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HYPERPARATHYROIDISM AFTER KIDNEY HOMOTRANSPLANTATION

I. RELATION TO HOMOGRAFT FUNCTION

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INTRODUCTION

Secondary hyperparathyroidism is present in most patients with chronic renal failure (11, 20, 21). The effect of renal transplantation on parathyroid function has been generally studied over a relatively short period of time after surgery (1, 6). Thus the information which could be obtained was insufficient to provide evidence regarding the long-term variations in the parathyroid activity in renal homograft recipients. Acute hypercalcemia immediately after kidney transplantation has been reported in detail by several investigators (12, 11, 19). Parathyroidectomy which was the treatment of choice resulted in a prompt reduction of the high serum calcium concentrations and a relief of the attendant clinical manifestations in the reported cases (12, 11, 19). The pathogenesis of acute post-transplant hypercalcemia has not

been fully defined, yet several contributing factors could be implicated: *(1)* the presence of high levels of parathyroid hormone with restored to normal bone responsiveness to the hormone, *(2)* fall in serum concentration of phosphorus with a reciprocal rise in serum calcium, and *(3)* correction of the abnormal metabolism of Vitamin D with an enhanced conversion of the vitamin to its active metabolites.

Several workers postulated that resolution of secondary hyperparathyroidism after kidney transplantation occurs almost universally whereas hypercalcemia is unfrequent and if present it is usually associated with phosphate depletion and can be easily controlled with phosphate supplementation (1, 6, 7). These considerations were consistent with the generally accepted concepts of non-autonomy of the parathyroid hyperfunction in chronic renal failure (21) which readily undergoes regression once normal homeostasis is reestablished by the renal homograft. However, these views, unfortunately, were not substantiated by long-term observations. Serial measurements of parathyroid hormone levels in the serum of transplanted patients utilizing a radioimmunoassay yielded conflicting results and discordant conclusions (6, 17). More precise definition of the relation between the measured radioimmunoreactive substance and the circulating biologically active hormone seems important for more meaningful conclusions in the future studies. The size and the morphology of parathyroid glands in autopsy material from deceased homograft recipients has not been studied systematically yet; in fact, pathological observations led to the first recognition of secondary hyperparathyroidism in patients with chronic renal disease (14).

Several factors which may affect parathyroid activity after kidney transplantation are worth short comment. First, recent studies demonstrated that glucocorticoids by lowering serum calcium concentration cause an increase in the secretion of parathyroid hormone (23). Thus the use of glucocorticoids as immunosuppressive agents especially in high doses may suppress hypercalcemia and at the same time exert a stimulating effect on the parathyroid glands. Likewise the antagonism of glucocorticoids to the action of Vitamin D (5, 2) may lead to a fall in serum calcium with further increase in parathyroid hyperactivity. Secondly, losses of phosphate after kidney transplantation caused by enhanced phosphaturia and antacids which bind phosphorus in the gut may result in hypophosphatemia (1). Hypophosphatemia has been implicated as responsible for the appearance of hypercalcemia (1, 6, 7, 19). In fact, the ensuing hypercalcemia is not necessarily an indication of additional stimulation of the

parathyroids but rather may reflect an increased skeletal response to parathyroid hormone. Conversely, supplementation of phosphate with a subsequent drop in serum calcium to normal or subnormal levels may actually become a stimulus for parathyroid hyperactivity (8, 9). Thirdly, thiazide diuretics have been shown to induce hypercalcemia under certain conditions (15). In dogs, thiazides have been reported to cause hyperplasia of the parathyroid glands (16), but their effect on human glands remains to be determined. The frequent use of thiazides in renal homograft recipients may play a definitive yet unknown role in parathyroid function.

The present study which was undertaken to characterize the course of secondary hyperparathyroidism after kidney transplantation suggests that persistent hyperparathyroidism may be detrimental to the function of renal homograft and therefore its prompt detection and treatment are of paramount importance.

MATERIAL AND METHODS

Eighteen renal homograft recipients with surgically proved parathyroid hypertrophy in which parathyroid hyperplasia was demonstrated by microscopic examination serve as the basis for the present communications *. The clinical data of all patients are listed in table 1. All had chronic renal failure and all except for two were treated with hemodialysis before homotransplantation. Fourteen received renal homografts from related donors and 4 from cadavers. The creatinine clearances after kidney transplantation ranged from 46 to 95 with a mean value of 70 ml/min. Four patients showed roentgenographic evidence of osteitis fibrosa cystica, 7 presented with calcium deposits in soft tissues and in the remainder varying degrees of skeletal rarefaction were noticed, before parathyroidectomy. The interval between transplantation and parathyroidectomy ranged from 2 to 63 months with a mean duration of 22 months. Eight patients were subjected to total parathyroidectomy with autoimplantation, the remainder underwent subtotal parathyroidectomy. The technique of the former surgical procedure is outlined in figure 1. This technique was designed to reduce the blood supply to the residual parathyroid tissue so as to minimize the risk of recurrent hypertrophy. Serum concentrations of phosphorus, total and ionic calcium were determined in all patients. Creatinine clear-

* These patients do not represent the incidence of persistent hyperparathyroidism in our patient population but constitute a small portion of a large group of homograft recipients which are undergoing currently evaluation for parathyroidectomy.

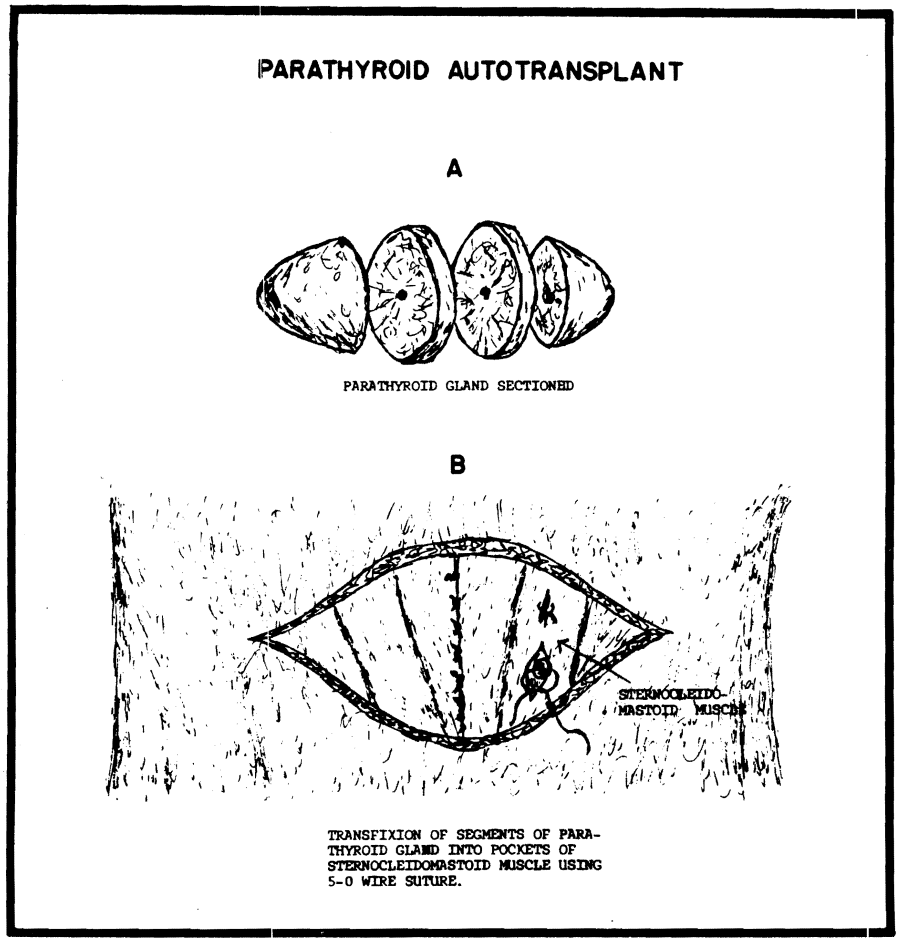

Fig. 1.—Technique of parathyroid autotransplantation. A) A single gland is removed and sliced into two 50 mg segments. B) Each of two segments is inserted into a small pocket of sternocleidomastoid muscle and transfixed with 5-0 stainless steel wire.

ances based on 24 hr urine collections were used as estimates of glomerular filtration rate. Tubular reabsorption of phosphorus was calculated on the basis on 24 hourly excretions of phosphorus in the urine. The indication for surgery was persistently elevated serum concentration of ionized calcium with or without elevated above normal total serum calcium. The normal range for total serum calcium in our laboratory as determined by atomic absorption spectrophotometry is 8.8 to 10.8 ml/100 ml whereas the normal range for ionized calcium as determined by Orion ion exchange electrode ranges from 4.0 to 4.9 mg/100 ml.

