Subtotal Parathyroidectomy in Chronic Renal Failure: A Seven-Year Experience in a Dialysis and Transplant Program

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IT is well known that chronic renal disease is associated with a profound alteration of calcium homeostasis. Although the exact etiology is unsettled, there are complex aspects involved in the pathogenesis of renal osteodystrophy. These include abnormalities in vitamin D action on intestinal mucosal function, intracellular and extracellular pH, parathyroid gland activity and end organ susceptibility to parathyroid hormone (PTH). The incidence of symptomatic osteodystrophy in renal failure patients seems to be increasing and is probably related to the prolongation of life in a mild uremic state afforded by chronic hemodialysis. Transplantation of a well functioning kidney into a patient with osteodystrophy is capable of completely reversing the metabolic derangement with subsequent correction of symptomatology. Subtotal parathyroidectomy (STPx) may also produce dramatic improvement of the bone disease, metastatic calcification and uncontrollable itching in uremic patients with secondary hyperparathyroidism. The dilemma is to select the proper patient for the procedure and the ideal time relationship to dialysis and transplantation for any given patient. Our investigations of the problem have involved an effort to consider metabolic, hormonal and clinical aspects of renal osteodystrophy and calcium homeostasis in uremic patients before and after the onset of dialysis and in relation to renal allotransplantation.

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Materials and Methods

In the 7-year period between January 1, 1964, and January 1, 1971, approximately 800 patients with various types of chronic disease have been treated at the Peter Bent Brigham Hospital. Of this number, 237 patients have received renal transplants from living related or cadaveric donors. From this population of uremic patients, 28 had disorders of calcium homeostasis severe enough to warrant 85–90% STPx. The mean age of these individuals was 35.6 years and there were 16 men patients and

TABLE 1. *Timing of Subtotal Parathyroidectomy in Renal Failure Patients January 1964—January 1971*

	No. of Pts.
Operation before onset of hemodialysis	8
Operation during hemodialysis	18
Operation after renal transplantation	2
Total	28
Male 16	
Female 12	
Mean age of patients	35.6 years

12 women patients (Table 1). Two patients had STPx after having regained normal renal function following renal allografting. Eight uremic patients had STPx performed before hemodialysis was ever initiated. Eighteen patients underwent STPx while on the chronic hemodialysis program but before they received transplants. One of these individuals was awaiting a second transplant, the first having been removed for reasons of sepsis.

Table 2 records the present status of the 28 patients that have had STPx. Of the 26 individuals with chronic renal failure, 11 subsequently received renal allografts; eight are alive, one without her kidney and once again on dialysis. Fifteen of the parathyroidectomized patients have not yet received renal transplants. Ten are alive and three of these patients are in a stable uremic state and have not required hemodialysis. Of the five patients in this group who have died, one never received any hemodialysis.

Clinical Findings and Results

Diagnostic Considerations. The features of renal osteodystrophy in patients who had STPx performed can be considered as an exaggerated form of secondary hyperparathyroidism. The significant biochemical, radiological and clinical findings that led to operation are shown in Table 3. Hypercalcemia, defined as persistent levels of serum calcium greater than 10.6 mg./100 ml. was documented in 19 patients. Three patients had serum calcium levels between 9.0 and 10.0 mg./100 ml. and six others had levels between 10.0 and 10.6 mg./100 ml. No obvious correlation existed between serum calcium levels and the degree of bone damage. All four patients in this series with pathologic fractures secondary to osteitis fibrosa cystica fell in the group of nine patients with serum calcium levels no higher than 10.6 mg./100 ml. Eight of these nine patients had bone changes by x-ray and had symptomatic osteodystrophy. Levels of serum alkaline phosphatase correlated no better with the degree of bone involvement nor did the PTH levels. Once alkaline phosphatase levels in the serum were found to be abnormal, the degree of abnormality did not indicate minimal or extensive bone disease. All patients in whom PTH levels were measured prior to STPx showed some degree of elevation.

Radiological changes were identified preoperatively in 24 of the patients and these consisted of subperiosteal resorption, bone demineralization and pathologic fractures typical and indistinguishable from primary hyperparathyroidism. The major bones involved were the spine, clavicles, skull, phalanges, ribs and long bones. In addition, there were roentgenologic abnormalities more characteristic of the renal osteodystrophy patient; these included metastatic soft tissue calcification, usually periarticular, vascular calcification (arterial) and nephrocalcinosis. Of the four patients not manifesting radiologic bone abnormalities, one

TABLE 2. *Present Status of Patients after Subtotal Parathyroidectomy*

			No. of Pts.
Patients with chronic renal failure			26
Subsequently transplanted		11	
Alive with functioning kidney	7		
Alive without kidney	1		
Died after transplant	3		
Not transplanted		15	
Presently on dialysis	7		
Not yet requiring dialysis	3		
Died of complications of renal failure	5		
Patients already transplanted			2
Alive and well	1		
Died	1		

