Long-term Evaluation of Patients with Primary Parathyroid Hyperplasia Managed by Total Parathyroidectomy and Heterotopic Autotransplantation

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Since 1973, we have performed total parathyroidectomy and forearm parathyroid autotransplantation in 36 patients with generalized (four gland) primary parathyroid hyperplasia. Twenty (56%) patients had nonfamilial parathyroid hyperplasia (NFPH) and 16 (44%) patients had familial parathyroid hyperplasia (FPH). Twenty-one patients (Group A) were undergoing operation for the first time and 15 (Group B) were having either second, third or fourth re-explorations for persistent hyperparathyroidism. All patients in Group A and nine patients in Group B had parathyroid resection and immediate autotransplantation as a single procedure. Six Group B patients had hyperfunctioning parathyroid tissue resected, cryopreserved, and subsequently grafted when it was evident that they had been rendered aparathyroid. A sustained differential elevation (13.7 fold ± 2.7) of parathyroid hormone was detected in the antecubital vein of the grafted compared to the nongrafted arm in 35 (97%) patients. Two (5.6%) of the 36 patients (both with FPH; one Group A and one Group B) required permanent oral calcium and vitamin D replacement therapy and one (3%) patient (NFPH: Group A) had persistent hypercalcemia postoperatively, presumably due to a supernumerary gland. The remaining 33 (92%) patients became normocalcemic after surgery and 23 (70%) of them remained so. Ten (30%) of the 33 patients developed recurrent graft dependent hyperparathyroidism. Eight patients were from the group with FPH (8/14, 57%) and two were from the group with NFPH (2/19, 11%) (FPH vs. NFPH, $p < 0.005$). Because of symptoms of hypercalcemia or a serum calcium concentration exceeding 11 mg/dl, partial graft resection was performed in five patients and four became normocalcemic. Patients with generalized primary parathyroid hyperplasia may be difficult to cure, especially if the disease is familial. The technique of total parathyroidectomy and heterotopic autotransplantation of fresh or cryopreserved parathyroid tissue offers distinct advantages over alternative techniques.

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MOST PATIENTS WITH PRIMARY hyperparathyroidism are found at operation to have one large parathyroid gland and three of normal size. In virtually all such patients, resection of the enlarged parathyroid is curative. A small number of patients (usually less than 10%) have generalized parathyroid enlargement, a condition referred to as parathyroid hyperplasia. Water-clear cell hyperplasia[1] is rare and is seen much less frequently than when first described 50 years ago. Chief-cell hyperplasia[7] is more common and it may occur alone or in association with certain familial endocrinopathies: multiple endocrine neoplasia type I (MEN I),[22] multiple endocrine neoplasia type II (MEN II),[17] and familial hypocalciuric, hypercalcemic hyperparathyroidism (FHHH).[12]

Unlike patients with single gland hyperparathyroidism, those having generalized parathyroid enlargement are more difficult to manage. Before this disease entity was widely recognized surgeons often did not appreciate at operation that all of the parathyroid glands were enlarged and patients developed postoperative hypercalcemia because an insufficient amount of tissue was resected. Cope[8] defined the state of parathyroid hyperplasia and recommended that patients with this disease be treated by radical subtotal parathyroidectomy (removal of three enlarged parathyroid glands and a remnant of the fourth). The results with this technique have not been entirely satisfactory. In 1951, Castleman and Cope[4] evaluated 11 patients treated surgically for water-clear cell hyperplasia. Of nine patients who were studied one to ten years following three and one-half gland parathyroidectomy, five patients (56%) developed postoperative hypercalcemia. In another two patients, the serum calcium concentrations were 10.3 and 10.1 mg/dl.

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Castleman and Schantz[5] recently reported results in 66 patients undergoing sugery for hyperparathyroidism due to chief cell hyperplasia. The prevalence of postoperative hypercalcemia was 11% and of permanent hypocalcemia, 15%. However, only 50% of the 66 patients were evaluated beyond one year postoperatively. In a recent report by Edis,[11] of 55 patients undergoing subtotal parathyroidectomy for chief cell hyperplasia, permanent hypocalcemia developed in three patients (5%) and persistent hyperparathyroidism in seven patients (13%). Transient postoperative hypocalcemia lasting up to two years was noted in 15 patients (27%).