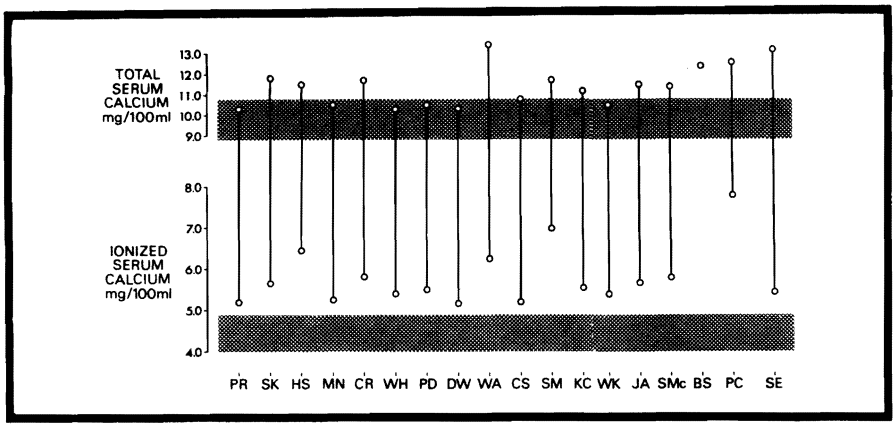

Fig. 2.—Peak serum levels of total and ionized calcium before parathyroidectomy. The hatched areas designate normal range for both total and ionized calcium.

Table I

Clinical data of all patients

Patient	Sex	Age years	Diag-nosis	Dialy-sis	Donor	C_{cr} ml/min	PTX Months	Bone osteop	Disease OFC	Extraskeletal calcifications
PC	M	41	CG	Yes	R	95	2	+	—	Vascular
SM	F	22	PN	Yes	R	70	7	—	—	—
HS	M	21	MD	Yes	C	81	14	+	—	—
CS	F	10	CG	Yes	R	55	18	+	—	Vascular
CR	F	39	CG	Yes	R	49	20	+	—	—
MN	F	43	CG	Yes	C	90	32	+	+	Soft Tissue
SK	M	27	CG	Yes	C	54	47	+	—••	Vascular Soft Tissue
WH	M	30	CG	Yes	R	90	54	+	—	—
PR	M	17	CG	Yes	R	50	63	+	—	Vascular Soft Tissue
KC	F	13	HD	Yes	C	51	53	+	—	—
SC	F	30	CG	Yes	R	53	6	+	+	—
WA	M	48	CG	Yes	R	89	6	—	+	Vascular
DW	F	32	CG	Yes	R	64	18	+•	—	—
WK	M	11	CG	No	R	46	19	+	+	Soft Tissue
BS	M	39	CG	Yes	R	74	39	+	—	—
PD	F	24	CG	Yes	R	87	44	+	—	—
SE	F	40	PK	Yes	R	75	2	+	••	Vascular
JA	F	39	LN	No	R	71	12	+•	—	—

Abbreviations:

CG: chronic glomerulonephritis.
PN: chronic pyelonephritis.
MD: medullary cystic disease.
PK: polycystic kidneys.
LN: lupus nephropathy.
R: related.
C: cadaveric.
PTX: time interval between transplantation and parathyroidectomy.
OSTEOP: osteoporosis.
OFC: osteitis fibrosa cystica.
• aseptic necrosis of femoral heads.
•• histological evidence of OFC.

RESULTS

TOTAL AND IONIC SERUM CALCIUM CONCENTRATIONS

Two patients with accelerated hypercalcemia and rapidly dete-

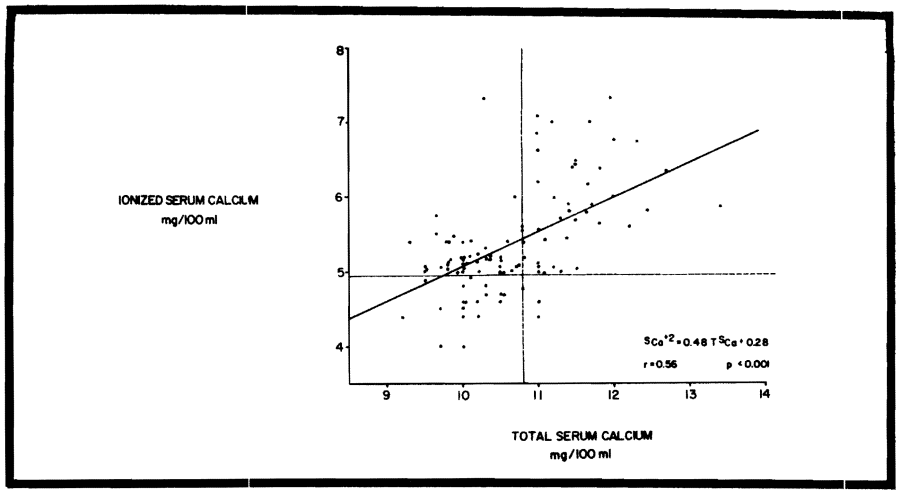

Fig. 3.—The relationship between total and ionized serum calcium concentrations. The data represent all preoperative available determinations in all patients. The broken vertical and horizontal lines denote the maximal normal values for total and ionized calcium respectively.

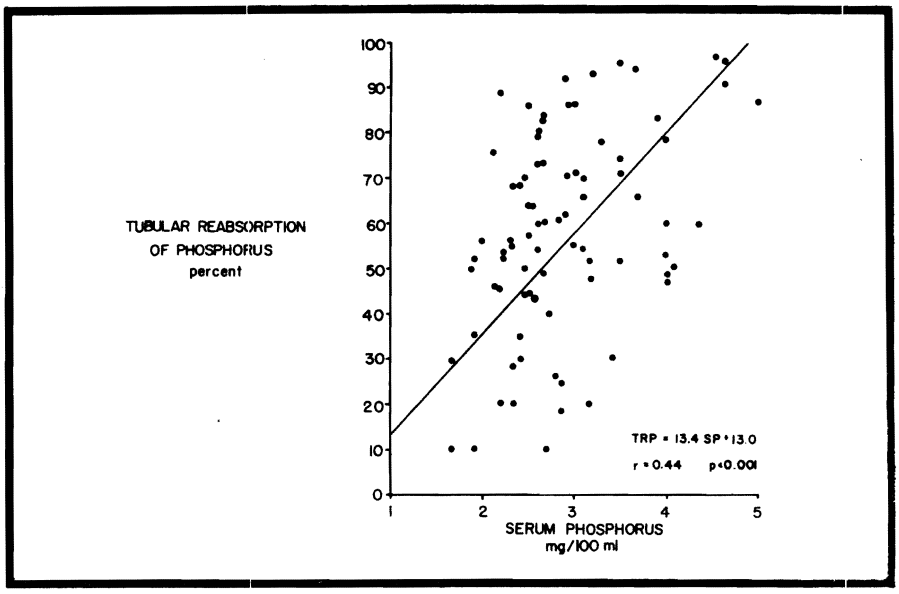

Fig. 4.—The relationship between serum concentration and tubular reabsorption of phosphorus in all patients on repeated determinations before parathyroidectomy.

riorating renal function were operated 2 months after transplantation; the remaining 16 were observed for longer periods of time and most were treated with phosphate supplements. The

maximal serum concentrations of total and ionized calcium before parathyroidectomy are shown in figure 2. Seven of 18 patients presented with total calcium within normal range whereas in all ionized calcium concentration was elevated above normal. Figure 3 illustrates in more detail the relationship between the total and the ionized serum calcium concentrations. The plotted data represent all preoperative determinations in all patients. There is a close direct relationship between both parameters. However, many determinations show high ionized calcium with normal total calcium concentration. 45.0 % of the plotted points fall in the upper left quadrant of the diagram showing high ionized serum calcium with normal total calcium concentration; only 35 % of all points are within the upper right quadrant indicating elevation of both serum calcium fractions.