TABLE 3. *Diagnostic Features of Secondary Hyperparathyroidism*

		No. of Pts.
Biochemical		
Hypercalcemia		
Serum calcium > 10.6 mg./100 ml.		19
Serum calcium 9.0–10.0 mg./100 ml.		3
Serum calcium 10.0–10.6 mg./100 ml.		6
Alkaline phosphatase elevation		28
Parathyroid hormone level elevation (only 8 patients studied)		8
Radiological		
Positive x-ray changes		24
Bone abnormalities	24	
Nephrocalcinosis	8	
Metastatic soft tissue calcification	10	
Vascular calcification	14	
Clinical		
Bone and joint pain		24
Severe itching		17
Gastrointestinal problems		8
Duodenal ulcer	4	
Persistent nausea, vomiting and pain	4	

had severe bone pain; this patient (C. S.) was later found to have multiple myeloma. The other three patients had uncontrollable itching among their major symptoms of parathyroid hyperfunction.

Clinical manifestations related to hyperfunctioning parathyroid tissuse, aside from the bone symptoms, usually were either related to the gastrointestinal tract or involved uncontrollable itching. Duodenal ulcers were present in four patients, all of whom had hypercalcemia. Both patients who had STPx after successful renal transplant had severe hypercalcemia and manifested nausea, persistent vomiting epigastric pain. Two other patients on hemodialysis had similar upper intestinal tract symptoms without documentation of duodenal ulcer disease. Itching to some degree is a frequent concomitant symptom of all seriously uremic patients. In 17 of the patients undergoing STPx, it was a severe and disabling complaint, not only unrelieved by dialysis but progressively worsening with time. This progressive increase in symptomatology was true of all other symptoms of secondary hyperparathyroidism. Two of these patients had grand mal seizures which were considered to be on the basis of metabolic encephalopathy. Muscle weakness, a well-known complaint of patients with primary hyperparathyroidism, was too difficult to document in these chronically ill uremic individuals, since it is such a common complaint in many such patients and may be associated with neuropathy and anemia, as well. Nonetheless, the sense of well-being, which was sometimes striking, often reported by the patients after STPx indicated to us that some of this weakness must have been related to the osteodystrophy and secondary hyperparathyroidism.

Operative Technic and Pathologic Findings. Subtotal parathyroidectomy was performed in the standard manner of parathyroid exploration under general anesthesia in all patients. Those on dialysis received hemodialysis the day before and the day after operation. At the time of neck exploration, all parathyroid glands were always identified and proven histologically by frozen section diagnosis before any parathyroid gland was excised. One patient had only three glands and all the rest had four parathyroid glands identified. A fifth gland was not found in any patient, a fact that was verified by the observation that each of the 26 patients operated upon prior to transplantation, whether on dialysis or not, manifested at least temporary parathyroid insufficiency by a precipitous fall in serum calcium after STPx.

After each parathyroid gland had been identified, one was selected for partial resection. This was performed first to guarantee adequate blood supply to the remnant prior to removal of any other parathyroid tissue. The decision as to which gland should be left in place was usually based on either technical or histologic indications. If one gland seemed less hyperplastic than the others, either because it was not as grossly enlarged or had some

fat cells among the hyperplastic chiefs cells on frozen microscopic section, then this was preferentially the gland only partially resected. In no patient was all parathyroid tissue removed. The second consideration for choosing the gland to be partially removed was the adequacy of its blood supply after dissection and biopsy. Resection of between one-half and two-thirds of the selected gland was performed; the arterial blood supply was often so rich as to require a hemostatic suture of the cut surface with fine vascular silk. Once it was ascertained that the remnant of the parathyroid gland to be left in place was satisfactory, then the other parathyroid glands were totally excised. The hyperplastic glands ranged between four and 200 times normal based on interoperative measurements; the normal parathyroid gland value was considered to have a volume of between 25 and 30 cubic millimeters.

The histologic findings for the total group of patients are shown in Table 4. Chief cell hyperplasia, involving all the parathyroid glands, was found in 26 patients. The glands were not always equally enlarged, and were virtually devoid of fat on histologic study. Pleomorphism was a constant histologic feature of these glands and the pattern was often indistinguishable from that of a parathyroid adenoma The presence of involvement in all glands, the absence of the classical compressed normal gland adjacent to a large hyperplastic gland and the underlying renal disease permitted the diagnosis of secondary hyperparathyroidism to be made in these cases.

One patient (J. O'N), a 47-year-old man with long-standing polycycstic renal disease and undergoing hemodialysis, was found to have a single hyperplastic gland with the other three glands being normal in size and fat distribution. The involved gland was one of the three totally removed and the final pathologic diagnosis in this case was primary parathyroid adenoma.

One patient was found to have multiple myeloma 2½ months after parathyroid exploration (C. S.). The preoperative immunoelectrophoresis had not been diagnostic, the patient had a serum calcium of 14 mg./100 ml. and was complaining of severe bone pain. Unfortunately, the exploration revealed four normal parathyroid glands and eventually multiple myeloma was found on bone marrow biopsy. No change in symptoms nor significant fall in serum calcium occurred in this patient despite STPx.

