Indications for Subtotal Parathyroidectomy in Patients with Renal Transplantation

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RENAL allotransplantation has allowed identification of a relatively small group of patients whose parathyroid overactivity is sufficiency severe to require surgical treatment either before or after correction of the uremia. Extirpation of parathyroid tissue in such cases might be considered when one the three following situations occurs: 1) severe hypercalcemia prior to transplantation, 2) persistent hypercalcemia after successful transplantation, or 3) bone disease resulting from secondary hyperparathyroidism severe enough to determine the course of the patients illness, even though hypercalcemia is not present.

Wilson *et al.*[1] reported one patient in the first category in whom subtotal parathyroidectomy was performed 6 months prior to renal transplantation. These authors describe in the same report another patient who responded successfully to subtotal parathyroidectomy performed for hypercalcemia persisting 4 months after allografting, and McIntosh[2] and McPhaul[4] add three similar cases which can be classified also in the second category.

The patient described in this report is an example of the third indication for parathyroidectomy, disabling bone disease. Although renal failure was then diagnosed, hypercalcemia was never demonstrated even during phosphate deprivation. He underwent subtotal parathyroidectomy, responded with marked bone healing and then received a kidney transplant. A summary of this case follows:

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Case Report

K. B., a boy 14 years of age was well until 1963, when he was admitted to the Primary Children's Hospital, Salt Lake City, Utah, with stiffness in both legs of recent onset. He was found to have poorly calcified bone and bilateral femoral epiphyseal displacements. Laboratory tests showed proteinuria, azotemia (blood urea nitrogen 90 mg./100 ml.) and anemia. Cystoscopy and retrograde pyleography showed no urinary tract obstruction. The kidneys were contracted and the caliceal pattern irregular, suggesting chronic pyelonephritis, but the urine cultures were sterile. The prognosis seemed poor because of renal disease, and no operative correction of the epiphyseal displacements was undertaken. Ambulation was forbidden, except with crutches, and he received active and passive exercises of the hip joints.

Renal function remained poor in the ensuing months, and he was referred to the University of Utah Hospital in August, 1965, for consideration of renal allotransplantation. Laboratory data at that time were (in mg./100 ml.): BUN 78, serum creatinine 6.2, serum calcium 9.8, and serum phosphorus 6.3. The urinary protein excretion was 1.3 Gm. in 24 hours. Roentgenograms showed further displacement of both femoral epiphyses. In addition, displacement of the humoral epiphyses was evident. Marked demineralization, irregular coarsening of bone tabeculation, and widening of all epiphyseal lines were evident. To determine whether the predominant bone disease was osteitis fibrosa or osteomalacia[3] a biopsy of bone was taken from the right iliac crest (Fig. 1). This specimen showed typical changes of osteitis fibrosa cystica. Renal function seemed sufficiently stable to warrant continued medical treatment short of renal transplantation, and he returned home.

In April, 1966, progressive demineralization of bone (Fig. 2) and anemia were noted, although BUN of 94 mg./100 ml. and serum creatinine of 7.5 mg./100 ml. had not changed appreciably. The serum level of phosphorus was 9.4 and calcium 9.5 mg./100 ml. Phosphorus deprivation for