SERUM PHOSPHORUS AND TUBULAR REABSORPTION OF PHOSPHORUS

Hypophosphatemia has been considered as a factor contributing to the appearance of hypercalcemia after kidney transplantation. In primary hyperparathyroidism hypophosphatemia is due to a decreased tubular reabsorption of phosphorus and its correction with oral phosphate supplements may lower serum calcium concentration but the benefit accrued from chronic administration of phosphate salts is questionable (3). Figure 4 shows a direct relationship between serum concentration of phosphorus and fractional tubular reabsorption of phosphorus. The lowest serum concentrations are associated with the lowest tubular reabsorption of phosphorus, suggesting that excessive urinary losses are to a great extent responsible for the hypophosphatemia. Furthermore, it appears that urinary losses are primarily due to high levels of circulating parathyroid hormone and not due to tubular defect in phosphorus reabsorption. The intactness of the transplanted nephrons with regard to phosphate reabsorption is shown in figure 5 which illustrates the changes in the fractional tubular reabsorption of phosphorus after total parathyroidectomy in 7 patients. The reabsorbed fraction reached 100 % despite the administration of thiazide diuretics and glucocorticoids which are known to have phosphaturic action. Inverse relationship between serum ionized calcium and tubular reabsorption of phosphorus is shown in figure 6. A marked scatter of the data is apparent and many points representing high ionized calcium correspond with a high fractional reabsorption of phosphorus even in excess of 80 %. In two patients TRP was consistently high before surgery. Thus normal TRP values did not preclude the presence of persistent hyperparathyroidism.

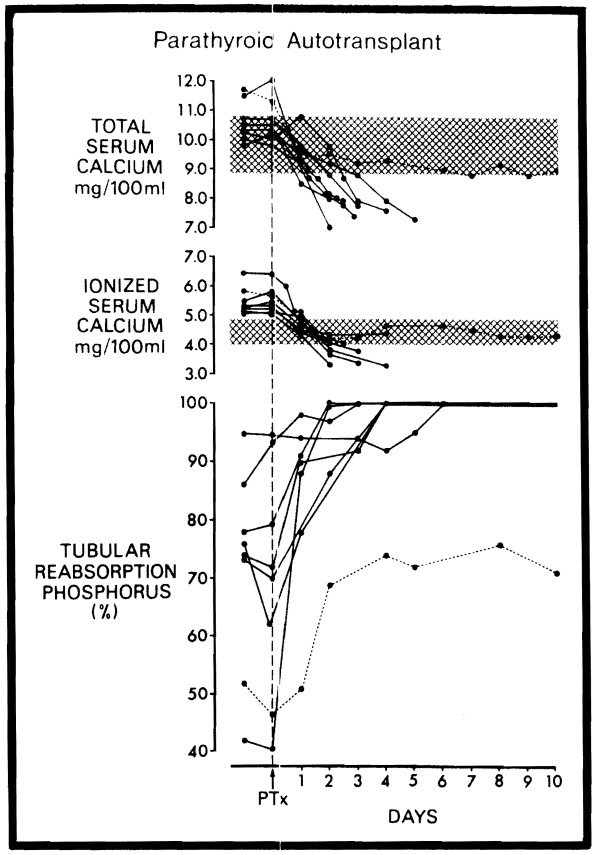

Fig. 5.—Serial determinations of serum levels of calcium and tubular reabsorption of phosphorus after total parathyroidectomy (PTX) with autotransplant. The broken line relates to a patient in whom the completeness of parathyroidectomy was questionable.

Hypophosphatemia was not consistently present in patients with hypercalcemia. Inverse relationship between serum phosphorus and ionized calcium levels is shown in figure 7. Although the highest levels of ionized calcium were associated with the lowest concentration of serum phosphorus, most of the data representing abnormally high concentration of ionized calcium fell within normal range for serum phosphorus (2.5 mg/100 ml and above).

THE EFFECT OF ORAL PHOSPHATE SUPPLEMENTS ON TOTAL AND IONIC SERUM CALCIUM

Figures 8, 9 and 10 illustrate sequential variations in total and ionized serum calcium levels in all patients with and without oral supplements of phosphate.

Oral phosphate supplements were given either as potassium phosphate (0.5-1.5 g elemental phosphorus per day) or as aluminum phosphate gel (Phosphaljel) 120 ml/day. In 6 patients

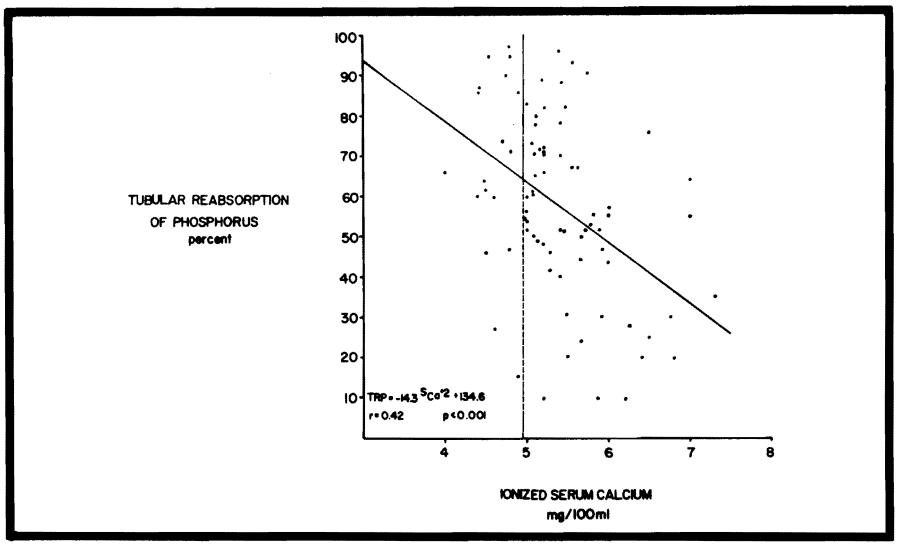

Fig. 6.—The relationship between ionized serum calcium and tubular reabsorption of phosphorus. The broken vertical line designates upper normal value for ionized calcium.