TABLE 4. *Histologic Findings in Parathyroid Glands*

	No. of Pts.
Chief cell hyperplasia in all glands	26
Single gland adenoma (other 3 glands normal)	1
All 4 glands normal (pt. had multiple myeloma)	1

The postoperative management of these patients demonstrated many of the differences between a well functioning kidney, good hemodialysis and no dialysis at all. In all patients, no calcium or vitamin D therapy was instituted until a symptomatic requirement for this medication was demonstrated. Perioral tingling, numbness of the fingers and toes, positive Chvostek sign and positive Trousseau sign were the usual manifestations of severe hypocalcemia. All patients that had STPx without being on

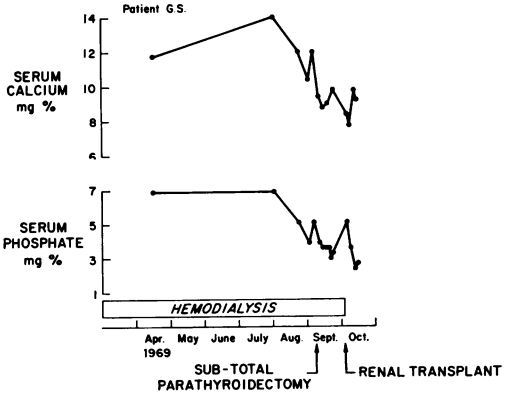

FIG. 1. Course of patient G. S. in Group I. The hypercalcemia was corrected by subtotal parathyroidectomy and serum calicum levels were returned to normal after renal transplantation. No calcium or vitamin D support was required after parathyroidectomy while the patient was on hemodialysis.

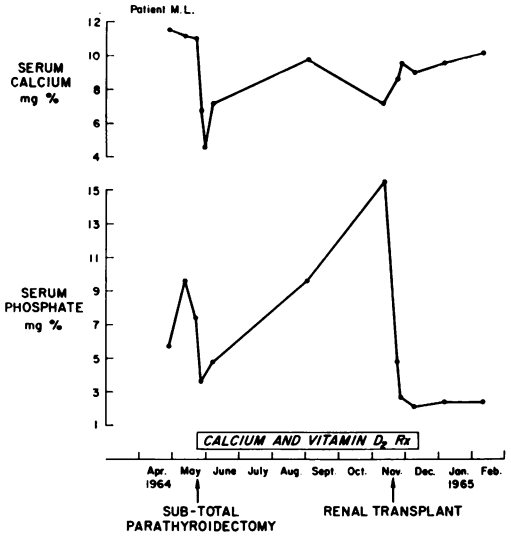

FIG. 2. Course of patient M. L. in Group I. This patient was not on hemodialysis after subtotal parathyroidectomy and large doses of calcium and vitamin D were necessary to control the profound hypocalcemia. Serum calcium levels returned to normal immediately after successful renal transplantation.

dialysis manifested these complaints within three days of operation, usually by 36 hours. With adequate calcium and vitamin D therapy, these complaints could always be controlled. Calcium gluconate was given intravenously, usually in a drip infusion of 3 to 6 Gm./500 ml. of 5% D/W as well as an intravenous bolus of 1 to 2 Gm. of calcium gluconate when it was decided that the symptoms warranted treatment. Calcium lactate was given orally at a dose of 2 to 5 Gm. per day. AT-10 was usually given as the initial vitamin D therapy, with ergosterol being administered for chronic treatment. While all patients that had STPx before initiation of dialysis required calcium and vitamin D therapy for control of tetany, only two patients in the dialysis group had a requirement for calcium support. Many of these patients were given courses of calcium and vitamin D to help heal bone lesions more rapidly. Even though total serum calcium levels might be just as low in the dialysis patient as in the non-dialysis patient, the ionized calcium provided on an alternate day schedule by the dialysis bath (usually maintained at 5 mg./100 ml. appeared to be enough to prevent symptomatic tetany. Figures 1 and 2 demonstrated the calcium and phosphate levels in patients operated upon under these circumstances.

Neither patient operated on after a well-functioning renal allograft had been in place showed any sign of hypocalcemia after STPx, as can be seen from Figures 3 and 4. In no patient was further parathyroid operation necessary because of recurrent hyperparathyroidism. Those patients operated upon without hemodialysis all were able to discontinue calcium support once a functioning kidney was transplanted; those patients with STPx performed while dialysis was in progress would return their serum calcium levels to normal once transplantation of a kidney was accomplished but not usually while on dialysis alone.