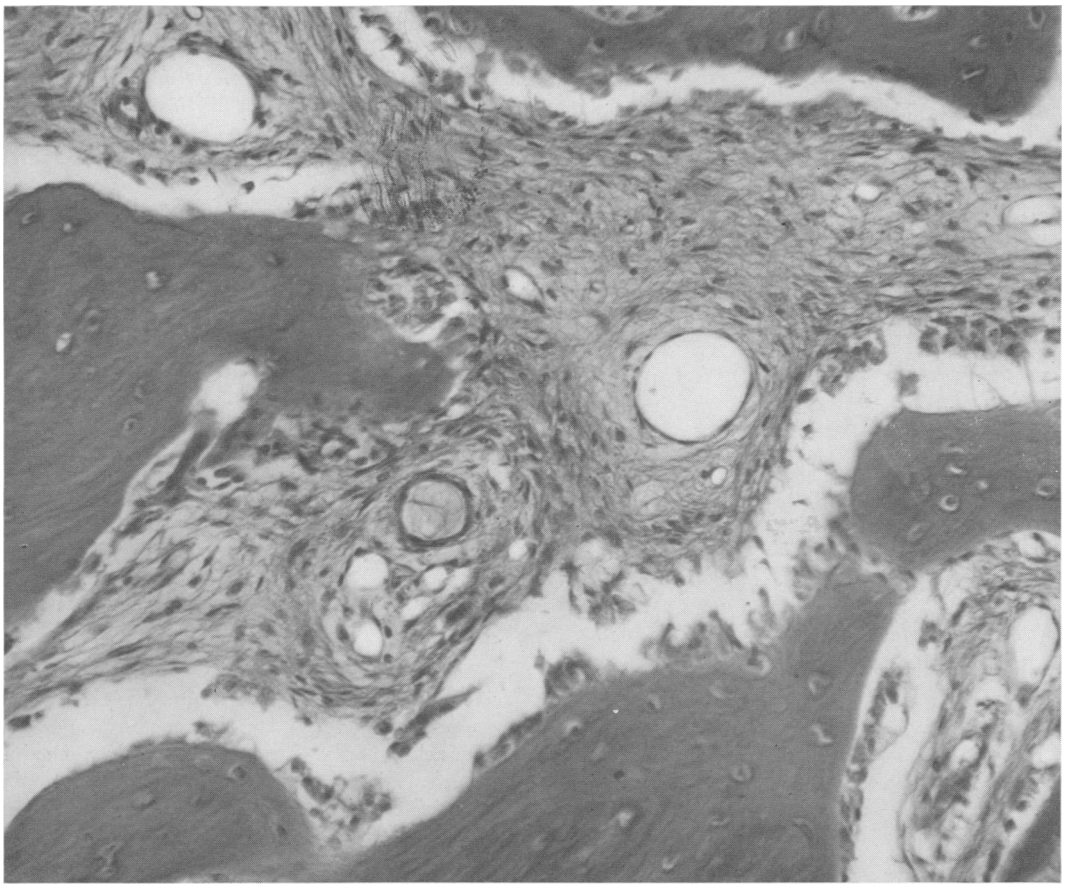

FIG. 1. Photomicrograph (H&E) of bone tissue removed from the right iliac crest. Large cystic areas, delicate fibrous trabeculae and numerous large osteoclasts are noted substantiating the diagnosis of osteitis fibrosa cystica.

2 weeks did not induce hypercalcemia. The patient was confined to a wheel chair at this time.

Excision of three and two-thirds of the four parathyroid glands was performed April 18, 1966, in the hope of improving bone lesions prior to renal transplantation. The excised glands were large, homogenous, light tan in color, and were located in typical anatomical positions. Measurements of the three excised glands were (in mm.): $5 \times 5 \times 2$, $10 \times 11 \times 15$, and $12 \times 12 \times 7$. A portion of the fourth gland measuring $4 \times 4 \times 3$ mm. was left intact with a vascular pedicle, and this tissue was estimated to be one-twelfth of the parathyroid tissue present preoperatively. Chief cell hyperplasia was demonstrated histologically in the parathyroid tissues removed (Fig. 3).

Symptomatic hypocalcemia appeared 6 hours postoperatively with the serum calcium reaching a low value of 5.4 mg./100 ml. on the third day and required treatment with calciferol 300,000 units and calcium lactate 12 Gm./day to control tetany. His clinical course during this period is outlined in Figure 4. Postoperative course was marked by a grand-mal seizure on the fourth day and a subcutaneous wound infection culturing *Staphylococcus aureus* which healed slowly. Serum calcium values gradually returned to normal over a 3-month period and the medications were discontinued. Alkaline phosphatase values remained slightly above normal values. Recalcification of bone and beginning epiphyseal closure were evident 6 months later (Fig. 5).

The patient suffered rapid deterioration in renal function, and an episode of acute pulmonary edema necessitated peritoneal dialysis in December, 1966. Repeated dialyses were required to prevent hyperkalemia and mental obtundation.