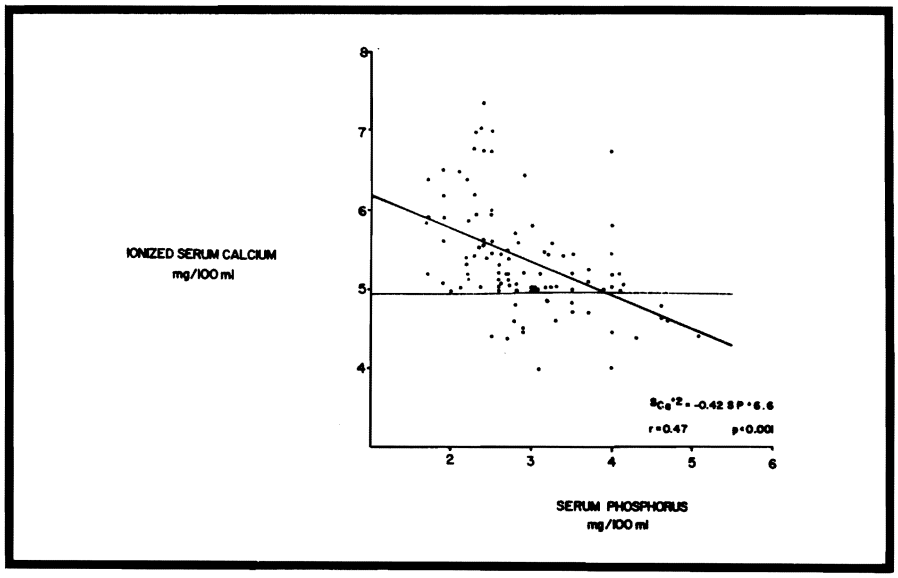

Fig. 7.—The relationship between serum phosphorus and ionized calcium. The horizontal broken line denotes upper normal value for ionized calcium.

(fig. 8), the initially high serum calcium was reduced with phosphate supplements and remained within the normal range throughout the study till parathyroidectomy; however, the ionized calcium was persistently elevated. In 6 additional patients (fig. 9) elevated total serum calcium was reduced to normal with

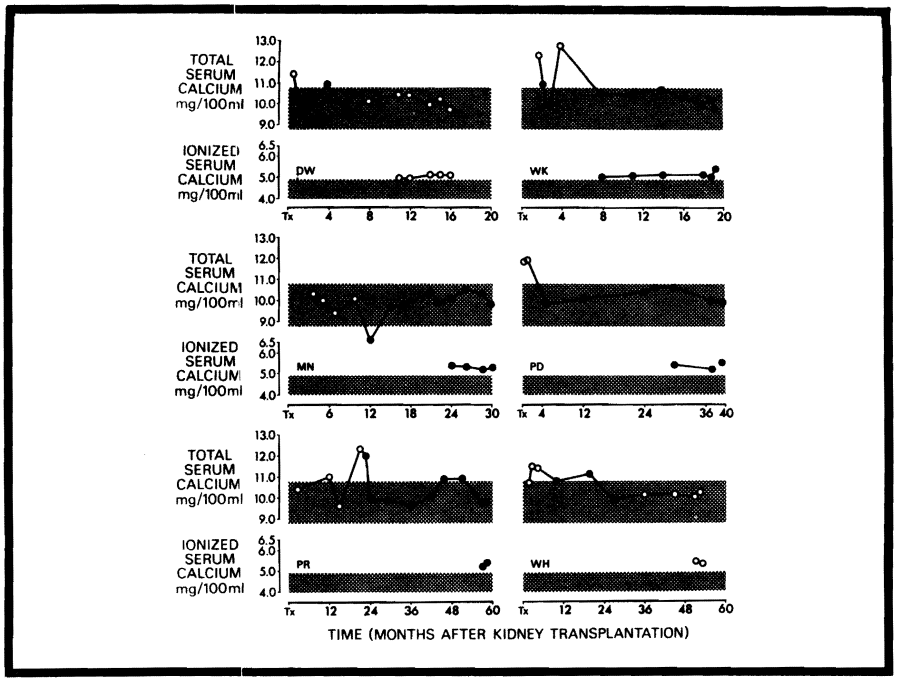

Fig. 8.—Serial variations in total and ionized serum calcium in 6 patients showing a decrease in total calcium. Closed circles denote periods of phosphate supplementation and open circles periods without supplementation. Hatched areas denote normal range for total and ionized calcium.

phosphate supplementation, however, recurrent hypercalcemia became apparent either when the patients were still on phosphate supplements or when those were discontinued. Ionized calcium in most instances was elevated above normal. Another pattern of variations in serum calcium is shown in figure 10. In these patients (left column), total and ionic serum calcium failed to respond to phosphate supplementation and remained elevated. Additional 3 patients (right column) which were included in figure 10 were not treated with phosphate supplements. In the latter patients serum calcium fluctuated between normal and above normal range however ionized calcium was persistently elevated.

THE EFFECT OF GLUCOCORTICOIDS ON SERUM CALCIUM CONCENTRATION

Glucocorticoids have been used in treatment of hypercalcemia associated with conditions other than hyperparathyroidism, however reduction of calcium with glucocorticoids was also reported in primary hyperparathyroidism (4). Figure 11 shows the rela-

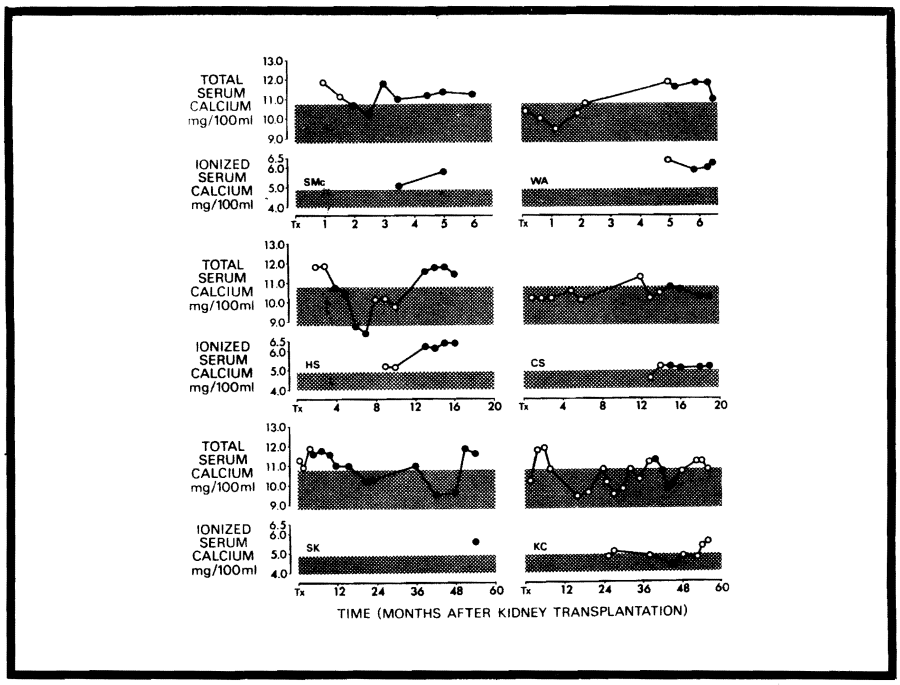

Fig. 9.—Serial changes in total and ionized calcium in 6 patients with late and recurrent hypercalcemia. Closed and open circles denote periods with and without phosphate supplementations respectively. Hatched areas denote normal range for total ionized calcium.

tionship between the dose of prednisone and serum concentration of total calcium before phosphate supplementation was started. In two patients (broken lines) the dose of glucocorticoids was tapered and discontinued abruptly because of a life threatening infection. Hypercalcemia ensued rapidly even though there was no change in serum phosphorus. In the other patients (solid lines) the dose of prednisone was decreased gradually after that stable homograft function was established. Lowering of the dose of prednisone was associated with a rise in serum calcium leading to the appearance of hypercalcemia. The variable time of onset of hypercalcemia in our patients could be partly due to the suppressive effect of glucocorticoids which also might be responsible for a continuous stimulation of the parathyroid glands (23, 22).