The clinical results from this procedure have been gratifying. No deaths occurred as a result of the operation. Four patients on chronic dialysis have since died as a result of the progression of their renal disease and its complications; these were; respectively, (1) cardiac arrhythmias, (2) ruptured diverticulitis, (3) cerebral vascu-

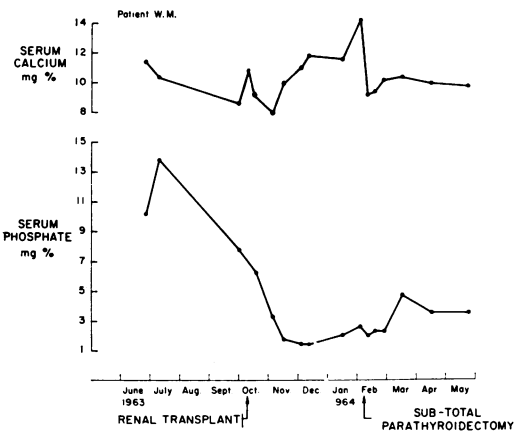

FIG. 3. Course of patient W. M. in Group IV. Hypercalcemia was present prior to renal transplantation and the serum calcium levels continued to rise despite normal renal function. Subtotal parathyroidectomy produced normocalcemia without any subsequent requirement for calcium therapy.

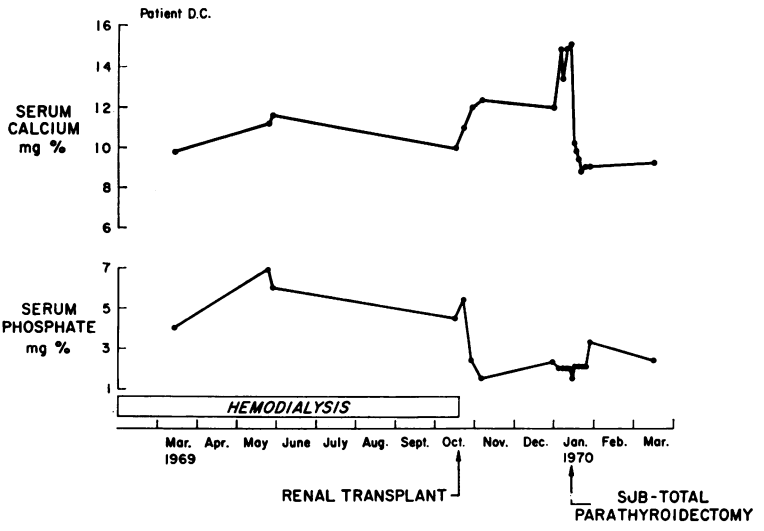

FIG. 4. Course of patient D. C. in Group IV. The serum calcium levels progressively rose after successful renal transplantation, despite intravenous and oral phosphate therapy. STPx provided immediate reversal of the hypercalcemia without additional therapy.

lar accident, and (4) hepatic failure secondary to viral hepatitis. The fifth patient died from progressive renal failure without even receiving dialysis. Three patients died from septic complications of their subsequent transplantation. All patients but the one with multiple myeloma had virtually complete relief of their hyperparathyroid complaints.

The usual time required for the initial appearance of recalcification of cystic bone disease was about 6 weeks. Metastatic calcification disappeared most rapidly of all the x-ray changes and was often completely absent after 2 months. Vascular calcification was the slowest to be reversed, if at all. Control of itching and relief of gastrointestinal symptoms were the most dramatic. Within 24 hours of parathyroidectomy, relief usually occurred from these complaints. Bone and joint pain and painful soft tissue calcium deposits have usually been relieved within the first 7 to 10 days after STPx. Two patients had grand mal type seizures, which had apparently been on a metabolic basis, since STPx completely relieved them of further episodes. One patient with severe angina and coronary artery calcification showed improvement in the angina symptoms after 6 months with concomitant reduction of calcification in the vessels by x-ray. Most patients noted improvement in the weakness that they had particularly seemed to notice and the sense of well-being was evident in most patients after STPx but was impossible to quantify.

Several of these patients were studied with careful calcium, phosphate and magnesium balance determinations before and after STPx. Some patients were also studied again after renal allografting. These data are being reported in greater detail elsewhere [9, 10] but may be summarized as follows:

1. Mean calcium balance did not change after STPx. Calcium balance improved in five patients but became more negative in four.

2. Mean phosphate balance after STPx did not differ from that found preoperatively. Six patients had improved balance and three showed worsening.

3. Mean magnesium balance also did not change. Seven patients had improved magnesium balance after STPx, two had more negative balance data. (Pletka *et al.* Personal Communication)

4. Two of three patients with pretransplant STPx had improved calcium balance after renal transplantation.

5. There appears to be an internal redistribution of calcium in response to STPx without any significant outward alteration of mineral balance involving not only cal-

TABLE 5. *Patients in Group I. Persistent, Symptomatic Hypercalcemia in Prospective Transplant Recipients*

	Patient	Sex	Age	On Dialysis	Highest Serum Calcium (mg./100 ml.)	Positive X-ray Changes	G.I. Symptoms	Severe Itching	Calcium Therapy Needed	Pathology
T*	N. L.	F	38	yes	10.8	+	+ (ulcer)	−	−	hyperplasia
	J. O'N.	M	47	yes	11.2	+	+ (ulcer)	+	−	adenoma
T	J. P.	F	24	yes	11.6	+	+	+	−	hyperplasia
T	M. L.	F	14	no	11.6	+	+	−	+	hyperplasia
T	D. F.	F	37	no	12.4	+	+ (ulcer)	+	+	hyperplasia
T	G. S.	M	47	yes	14.0	+	−	+	−	hyperplasia
T	E. T.	F	28	yes	11.8	+	−	+	−	hyperplasia
T	D. M.	M	30	yes	12.2	+	−	+	−	hyperplasia
T	B. S.	F	53	yes	12.4	−	−	+	−	hyperplasia
T	G. W.	M	24	yes	12.8	−	−	+ (seizures)	−	hyperplasia

* Subsequently received renal transplant.

cium but phosphorus and magnesium as well.