A kidney from an adult cadaver of compatible major blood type was transplanted into the retroperitoneal area of the right iliac fossa of the patient on December 12, 1966. After a period of oliguria lasting eight days, diuresis ensued and

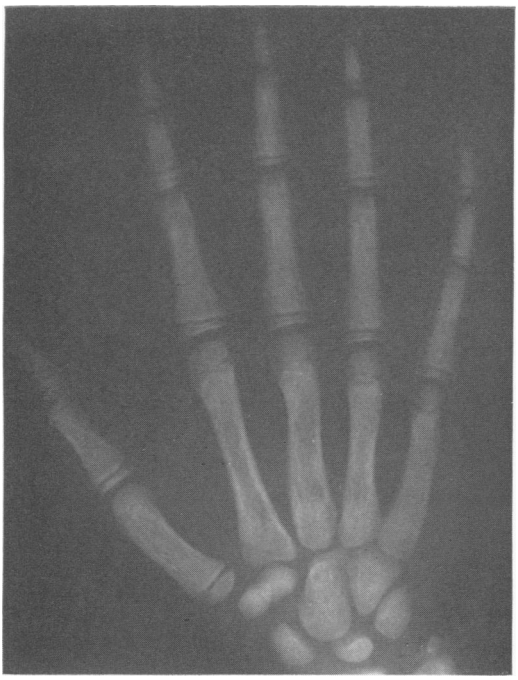

FIG. 2a. Roentgenogram of patient's hand *before* parathyroidectomy.

renal function of the graft has been excellent since (Fig. 4). Azathioprine and methylprednisolone were given following transplantation, and an episode of rejection occurring 4 weeks after the transplant procedure was reversed by increasing the steroid dosage from 60 to 120 mg./day. A wound infection (*Staphylococcus aureus*) healed slowly, finally closing after three and one-half months. Tachypnea and tachycardia occurred throughout the first month postoperatively, but pneumonitis was never demonstrated. The question arose whether high-output cardiac failure could explain these findings. An arteriovenous fistula at the wrist, which had been created earlier to facilitate hemodialysis, was closed and packed red blood cells were administered to increase the volume of packed red blood cells to 32 per cent. Pulse and respiratory rates slowly improved to normal over the next 4 weeks. Two episodes of urinary tract infection (*Aerobacter aerogenes*) responded successfully to intravenous sodium cephalothin.

Fifteen months following renal transplantation the patient's serum creatinine is 1.1, BUN 17, calcium 9.0 and phosphorus 6.6 mg./100 ml. The alkaline phosphatase is 23 King-Armstrong units (normal range 2–14 units). All epiphyseal defects have closed and recalcification of osteitic bone appears complete by roentgenograms. Femoral head dislocations with excessively shallow acetabular surfaces have resulted from the osteodystrophy and subtrochanteric femoral osteotomies are planned at a later date to facilitate ambulation.