THE EFFECT OF PARATHYROIDECTOMY ON RENAL FUNCTION

Eleven of 15 patients (three patients had not sufficient data to be included) showed deterioration of kidney function prior to

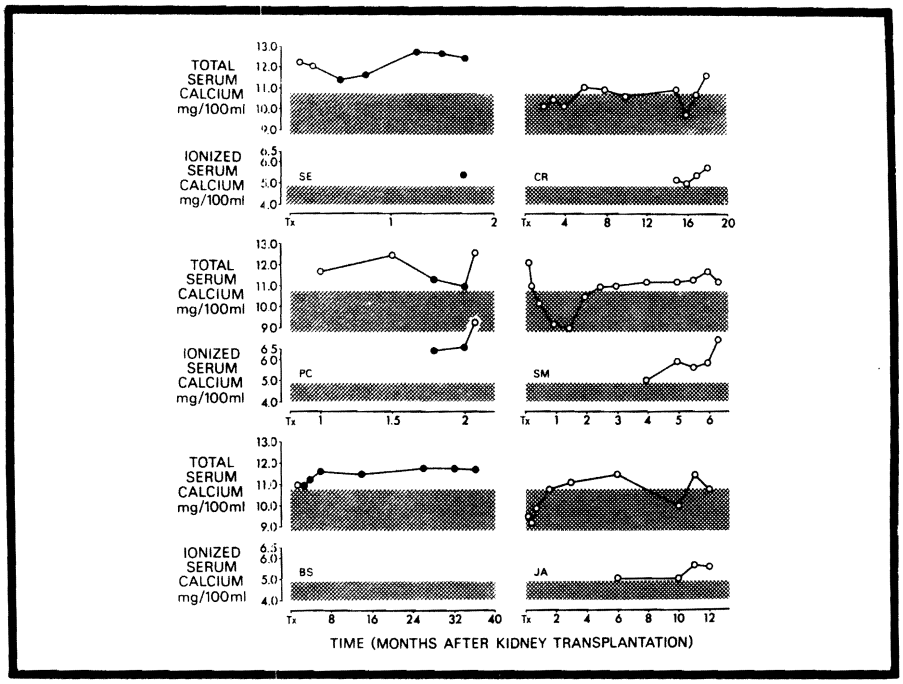

Fig. 10.—Serial changes in total and ionized calcium in 3 patients who did not respond to phosphate supplementation (left column) and in 3 patients who were not treated with phosphate supplementation (right column). Closed and open circles denote periods with and without supplementation respectively. Hatched areas denote normal range for total and ionized calcium.

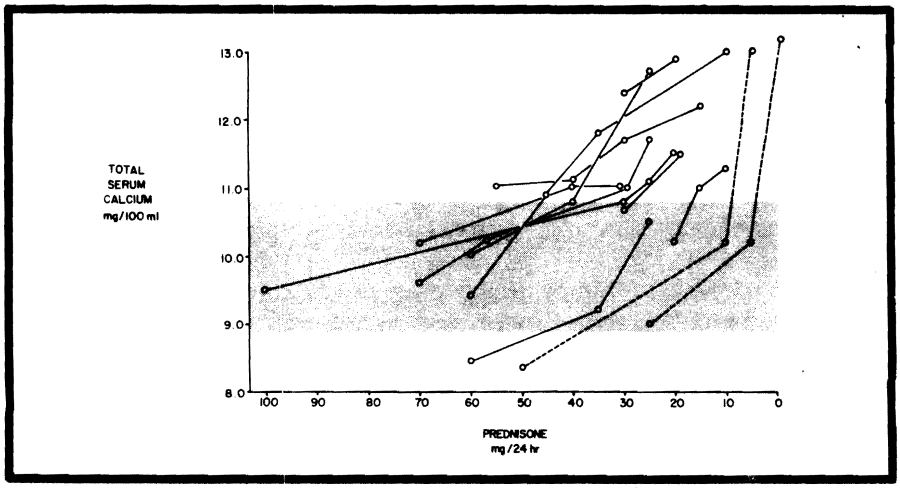

Fig. 11.—Serum total calcium and the maintenance dose of prednisone before phosphate supplementation was started. The hatched area designates normal range of total calcium.

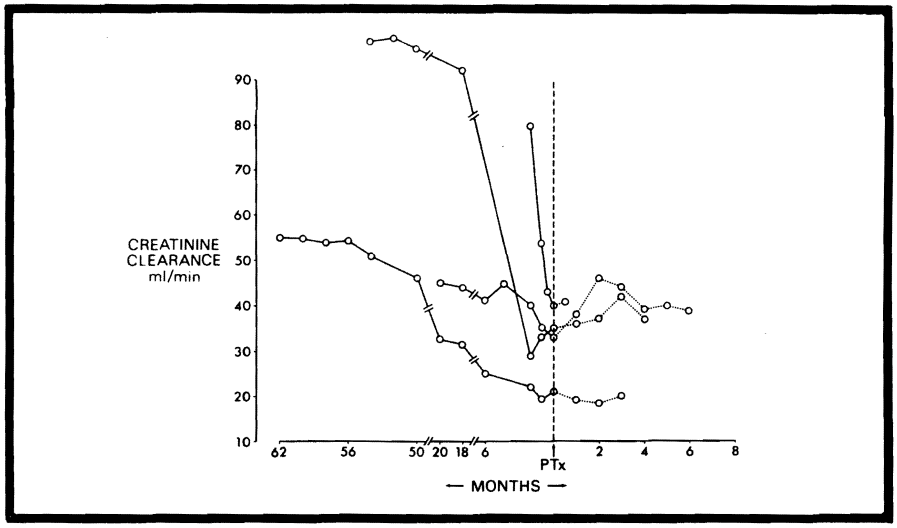

Fig. 12.—Sequential variations in creatinine clearance in 4 patients who exhibited a decrease in renal function before parathyroidectomy (PTX) without change after surgery.

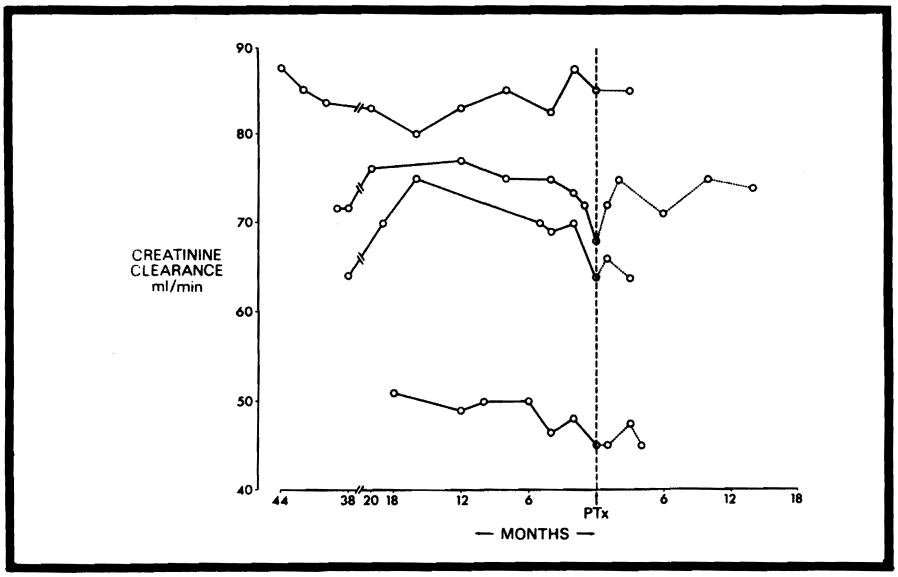

Fig. 13.—Serial determinations of creatinine clearance in 4 patients who maintained relatively stable renal function, before and after parathyroidectomy (PTX).

parathyroidectomy. Four patients with failing renal function (fig. 12) showed no noticeable change in creatinine clearance after parathyroidectomy and so did four patients with stable renal function (fig. 13). Seven patients who exhibited progressive deterioration of kidney function prior to parathyroidec-