PTH assays were performed in eight of these patients. All patients with renal osteodystrophy who underwent STPx had elevated levels of PTH preoperatively. It was not possible to correlate the level of PTH with the degree of hypercalcemia or bone involvement. Patients initially placed on hemodialysis showed a fall in PTH levels but eventually a rise in PTH occurred in these dialysis patients which persisted until transplantation of a functioning kidney. Within one month of transplantation, PTH levels fell dramatically in 10 of the 11 patients studied,[9] and they were virtually undetectable after 3 months following transplantation. While on dialysis, PTH levels could be made to fall with high calcium baths for the dialysis or with calcium infusions, demonstrating some degree of responsiveness at all times even if it was inefficient.

Indications for Subtotal Parathyroidectomy

There have been four major indications for STPx in these 28 patients. Each patient has been placed in a group, numbered I–IV, according to their specific indications for operation and these are then listed in Tables 5 through 8. Whether or not they have subsequently received a renal transplant is indicated by a "T" in the lefthand column.

Group I (Table 5). The indication in this group was persistent and symptomatic hypercalcemia in prospective renal transplant patients. Ten of the patients fell into this category and nine subsequently received renal transplants. All but two were on dialysis and the one patient with a primary adenoma was in this group.

Group II (Table 6). When pathologic fractures secondary to osteodystrophy occurred in uremic patients, whether or not they were immediate transplant candidates, this was considered an indication for STPx. None of these four patients had hypercalcemia, although the normal levels of calcium that they demonstrated were distinctly abnormal for patients with chronic renal failure. All four demonstrated excellent healing and symptomatic relief of bone pain after STPx.

Group III (Table 7). Symptomatic hyperparathyroidism, including bone pain, ectopic calcification and intractable itching were considered indications for STPx in patients on, or soon to be on, chronic hemodialysis. These patients had failed to respond to phosphate depletion and they generally had normal or high normal serum calcium levels with an occasional patient

TABLE 6. *Patients in Group II. Pathologic Fractures Secondary to Renal Osteodystrophy*

	Patient	Sex	Age	On dialysis	Highest serum calcium (mg./100 ml.)	Severe itching	Calcium Therapy needed	Pathology
	M. F.	M	20	no	9.0	−	yes	hyperplasia
T*	N. U.	F	18	no	10.6	+	yes	hyperplasia
	W. M.	M	54	yes	9.6	−	no	hyperplasia
	R. S.	M	48	yes	10.6	+	no	hyperplasia

* Subsequently received renal transplant.

having hypercalcemia. Intractable, unmanageable itching was an important component of the majority of this group. There were 12 patients in the group, including the man who was later found to have multiple myeloma, the only non-responder. Seven of the 12 patients had hypercalcemia and most had bone changes and itching. All but four were already on dialysis at the time of STPx.

Group IV (Table 8). Progressive and symptomatic hypercalcemia in patients with well functioning renal transplants has been a rare but important indication for STPx in our series. These are patients who did not respond to the most thorough medical management, including oral phosphates. These were the only two patients in our series and, as shown in Figures 3 and 4, both were hypercalcemic prior to renal transplantation and the serum calcium levels rose continually after transplantation. Operation was performed 3 to 4 months after transplantation. In both instances, serum calcium returned to normal levels promptly, but there was no hypocalcemia or tetany apparent.

Discussion

The pathophysiology governing the development of renal osteodystrophy provides clues to the management of this problem at various stages of the syndrome. There is depression of calcium absorption from the gastrointestinal tract early in the course of patients with chronic renal disease [13, 20]

TABLE 7. *Patients in Group III. Symptomatic Hyperparathyroidism (Bone Pain, Ectopic Calcification, Intractable Itching) in Chronic Renal Failure*

	Patient	Sex	Age	On Dialysis	Highest Serum Calcium (mg./100 ml.)	Positive X-ray Changes	Bone Pain	Severe Itching	Calcium Therapy Needed	Pathology
	J. M.	M	49	yes	11.0	+	+	+	−	hyperplasia
	S. F.	M	46	yes	10.8	+	+	+	+	hyperplasia
	C. S.	M	52	yes	14.0	−	+	+	−	normal
	E. M.	F	22	yes	12.0	−	−	+	−	hyperplasia
T*	P. B.	F	22	no	10.6	+	+	−	+	hyperplasia
	W. C.	M	21	no	12.2	+	+	+	+	hyperplasia
	M. K.	F	33	no	11.3	+	+	−	+	hyperplasia
	G. S.	F	54	yes	9.1	+	+	+ (Seizures)	−	hyperplasia
	W. H.	M	64	yes	10.0	+	+	+	−	hyperplasia
	J. G.	M	40	yes	14.6	+	+	+	−	hyperplasia
	J. D.	M	44	yes	10.2	+	+	+	+	hyperplasia
	A. E.	F	26	no	10.0	+	+	−	+	hyperplasia

* Subsequently received renal transplant.