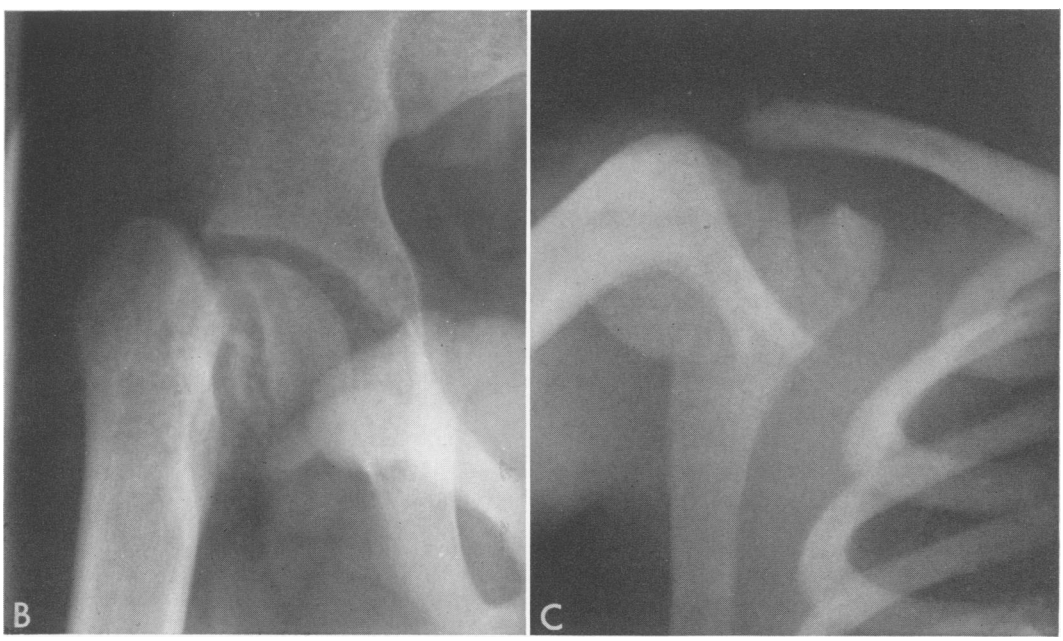

FIG. 2b. Right hip before. FIG. 2c. Right shoulder before. The demineralization, epiphyseal slipping and cystic changes of secondary hyperparathyroidism are evident.

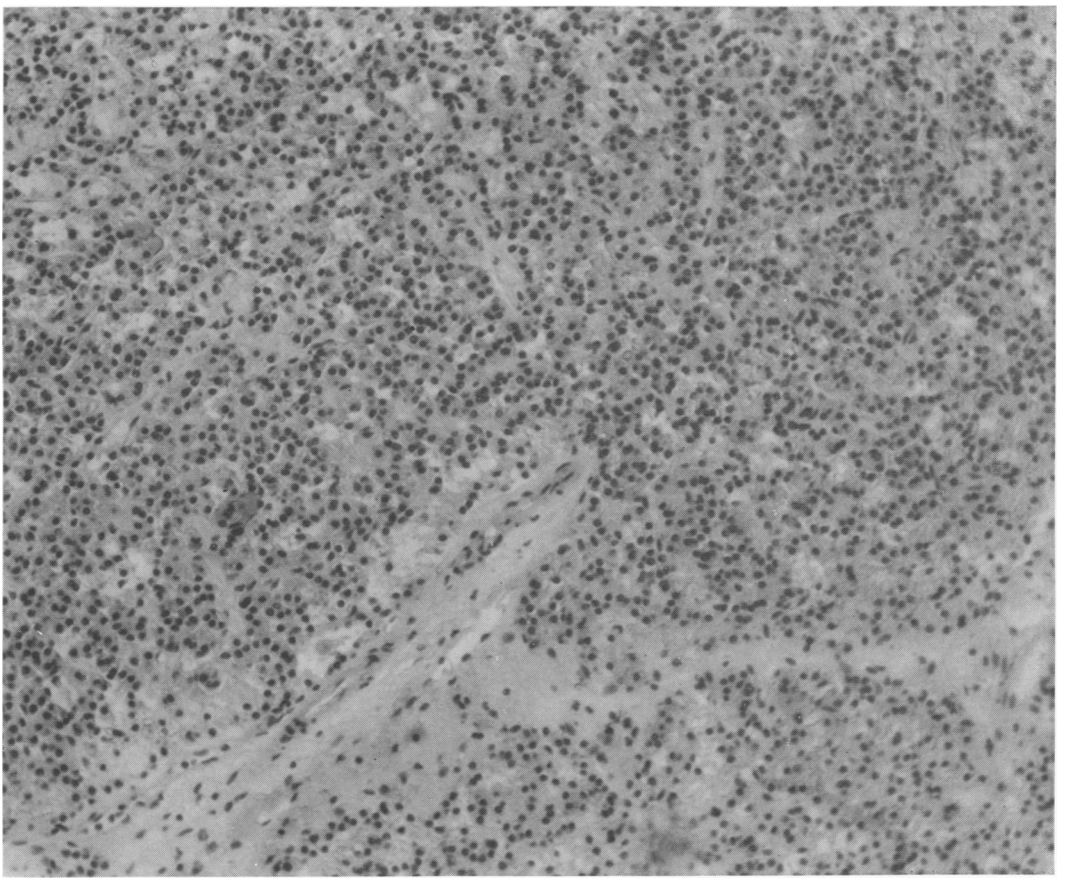

FIG. 3. Photomicrograph (H&E) of excised parathyroid tissue, demonstrating chief cell proliferation throughout the gland.