Several investigators have recorded poor surgical results in patients with familial hyperparathyroidism. Clark[6] in a literature review reported recurrent hypercalcemia in 33% of 24 patients with familial hyperparathyroidism, 70% of whom had multiple gland disease. Similarly, Lamers[13] reported recurrent hyperparathyroidism in five (38%) of 13 patients with MEN I and Scholz and associates[16] detected postoperative hypercalcemia in two (22%) and hypocalcemia in two (22%) of nine patients with MEN I. Marx and associates[14] evaluated seven patients with FHHH who were operated on a total of nine times. Six patients remained hypercalcemic and one developed chronic hypocalcemia.

The cure rate in patients re-explored for hyperparathyroidism persisting or recurring after a failed operation is much lower than in patients undergoing primary surgery. In Beazley's series of patients re-explored for hyperparathyroidism,[2] only 18 (55%) of 33 patients were rendered normocalcemic, seven patients (21%) remained hypercalcemic, and eight (24%) became permanently hypocalcemic. In Brennan's series[3] of 30 patients, five (17%) remained hypercalcemic and 11 (37%) became hypocalcemic. In Edis's series of 51 patients,[10] 71% were cured by re-exploration, however, 15 (30%) of the 51 patients required permanent calcium and vitamin D replacement after surgery.

Appreciating the difficulties which others had encountered in managing patients with hyperparathyroidism due to generalized parathyroid enlargement, we devised a surgical technique which both decreased the parathyroid mass without inducing permanent hypocalcemia and provided a simple means of managing recurrent hyperparathyroidism should it develop. This technique was also directly applicable to the treatment of patients undergoing repeat operation for persistent or recurrent hyperparathyroidism.

Previous work in experimental animals[15,18] had demonstrated the facility of transplanting isologous or autologous parathyroid tissue and had clearly shown that the recipient could be maintained in a normocalcemic state with the grafted parathyroid as the only source of hormone. We proposed[21] for patients with primary parathyroid hyperplasia, that all parathyroid glands be resected from the neck and small slices from one be implanted into the forearm muscle. Should graft-dependent hypercalcemia subsequently develop, it could be successfully managed by resecting pieces of the transplanted tissue under local anesthesia, thereby obviating the need for repeat neck exploration with subtotal or total extirpation of residual *in situ* parathyroid. The parathyroid grafts were successful in each of the first four patients reported by our group.[21]

Patients who require a second neck exploration are at a much greater risk for developing hypoparathyroidism for two reasons. During the process of re-exploration, normal parathyroid tissue may be inadvertently damaged. More commonly, a discovered enlarged parathyroid gland may represent the only functioning tissue and with its removal the patient is rendered aparathyroid, a complication preventable by parathyroid autotransplantation. When the surgeon is certain, from reviewing previous operative notes and pathology material, that three parathyroid glands have been removed, then any enlarged parathyroid gland identified at re-exploration may be resected and autografted during the same procedure. If, however, it is not clear that the enlarged parathyroid gland identified represents the patient's only remaining parathyroid tissue, or if it is suspected that other parathyroid tissue may reside in the neck, the resected parathyroid gland should be sliced into small slivers and cryopreserved for subsequent autografting when and if the patient becomes aparathyroid.

Since 1973 we have treated 36 patients with primary hyperparathyroidism due to generalized (four-gland) enlargement using total parathyroidectomy and forearm autotransplantation. The present report describes our experience with these patients.