TABLE 8. *Patients in Group IV. Progressive, Symptomatic Hypercalcemia in Recipients of Functioning Renal Transplants, Unresponsive to Medical Management*

Patient	Sex	Age	Months Post-Transplant	Highest Serum Calcium (mg./100 ml.)	Pre-transplant Serum Calcium (mg./100 ml.)	Positive X-ray Changes	G.I. Symptoms	Severe Itching	Calcium Therapy Needed	Pathology
W. M.	M	32	4	14.2	11.6	+	+	−	−	hyperplasia
D. C.	M	20	3	15.0	11.6	+	+	−	−	hyperplasia

and this appears to be the primary driving force behind subsequent events leading to secondary hyperparathyroidism. There is evidence that abnormal metabolism of vitamin D_3 exists in patients with uremia, with decreased plasma concentration of a vitamin D_3 metabolite, 25-hydroxycholecalciferol.[2] Blunt and co-workers [5] identified this very potent effector of intestinal transport of calcium and it has been suggested that the metabolite of vitamin D was responsible for the induction of a calcium binding protein in intestinal mucosal cells.[22] Avioli and colleagues [3] have further demonstrated that calcium binding protein levels in duodenal mucosa cells of uremic rats were decreased. Although viatmin D therapy could not raise the calcium binding protein levels in the uremic rat mucosa, 25-hydroxycholecalciferol not only reversed the abnormality in calcium binding protein levels but also returned ^{45}Ca binding to normal levels. Therapy with 25-hydroxycholecalciferol doubled the calcium transport across the duodenum in uremic rats whereas vitamin D_3 would not return the transport activity to normal. Although the 25-hydroxycholecalciferol did increase the calcium transport across the duodenum it was still only half the response obtainable in normal rats with similar therapy.

The progression from abnormal calcium absorption to eventual parathyroid stimulation has been well outlined by Stanbury and Lumb [20] and reviewed in our earlier publication on this subject in 1965.[23] In Figure 5 a diagram of the progression of this lesion is presented, based on present concepts. The early stages of this disorder in calcium homeostasis result in hypocalcemia, osteomalacia and mild parathyroid gland hyperplasia. Judicious use of vitamin D, phosphate depletion and calcium therapy might slow the progress of the osteodystrophy. It remains clear from our patient population and those of other authors [1, 14] that only a small number of patients in chronic uremia convert their bone disease and clinical status to hyperparathyroidism. Those patients that do, however, have a full-blown picture of parathyroid hyperfunction. They have exceedingly high levels of PTH, much higher than patients with single adenomas.[4] In addition to the usual cystic bone lesions, metastatic calcification is common in many sites. Hypercalcemia and gastrointestinal symptoms occur, although parathyroid intoxication with levels of serum calcium greater than 17 mg./100 ml. has not been described with renal osteodystrophy. The mechanism of this conversion to secondary hyperparathyroidism with bone lesions of osteitis fibrosa cystica is poorly understood, but is certainly related to the degree of hyperplasia of the parathyroid glands. The massive chief cell hyperplasia involving all the four glands, so often seen at parathyroid exploration in these patients, easily explains the clinical picture. The speed with which parathyroid glands can hypertrophy and produce hypercalcemia and elevated PTH levels is demonstrated by reports of this occurring during the diuretic phase of acute renal

failure.[15] In the seven patients described by these authors, the mean time for hypercalcemia to occur was the 11th day after the onset of diuresis. All of the evidence from our studies indicates that these glands are not totally autonomous to feed-back control produced in normal parathyroid glands by elevating the serum calcium level. Johnson *et al.*[9] have demonstrated that increasing the calcium concentration in the dialysis bath could reduce the PTH level acutely, but not to normal. The problems appear to be that the parathyroid mass is so great that even if PTH output per cell is reduced the total output is overwhelming. On a chronic basis, Goldsmith and colleagues[11] have reported that the dialysis concentration of ionized calcium must be maintained at 8 mg./100 ml. to prevent PTH elevation. This would explain why patients on most dialysis programs show progressive increase in renal osteodystrophy with time, since the standard calcium levels range between 5 and 6 mg./100 ml. in the dialysis baths. Raising the magnesium level in the dialysate from 3 mg./100 ml. to 5 mg./100 ml. had a similar effect in reducing PTH levels in patients on chronic dialysis (Pletka *et al.*, personal communication). The longer these patients live in this abnormal pattern of body support with hemodialysis but inadequate calcium homeostasis, the greater is the absence for secondary hyperparathyroidism to occur. We prefer the term secondary hyperparathyroidism to "tertiary," since diffuse chief cell hyperplasia has been our constant finding except the one patient with an adenoma. The other three glands in this man were normal sized with normal fat distribution and there was no indication of a hyperplastic parathyroid gland progressing to an adenoma, which is the definition of "tertiary" hyperparathyroidism.