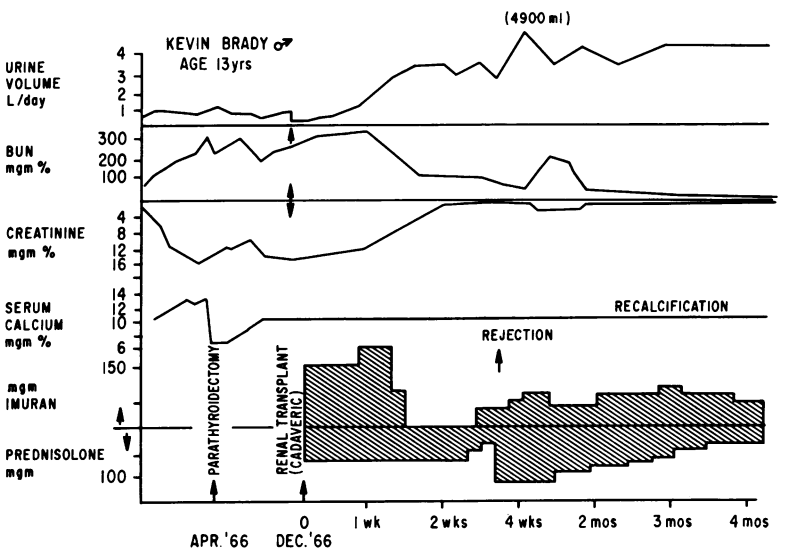

FIG. 4. Charting of the clinical course of the patient.

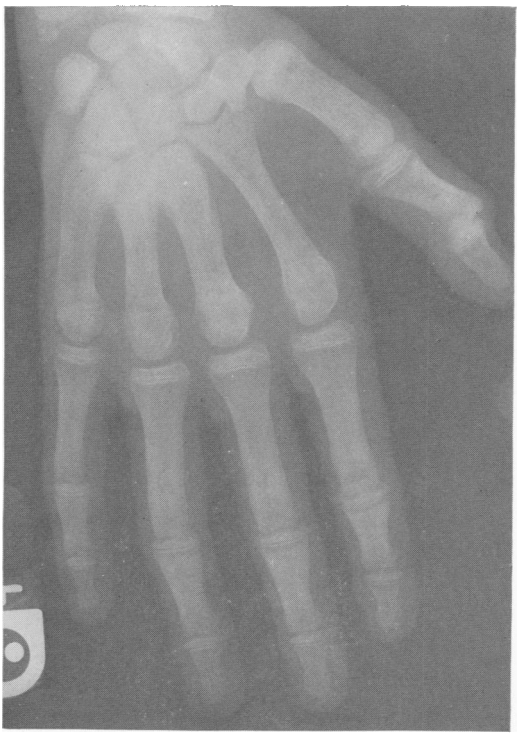

FIG. 5a. Roentgenogram of patient's hand *after* parathyroidectomy.

The patient currently takes azathioprine 25 mg. /day and prednisone 5.0 mg./day.

Discussion

Hyperparathyroidism secondary to chronic renal failure has been recognized for four decades, and is characterized by hypertrophy and chief cell hyperplasia in the parathyroid glands, decalcification of bone and soft tissue calcification. This secondary hyperparathyroidism has been regarded as a compensatory response to hypocalcemia resulting from defective absorption of calcium from the gut in chronic renal failure. In most instances, the serum calcium remains low or normal through the course of the disease and continues to be normal after correction of the uremia by transplantation. In some instances, however, the serum calcium is elevated persistently, suggesting that prolonged stimulation of the parathyroids has resulted in hyperplasia of the gland and over-production of parathormone which persists autonomously after the hypocalcemic stimulus is no longer present. This situation has been termed