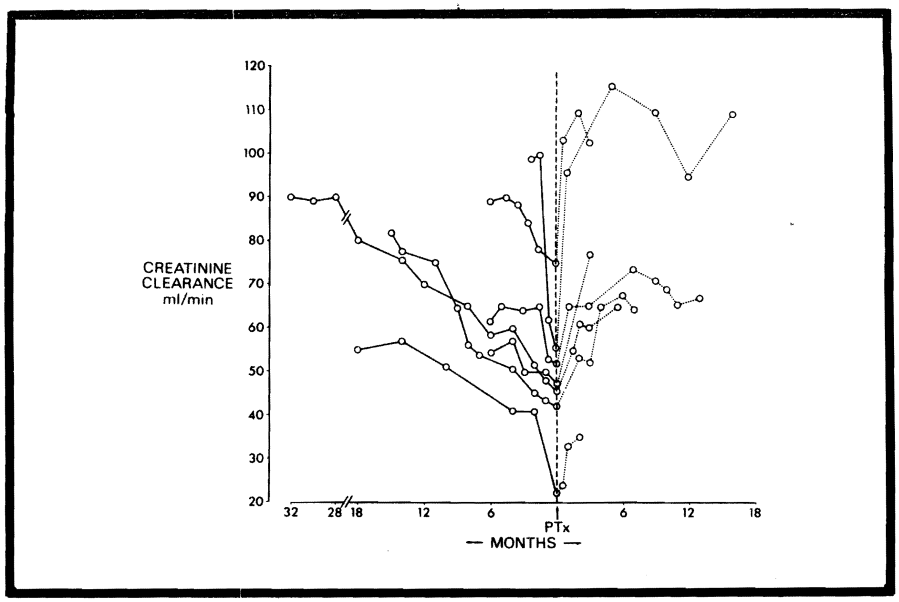

Fig. 14.—Serial determinations of creatinine clearance in 7 patients who exhibited a deterioration in renal function with an improvement after parathyroidectomy (PTX).

tomy exhibited a substantial increase in creatinine clearance after surgery (fig. 14). The degree of improvement seemed to be inversely related to the time interval between transplantation and parathyroidectomy, thus the sooner the parathyroidectomy was performed after transplantation the better was the improvement in kidney function. Figure 15 illustrates a typical clinical course as seen in one patient.

In all patients there was a hypertrophy of the parathyroid glands. The weights ranged between 200 to 2.300 mg with a mean value of 875 mg. No correlation was found between the parathyroid mass and the preoperative level of ionized calcium and neither the duration of hypercalcemia. The drop in serum calcium concentrations and the increase in tubular reabsorption of phosphorus were more pronounced in patients undergoing total parathyroidectomy (fig. 5) than in those subjected to subtotal parathyroidectomy (fig. 16).

CLINICAL MANIFESTATIONS

The clinical manifestations related to hyperparathyroidism are presented in table II. Three patients experienced bone pain which improved or resolved 2 to 4 months after parathyroidectomy. Pain was related to aseptic necrosis of the hip in one

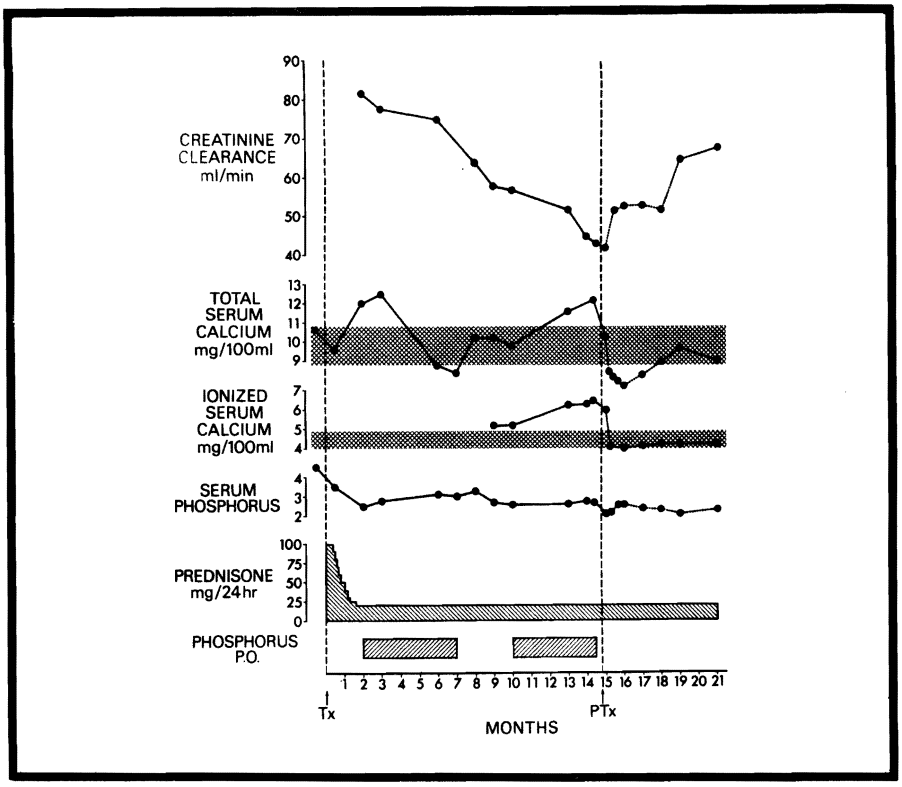

Fig. 15.—Typical course of variations in total and ionized serum calcium, serum phosphorus and creatinine clearance in patient H.S. after transplantation (TX). Appearance of hypercalcemia with decreasing the dose of prednisone. Initial response to oral phosphorus with a late failure resulting in recurrent hypercalcemia. Deterioration of renal function with marked improvement after parathyroidectomy (PTX).

patient and to osteoporotic compression fractures of thoracic and lumbar vertebrae in one patient. Pain in the back muscles occured in one patient and resolved in one month. Generalized weakness was present in 8 patients. A dramatic improvement occured in all these patients from 1 to 4 months following parathyroidectomy. Severe recurrent headaches occured in two patients. Each of these had extensive neurological examinations and no etiology was obtained. One of these patients experienced immediate and permanent loss of headache symptoms following parathyroidectomy while the other had dramatic decline in the frequency and intensity of headaches. Four patients related profound improvement in facial hyperemia which occurred within the first two weeks after parathyroidectomy.

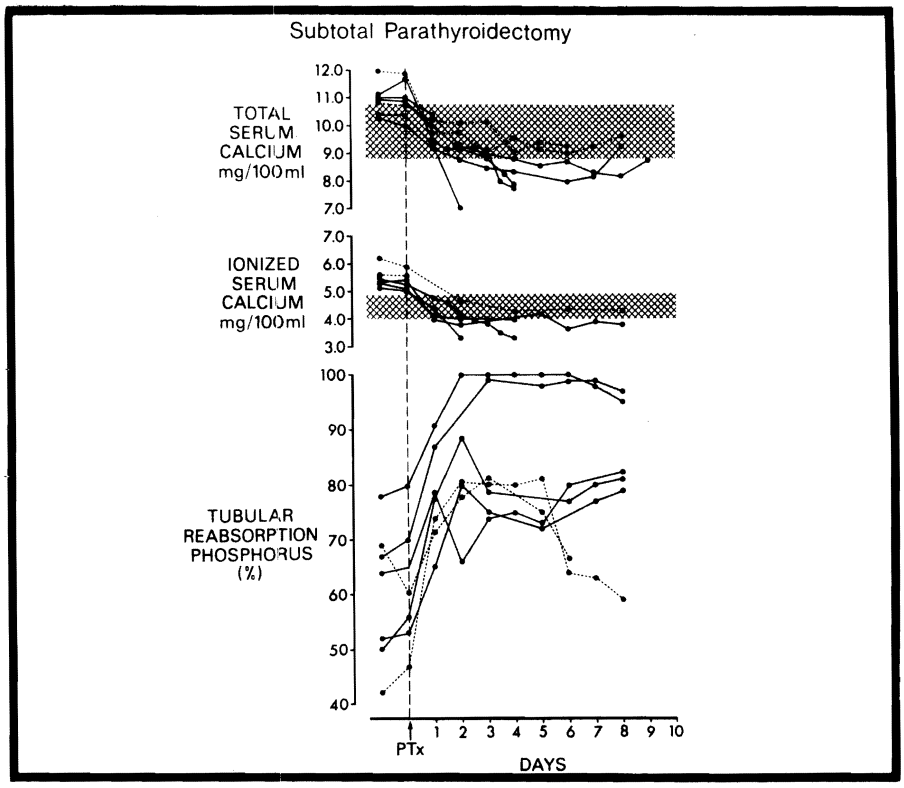

Fig. 16.—Serial changes in total and ionized serum calcium and tubular reabsorption of phosphorus after subtotal parathyroidectomy (PTX). Broken lines denote 2 patients in which only 3 parathyroid glands were identified.