Materials and Methods

Patients

The 36 subjects represented patients undergoing operation at Duke University Medical Center since 1973 who had a clinical and pathologic diagnosis of primary parathyroid hyperplasia (enlargement of all four parathyroid glands). Twenty (56%) of the patients had nonfamilial parathyroid hyperplasia (NFPH) and 16 patients (44%) had familial parathyroid hyperplasia (FPH); nine of the 16 had MEN I, three patients had MEN II and four had FHHH. In 21 patients who were undergoing operation for the first time, four parathyroid glands were removed from the neck and parathyroid tissue was immediately implanted in the forearm.

Fifteen patients were undergoing second, third or fourth re-explorations for hyperparathyroidism. In nine, an enlarged parathyroid gland was removed and pieces of it were immediately autografted because it was known that three large parathyroid glands had been removed previously. In six patients it was not clear whether the identified parathyroid gland(s) was the only remaining parathyroid tissue, therefore, the parathyroid(s) was resected and slivers were cryopreserved and subsequently autografted under local anesthesia when it became evident that the patient had been rendered aparathyroid. Patients were studied preoperatively and postoperatively on the General Clinical Research Unit and all 36 were evaluated within six months of submission of this manuscript.

Technique of Parathyroid Autotransplantation

The parathyroid tissue was removed and immediately placed into a sterile ice bath containing either Waymouth's MB752/1 tissue culture media (early in the series) or normal saline (later in the series). After obtaining frozen section confirmation of each gland, the smallest parathyroid was sliced into slivers measuring approximately 1 × 1 × 3 mm. These were maintained at 4 C. The nondominant forearm was prepared, draped sterilely and stabilized in the supine position. An incision was made and 15–20 parathyroid pieces were implanted intramuscularly. Each parathyroid piece was embedded in a single pocket and the overlying superficial fascia and muscle were closed with nonabsorbable suture. The technique has been described previously.[19]

Technique of Cryopreservation

The parathyroid tissue was removed from the neck, placed in a sterile ice bath and 30–40 slivers were prepared as described. These were transported to the laboratory and placed into three or four one-dram vials (10 slivers to a vial) containing 10% dimethyl sulfoxide, 10% autologous serum and 80% Waymouth's MB752/1 tissue culture media. These were then placed in the liquid nitrogen freezing compartment of a controlled rate freezer (Linde BF-4/6 Biological Freezing System; Linde Division, Union Carbide, Indianapolis, IN) and frozen at −1 C per minute to −80 C. The vials were then transported immediately into an LR 1,000 liquid nitrogen storage freezer (Linde Division, Union Carbide) where they were maintained at −170 C.

Postoperative Evaluation

In most patients the serum calcium concentration fell to 6.5–7.5 mg/dl within three to four days after surgery at which time dihydrotachysterol (0.625 mg a day) and glubionate calcium (15 cc four times a day) were begun. For severe symptoms of hypocalcemia, which developed in some patients, calcium gluconate was administered intravenously. As soon as the serum calcium concentration reached 8 mg/dl the patients were discharged on glubionate calcium and a reduced dosage (0.125 mg a day) of dihydrotachysterol. Patients were then evaluated biweekly and in most cases the dihydrotachysterol was discontinued four weeks and the glubionate calcium six weeks after surgery. Thereafter, patients were evaluated at six month intervals for one year and then were seen yearly. At each visit the serum calcium concentration was measured and parathyroid graft function was evaluated by determining the concentration of PTH in the antecubital vein of the grafted arm and comparing it to that in the nongrafted arm.

Determination of Serum Calcium

The serum calcium concentration was determined by atomic absorption spectrophotometry (Model 151, Instrumentation Laboratory, Inc., Wilmington, MA). The normal range of serum calcium determined by evaluating 134 normal control subjects in our geographic area was 8.5 to 10.2 mg/dl.