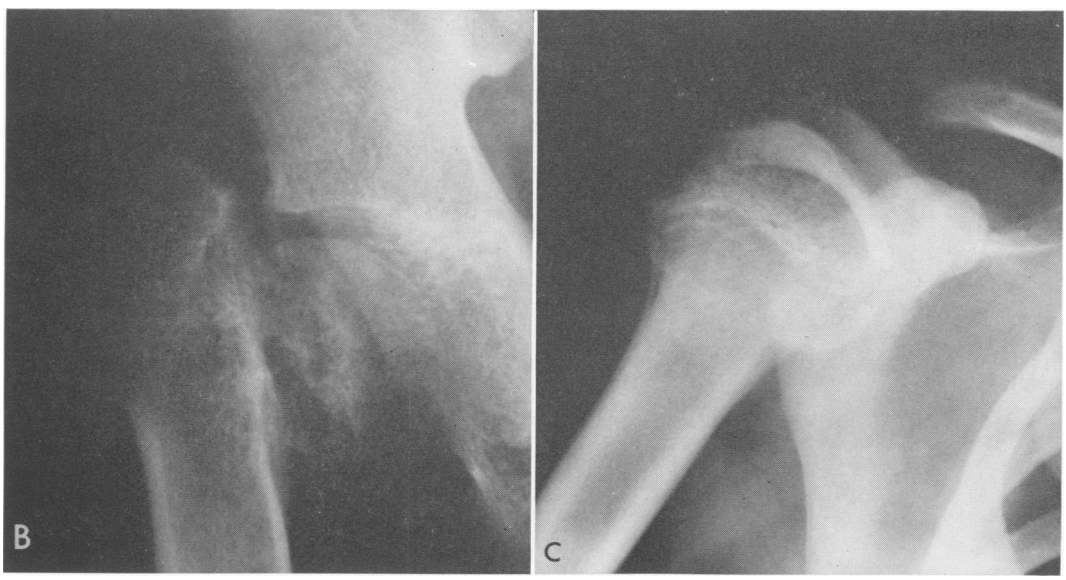

FIG. 5b. Right hip after. FIG. 5c. Right shoulder after. Remineralization and epiphyseal closures are evident and have resulted from parathyroid removal prior to correction of his uremia.

"tertiary" hyperparathyroidism. In either of these conditions, the bone disease may become so severe as to overshadow manifestations of the original renal disease. For many years it has been known that surgical removal of most of the hyperplatic parathyroid tissue in such instances would reverse the bone disease, but the prognosis of the chronic renal failure had been so poor that the operative effort did not seem worthwhile. Correcting uremia through transplantation or maintenance hemodialysis has dramatically reversed renal failure and increased the life span of these patients with secondary or tertiary hyperparathyroidism, and parathyroidectomy assumes new importance for them.

Our patient had severe bone disease resulting from hyperparathyroidsm secondary to renal failure, but never developed hypercalcemia. By definition he had secondary, rather than tertiary or autonomous, hyperparathyroidism. Such patients nonetheless make up a group which can benefit by parathyroidectomy. Our patient illustrates the applicability of subtotal parathyroidectomy in patients with severe and predominant bone disease in the absence of hypercalcemia.

One may question whether the bone disease would have been reversed simply by correcting his uremia without parathyroidectomy. We felt the bone disease was so severe as to dominate his clinical course and to jeopardize chances for survival prior to and during receipt of a transplanted kidney. Reversal of bone disease prior to renal grafting seems essential in retrospect for the successful outcome enjoyed by this patient.

Tetany was not reported in the previous cases following subtotal parathyroidectomy.[1, 2, 4] The authors describe removal of three and one-half parathyroid glands, while we undertook a slightly wider resection of the remaining gland (two thirds). The marked hypocalcemia which our patient encountered within a few hours of parathyroidectomy responded only after vigorous treatment. After finally stabilizing, serum calcium values have continued normal for longer than one year without therapy. We presume that enough functioning parathyroid tissue remains to meet physiological needs, and no parathyroid overactivity has been detected.

Conclusions

A number of patients have emerged from renal allotransplantation and maintenance hemodialysis who have required subtotal parathyroidectomy for control of persistent hypercalcemia. These cases probably represent autonomous or tertiary hyperparathyroid states. Similar patients with severe bone disease but without hypercalcemia also benefit from parathyroidectomy, and such a case is presented in this report. Our current indications for subtotal parathyroidectomy in patients whose terminal chronic renal failure can be corrected are: 1) severe, persistent hypercalcemia before renal transplantation or maintenance dialysis; 2) persistent hypercalcemia after transplantation or during maintenance hemodialysis; and 3) crippling bone disease resulting from the chronic renal failure.

Acknowledgment

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