This review of mechanisms involved in the development of secondary hyperparathyroidism in renal osteodystrophy indicates that many uremic patients can be effectively managed without STPx. Early

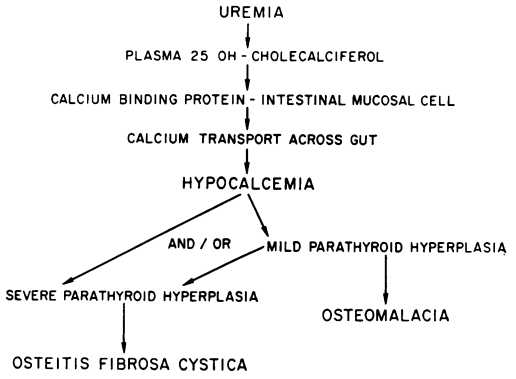

FIG. 5. The role of uremia in initiating hypocalcemia and renal osteodystrophy is shown in this diagram. The synthesis of calcium binding protein is reduced, resulting in inadequate absorption of calcium. Whether or not all patients developing severe parathyroid hyperplasia, osteitis fibrosa cystica and secondary hyperparathyroidism pass through a preliminary phase of mild parathyroid hyperplasia is not certain.

attention to phosphate deprivation and calcium and vitamin D support, as well as new considerations of calcium and magnesium levels in the dialysate, all will reduce the degree of parathyroid hyperplasia. Kaye *et al.*[14] have recently shown that in humans dihydrotachysterol was effective in improving active bone disease in patients on a chronic dialysis program, whereas vitamin D_2 and D_3 were not. This agent was not converted to 25-hydroxycholecalciferol, mentioned earlier, which is a metabolic product of vitamin D_3. Only further studies will identify completely the interrelationships of the D vitamins.

Once the full-blown picture of renal osteodystrophy with hypercalcemia develops, these measures can no longer alter the progressive pattern of the disease. In fact, giving calcium and vitamin D under those circumstances increases the amount of metastatic calcification and bone symptoms. Two alternatives are then open for this type of patient. The first is renal transplantation and the second is STPx. Renal transplantation can immediately improve the action of vitamin D or gut absorption of calcium and reverse the cycle of parathyroid stimulation. If the patient has not had florid hyperparathyroidism or patho-

logic fractures, we have refrained from performing STPx in patients who are soon to have a renal transplant.[8] As has been stressed by Alfrey,[1] avoidance of phosphate depletion in this postoperative period will lessen the chances for parathyroid stimulation and hypercalcemia, while the relatively mild degree of parathyroid hyperplasia gradually subsides. As demonstrated by the PTH investigations in our patients[9, 12] between 1 and 3 months after successfully functioning renal transplants, PTH levels were lowered in all instances studied. The only patients in our series that have required STPx after transplant had clear-cut hypercalcemia and bone changes by x-ray prior to transplantation. In retrospect, they should have had STPx before renal transplant because we believe it is better tolerated at that time and can be performed more electively. Patient W. M. had calcium deposition in the transplanted kidney 5 days after allografting, which subsequently reversed on later biopsy following STPx. Schwartz *et al.*[19] reported post-transplant STPx in five patients out of a group of 34 patients transplanted. All five had show hypercalcemia pretransplant while two other patients with transient hypercalcemia post-transplant had been normocalcemic before allografting. These two did not require STPx. Three of the five patients had STPx performed acutely after renal transplantation on the third, fourth and twentieth days, respectively; the other two were performed later. Renal function had rapidly deteriorated in those patients associated with early hypercalcemia. Alfrey[1] chose 17 patients from among 175 transplant recipients and studied their calcium metabolism after transplantation. Only one patient in the entire series needed STPx, and that was performed as late as 9 months postoperatively. None of the 17 selected patients had pretransplant hypercalcemia, only five had bone disease by x-ray and only six patients received more than acute hemodialysis prior to renaltransplantation. This appears to be a population of patients less severely involved than the ones for whom we have performed pretransplant STPx, and their excellent response to medical management stresses the importance of careful attention to those details in the post-transplant patient.

