease have a deficiency of the active metabolite of vitamin D, $1,25(OH)_2D_3$ and that vitamin D stimulates Mg^{++} absorption in vitamin D deficient animals (33). Most likely, the malabsorption of Mg^{++} in patients with renal disease is due to vitamin D deficiency. The fact that Mg^{++} absorption in renal disease is so markedly depressed suggests that Mg^{++} absorption is exquisitely dependent on vitamin D and is further evidence that passive diffusion of Mg^{++} is of little importance in the absorption of Mg^{++} from the human small intestine. Perhaps Mg^{++} malabsorption helps protect renal disease patients from the hazards of magnesium overload. If this latter hypothesis is proven correct by future experimental data, one should be extremely conservative in randomly utilizing the active metabolites of vitamin D which will become available in the not too distant future. Under these circumstances, serum magnesium would have to be monitored very closely and the possibility of an increased incidence of visceral metastatic calcification (composed of $(Ca.Mg)_3(PO_4)_2$ (24) be kept in mind and followed closely.

THERAPY

A. The therapy of renal osteodystrophy as all therapeutic endeavors in the field of medicine is best based on the premise that prevention is the best of all possible therapy. Slatopolsky (34) has shown in dogs that if the phosphate intake is restricted as the glomerular filtration decreases the levels of PTH remain in the normal range. On the basis of this premise, it appears that patients should be treated early (GFR's 50?) but controlled studies have never,

as yet, been undertaken for several reasons.

1. The onset of renal failure may be insidious.
2. Antacids are nonpalatable, constipating and expensive.
3. Under these circumstances, if the patient is not monitored closely, hypophosphatemia may develop.

Even though there are certain drawbacks, I strongly feel that the patient should be motivated to use $Al(OH)_3$ basis so as to maintain the Ca x PO_4 product 50 to 60 range.

B. Induce a positive calcium balance.

This can be achieved either by large amounts of oral calcium (35) or on patients who are already undergoing hemodialysis by increasing the concentration of calcium in the dyalisate in the 6.5 to 7 mg% range (35). These latter two measures would maintain ionized calcium in a range where the secretion of PTH would be suppressed with a consequent decrease in bone disease.

Under these circumstances serum calcium should be closely monitored since hypercalcemia on the azotemic patient not yet on hemodialysis may decrease or destroy the remaining GFR and in both instances, if the phosphates are not controlled by antacids, metastatic calcifications will occur.

C. Vitamin D metabolites.

The mechanism of action has been discussed in a previous section. They should not be used on patients with elevated serum Ca^{++}. Always remember that a normal serum calcium on a hemodialysis patient means in fact hypercalcemia and secondary hyperparathyroidism. Of the 280 patients presently on dialysis

in Dallas, the probable mean calcium appears to be in the 8.5 to 9.5 range. As previously discussed, the possibility of hypermagnesemia should also be kept in mind until proven otherwise.

D. Parathyroidectomy (37,38)

The indications for subtotal parathyroidectomy (only 200 mg of glandular tissue should be left in place) are many and varied such as:

1. Failure of radiological improvement after medical therapy.
2. Hypercalcemia with systemic symptoms.
3. Metastatic tissue calcifications.
4. Severe pruritus since the latter has been associated with deposition of calcium salts in the skin.

If metastatic calcifications are present, it appears that the bone lesions will heal more rapidly but healing of the bones should be noted between 3 - 5 months post surgery. This should be performed by a fully trained surgical, medical and nursing team since post operative complications such as a severe hypocalcemia with concurrent laryngeal stridor or edema and respiratory arrest may not be unusual if the patient isn't followed carefully. In addition, if adequate amounts of parathyroid gland are removed and hypocalcemia is symptomatic and therapy with oral calcium supplementation and either a vitamin D derivative ($25(OH)D_3$ or $1,25(OH)_2D_3$) or dehydrotachysterol should be instituted.

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