Table II

Changes in clinical manifestations associated with parathyroidectomy.

Patient	Bone pain	Muscle pain	Weakness	Headaches	Facial hyperemia	Psychosis
P.C.	—	—	Resolved	—	—	—
S.M.	—	—	Resolved	—	—	—
H.S.	—	—	Resolved	—	Improved	Resolved
C.S.	—	—	—	—	—	—
C.R.	—	—	Improved	—	—	—
M.N.	Resolved	Resolved	—	—	—	—
S.K.	—	—	—	—	—	—
W.H.	—	—	Resolved	—	—	—
P.R.	Resolved	—	Improved	—	—	—
K.C.	—	—	—	Improved	Improved	—
S.Mc.	—	—	—	—	—	—
W.A.	—	—	Improved	—	Improved	—
D.W.	—	—	—	—	—	—
W.K.	—	—	—	Resolved	—	—
B.S.	—	—	—	—	—	—
P.D.	—	—	Improved	—	Resolved	—
S.E.	—	—	—	—	—	—
J.A.	Improved	—	—	—	—	—

DISCUSSION

The present communication demonstrated that parathyroid hyperfunction may continue many years after kidney transplantation even in the presence of relatively adequate kidney function. The association of hyperparathyroidism with deteriorating kidney function, and moreover the improvement in creatinine clearance as noticed in our 7 patients after parathyroidectomy strongly suggests that persistent hyperparathyroidism may have a detrimental effect on the renal homograft. Although many factors other than secondary hyperparathyroidism could contribute to a decrease in renal function, hyperparathyroidism should always be considered as an important alternative. Furthermore, the beneficial effect of parathyroidectomy on renal function should not be underestimated especially when the relatively low operative risk of this procedure is considered.

The importance of determining ionized calcium as a diagnostic aid is emphasized by our data. We have not found other criteria as useful as this single determination. Similar observations regarding the diagnostic value of ionized calcium determinations were reported in patients with primary hyperparathyroidism (10).

The factors responsible for persistent hyperparathyroidism after kidney transplantation are not well defined by the present study. Administration of phosphorus under various circumstances has been shown to be associated with parathyroid stimulation and occasionally with deterioration of renal function (13, 8, 9). Most of our patients were treated with phosphate supplements which by decreasing serum calcium could be responsible for sustained stimulation of parathyroid function especially when given over long periods of time.

The following observations regarding phosphate supplementation deserve emphasis: 1) phosphate supplementation may reduce total calcium concentration and in the absence of measured values of ionized calcium it may in fact mask the presence of hypercalcemia; 2) the suppression of total serum calcium may be temporary and a rebound may occur at unpredicted time. Frequent determinations of total calcium may be necessary to ascertain that hypercalcemia is recorded when it recurs. In addition ionized calcium may remain elevated despite normal total calcium and 3) in certain patients hypercalcemia will resist phosphate supplementation. These findings question the usefulness of prolonged phosphate supplementation for post-transplant hypercalcemia.

Glucocorticoids may suppress hypercalcemia especially when given in large doses as demonstrated by the appearance of hypercalcemia in our patients as the dose of the steroids was reduced. The suppression of serum calcium may be a stimulus for continuous parathyroid hyperactivity. This possibility is supported by recently reported experimental data (23) which demonstrated increased serum levels of immunoreactive parathyroid hormone during the administration of glucocorticoids. In addition, the effect of glucocorticoids on Vitamin D metabolism (2) may be an additional factor contributing to parathyroid hyperactivity.

At last the degree of renal impairment as a cause of secondary hyperparathyroidism deserves a comment. The extent of the loss of renal function at which secondary hyperparathyroidism becomes apparent has not been established with certainty yet, however several investigators proposed that a relatively small decrease in renal function is sufficient to trigger parathyroid hyperactivity. Reiss et al. reported elevated levels of circulating radioimmunoreactive parathyroid hormone in patients with renal disease with creatinine clearance of about 80 ml/min (18). Since many renal homografts seldom achieve 100 % of normal function and, in fact, in many creatinine clearance does not exceed 80 ml/min, it is not unlikely that the minimal to moderate decrease in kidney function plays a key role in maintaining hyperparathyroidism after transplantation.

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II.
RELATION TO BONE DISEASE

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INTRODUCTION

It has been generally assumed that azotemic osteodystrophy resolves after kidney transplantation (3, 4). This notion was consistent with the proposed regression of secondary hyperparathyroidism after kidney transplantation (1, 3, 4) to which an important role was attributed in the pathogenesis of uremic bone disease.

In spite of the apparent healing of azotemic osteodystrophy many recipients of renal homografts may suffer from various skeletal complications (2). The symptomatic bone disease is usually associated with varying degrees of radiographically demonstrable skeletal rarefaction. In addition spontaneous fractures of different bones may occur, most frequently the affected bones are the hips, the feet and other weight-bearing parts of the skeleton. Avascular necrosis is another lesion frequently noticed in various bones. Occasionally it is difficult to differentiate on the basis of roentenographic findings alone avascular necrosis from other destructive lesions of the bone such as osteomyelitis. These complications have been generally attributed to immunosuppressive therapy with glucocorticoids. Moreover since no definitive treatment has been available for steroid induced osteoporosis only general supportive measures could be recommended.

The present report is based on pathological findings pertinent to symptomatic bone disease in four renal homograft recipients.

Fig. 1.—Vertebral trabecular bone from patient A. Several osteoclasts are resorbing the left side of the trabecule. Decalcified paraffin embedded section, stained with hematoxycin and eosin. Original magnification, 200 x.

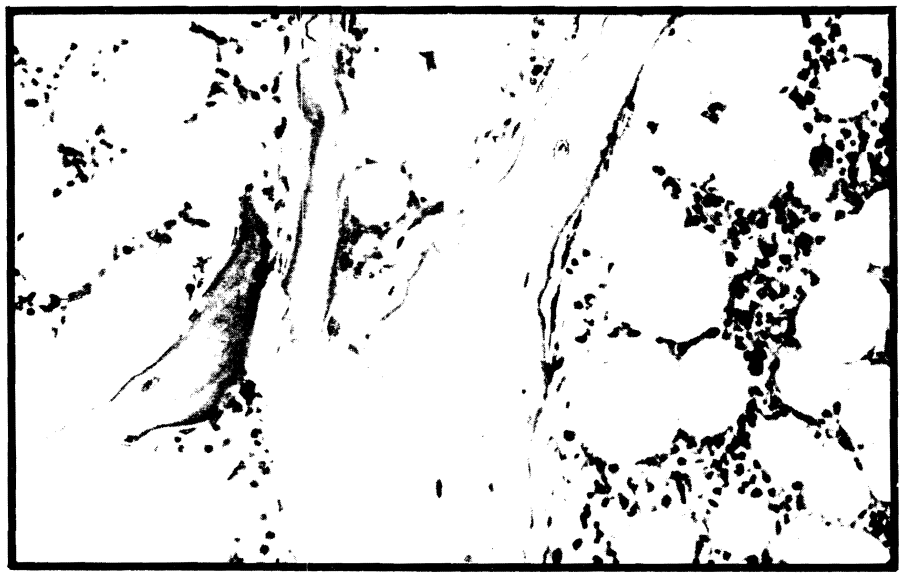

Fig. 2.—Vertebral trabecular bone from patient B. Extensive osteoclastic resorption of external (lower left) and internal (center) portions of trabecules. There is no evidence of osteogenic activity or fibrous replacement of the marrow. Tissue prepared as in figure 1. Original magnification, 200 x.