There is general agreement in support of STPx for patients falling into our groups I, II and IV (6, 17, 18, 21). Group III patients require more critical individualization and provoke greater controversy. The requirement for persistent hypercalcemia found in all Group I patients is not constant in Group III. Attempts at medical management and more efficient dialysis, as mentioned earlier, will be important in reducing this group to a minimum. One of the most important considerations for placing patients in this group is the specific plan for improvement of their uremic state. If a patient with this degree of hyperparathyroidism is to receive a renal transplant in the near future, then STPx would definitely be withheld. Those patients for whom a long course of chronic hemodialysis is contemplated, including some patients who are not transplant recipients at all, make up the bulk of group III. As more patients are returned to chronic hemodialysis after loss of one or more transplants and more become presensitized from blood transfusions and other cross-reacting antigens, this group will by necessity be expended because chronic dialysis tends to enhance the chances for parathyroid hyperplasia. Other complications of secondary hyperparathyroidism beside bone disease have been demonstrated to respond dramatically to STPx. These include severe and uncontrolled itching,[7, 16] metabolic encephalopathy and even angina secondary to coronary vascular calcification. As the complexities of calcium, phosphorus and magnesium metabolism become unravelled, other treatable aspects of these disturbances in mineral homeostasis so greatly exaggerated in patients with chronic renal failure will become apparent. Our present

policy is to make every attempt to control symptoms and biochemical abnormalities in our chronic uremic patients with conservative management. When this approach is no longer effective, STPx is performed with the certainty that it is a safe, easily tolerated and highly effective surgical procedure.

Summary

A series of 28 patients undergoing subtotal parathyroidectomy for renal osteodystrophy has been presented. The patients underwent operation after receiving renal allografts, 18 patients were on chronic hemodialysis and eight patients had subtotal parathyroidectomies before starting dialysis. Chief cell hyperplasia was the pathologic finding in the parathyroid glands of all but two patients, the exceptions being one patient who had a parathyroid adenoma and another who had normal parathyroid glands wth hypercalcemia, and was later found to to have multiple myeloma.

All 28 patients but the one with multiple myeloma responded very well to subtotal parathyroidectomy. Gastrointestinal symptoms and itching were usually relieved within 24 hours. Bone and joint pains frequently subsided within 7 to 10 days as patients became stronger and more active. Metastatic soft tissue calcifications disappeared earlier on radiologic examination, and some recalcification of cystic bone disease was usually apparent by 6 to 8 weeks. Vascular calcification was the slowest to regress.

The indications for subtotal parathyroidectomy in this series were: 1) persistent and symptomatic hypercalcemia in prospective renal transplant patents, 2) pathologic fractures secondary to renal osteodystrophy in uremic patients, 3) symptomatic hyperparathyroidism including bone pain, ectopic calcification and intractable itching in patients on chronic dialysis, and 4) progressive and symptomatic hypercalcemia in patients with well-functioning renal transplants. The patients in the third group represent the area of greatest controversy and are most likely to be helped by aggressive medical management and improved dialysis technics.

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Discussion

Dr. David M. Hume (Richmond): I agree completely with almost everything that Dr. Wilson has said. We have a smaller number of cases, because we do not have a chronic dialysis program *per se*. All of our patients on long-term dialysis are candidates for transplantation.

We have done two patients who had great bone difficulty after rejecting a third transplant. These are all patients who developed antibodies against the kidneys. They are not retransplantable. One of the patients had a convulsion and fractured her pelvis into about eight pieces, and we then did parathyroidectomy on both these patients, and they have both done well since this time.

We have done two patients prior to transplantation who were having a great deal of difficulty with bone pain, and for whom it seemed rather long-term dialysis was going to be necessary, because they were candidates for cadaver transplants.

We have done only one patient after transplantation, which is very similar to Dr. Wilson's experience. As you recall, he has done only two, and this indicates once again the very beneficial effect of transplantation on the hypercalcemia and hyperparathyroidism of renal failure.

We have done only two patients who were not candidates for transplantation, and this again reflects our limited number of chronic dialysis patients.

The only matters of dispute I have with Dr. Wilson are, first of all—I had an opportunity to read his paper, and is was suggested by him that one can make a diagnosis of secondary hyperparathyroidism on the basis of hyperplasia, and I would like to remind him that some primary hyperparathyroidism can be present with hyperplasia.

Secondly, tertiary hyperparathyroidism does occur, and may be due to hyperplasia, as it was in both of his cases and one of our own cases.

I think a point of caution is that one should not perform parathyroidectomy after transplantation too rapidly, because in most instances the transplant will correct the abnormalities within 6 weeks. If the abnormalities are not corrected within this period of time, then parathyroidectomy should be done. In the series reported by Schwartz, parathyroidectomy was done in five of 34 patients after transplantation, and I would have suggested that it probably was not necessary in any of these cases. If they had waited a little bit longer, the kidney would have corrected it.

Finally, in our patients we have had to give large amounts of calcium and vitamin K after parathyroidectomy, because the patients have such severely hungry bone syndromes that they develop tetany, apparently, at a greater rate than Dr. Wilson's.

Dr. John W. Raker (Boston): I shall describe a recent experience which was unique at our hospital, which I think is pertinent to this discussion. This has already been published as CPC case 19–1970 from the Massachusetts General in the *New England Journal of Medicine*, and therefore I shall try to summarize it here.

This woman was 29 years old when we first saw her at our hospital in 1951. At that time she had classical hyperparathyroidism, with the classical chemical findings. She also had a rather advanced deposition of renal stones and a well-established urinary tract infection.

She was operated upon at that time, and a parathyroid adenoma was removed. The serum calicum and phosphorous levels promptly fell to normal. In the 18-year interval before the second admission the patient was examined repeatedly.