Patient A. This 30 year old male died of hepatitis 5 years after successful renal transplantation. During the last two years he experienced diffuse bone pains. Roentgenographic survey of the skeleton revealed generalized rarefaction, this finding was interpreted as steroid induced osteoporosis. Microscopic examination of the bones at autopsy disclosed severe resorptive bone disease with minimal amount of fibrous tissue and thin trabecules (fig. 1).

Patient B. This 13 year old girl died four years after successful kidney transplantation of pneumonia. During the last two years, the patient complained of severe back pains and was found to have diffuse skeletal rarefaction which was interpreted as steroid induced osteoporosis. Microscopic examination of the bones at autopsy disclosed resorptive bone disease with poor fibrous tissue formation and thin trabecules (fig. 2).

Patient C. This 38 year old male died of encephalitis four years after successful renal transplantation. Severe bone disease which affected both his upper and lower extremities prevented his rehabilitation and restricted him to a wheel chair. The roentgenographic bone survey showed severe osteoporosis with destructive lesions in the left talus (fig. 3) and the right humeral head (fig. 4) which were interpreted as avascular necroses and

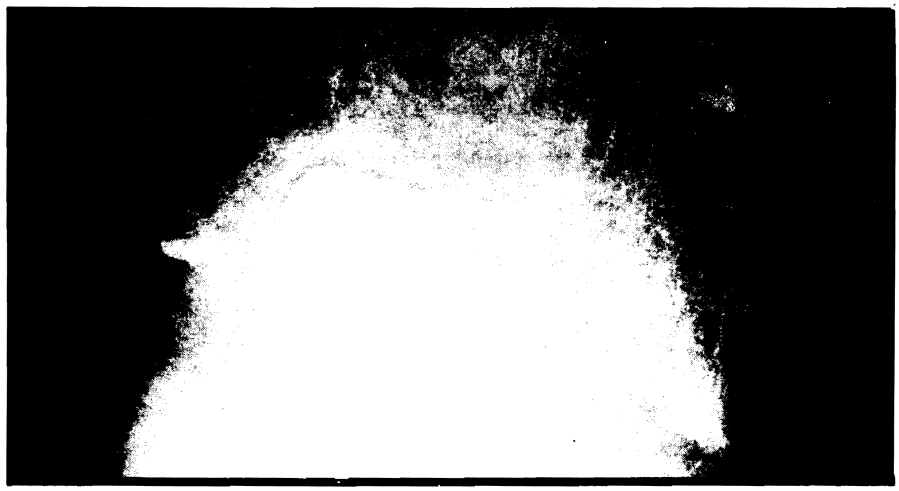

Fig. 3.—The roentgenographic appearance of the left talus with the adjacent bones in patient C demonstrating avascular necrosis.

Fig. 4.—The roentgenographic appearance of the right humeral head and the shoulder joint in patient C, showing avascular necrosis.

Fig. 5.—Vertebral trabecular bone from patient C. Extensive resorption has produced "railroad track" effect. The original trabecules are represented by thin bony walls enclosing a central marrow filled core. There is no evidence of an osteoeblastic or fibroblastic response. Tissue prepared and stained as in figure 1. Original magnification 79 x.

were attributed to the steroid therapy. At autopsy all 4 parathyroid glands were found to be enlarged and hyperplastic. The examination of the homograft revealed nephrocalcinosis. The microscopic examination of the bones revealed marked resorption with marked thinning of the trabecules and poor fibrous tissue formation (fig. 5).

Patient D. This 50 year old male died two years after kidney transplantation of systemic infection. During the last year, he had severe bone pains, sustained a spontaneous intertrochanteric fracture of the right upper hip which required pinning (fig. 6). Roentenographic bone survey revealed rarefaction which was interpreted as steroid induced osteoporosis. At autopsy all 4 parathyroid glands were large and hyperplastic. The microscopic examination of the bones revealed resorptive process with extremely thin trabecules and minimal fibrous tissue (fig. 7).

Fig. 6.—The roentgenographic appearance of the right upper hip in patient D, showing rarefaction and intertrochanteric fracture.

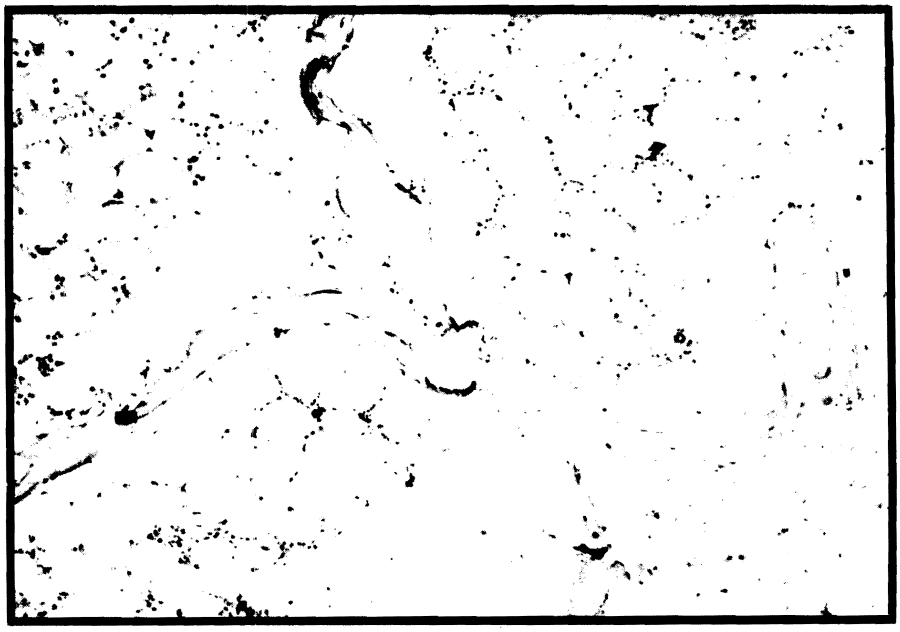

Fig. 7.—Vertebral trabecular bone from patient D. Osteoclastic resorption has produced changes similar to those described in the preceding illustration. Tissue prepared as in figure 1. Original magnification, 79 x.

DISCUSSION

The present report suggests that persistent parathyroid hyperfunction may be the underlying cause of disabling bone disease many years after successful kidney transplantation. The inability to establish the correct diagnosis during lifetime in the above 4 patients could be related to several factors. Firstly, the absence of characteristic roentgenographic findings of hyperparathyroidism such as resorption of cortical surfaces and the formation of cystic lesions. The roentgenographic feature of skeletal rarefaction which was present in all 4 patients could reflect lack of new bone formation after that extensive resorption took place as indicated by the microscopic findings; this could be secondary to the effect of steroids on bone metabolism. Secondly, the absence of hypercalcemia typical of hyperparathyroidism was misleading. This could be partly due to suppression of serum calcium with glucocorticoids and/or inadequate number of determinations of total and ionized calcium concentration in the serum. Thirdly, the lack of alertness to the possible presence of hyper-

parathyroidism many years after transplantation and its role in the bone disease could be partly caused by the early reports proposing resolution of secondary hyperparathyroidism after successful kidney transplantation. However, in a recent study persistently high levels of parathyroid hormone were found in patients with well-functioning renal homografts many years after transplantation; furthermore a direct relationship was found between the level of radioimmunoreactive circulating hormone and the incidence of avascular necrosis (5). The latter and our findings taken together support the possible role of hyperparathyroidism in the pathogenesis of symptomatic bone disease after renal transplantation. In retrospect it seems that an earlier diagnosis of osteitis fibrosa cystica which could be made with a bone biopsy might have provided the clue to the therapy of the symptomatic bone disease. It appears thus that the consideration of the diagnosis of persistent secondary hyperparathyroidism is imperative in patients with symptomatic bone disease after kidney transplantation.

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