Determination of Parathyroid Hormone

Carboxy-terminal parathyroid hormone (C-PTH) levels in plasma were determined by a radioimmunoassay of the classical limited reagent type in which labeled and unlabeled PTH compete for limited binding sites on specific antibodies. The guinea pig antiserum (GP 468) used has predominant specificity for the carboxy-terminal portion of the bovine PTH molecule (amino acids, 52–84). Two-hundred microliter plasma samples were incubated with 200 μl barbital buffer (0.025 M barbital, 0.025 M EDTA, 5% Trasylol, 0.5% bovine serum albumin and 0.025% Merthiolate, pH 8.6) containing anti-PTH antiserum (1:500,000) for three days in the cold. Then 100 μl of bovine PTH, ^{125}I (6,000 CPM) was added for an additional three days of incubation. Separation of antibody-bound PTH from free PTH was made with an additional overnight incubation with a goat anti-guinea pig second antibody system. After centrifugation, pellets and supernatants were counted and bound/free (B/F) ratios were computed. The unknown B/F values were interpolated into a standard curve constructed with serial dilutions of bovine PTH. The standards were exactly calibrated against an international reference preparation. †Nonspecific plasma interference in the assay was corrected for by assaying PTH-depleted aliquots of each un-

† We are grateful to the W.H.O. International Laboratory for Biologic Standards for their provision of the International Reference preparation.

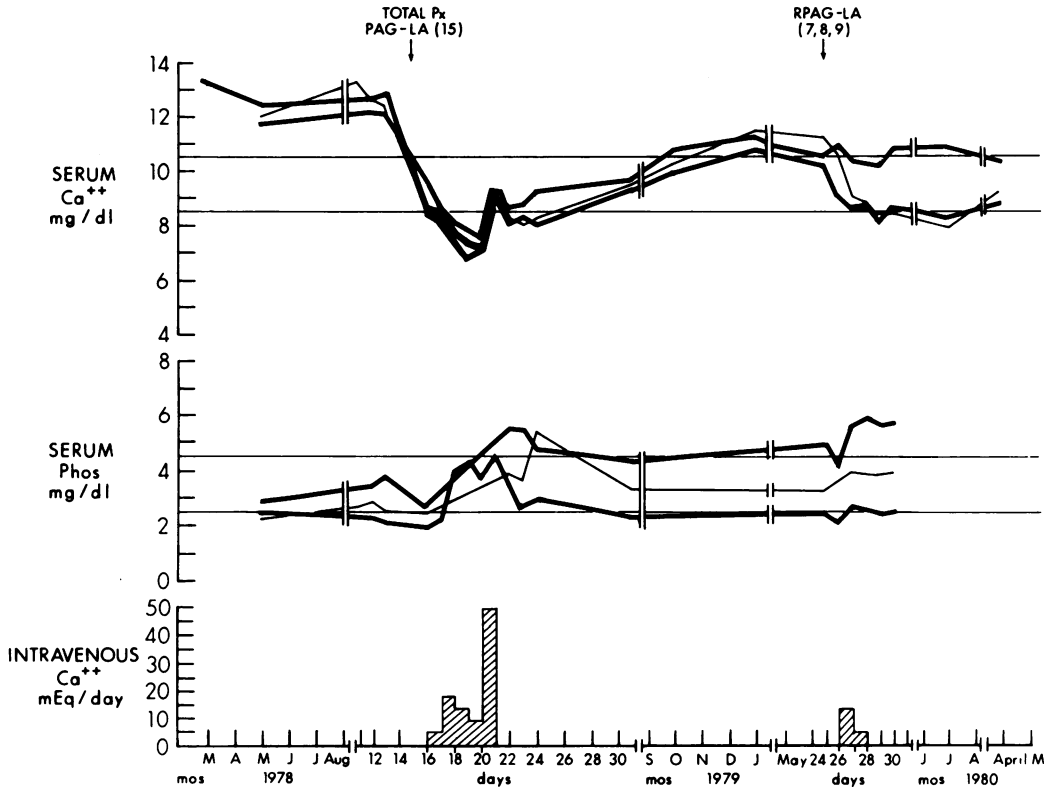

FIG. 1. The course of three patients with familial hypocalciuric, hypercalcemic hyperparathyroidism following total parathyroidectomy and autotransplantation. Intravenous calcium therapy was required briefly in the postoperative period (shaded area). Each of these patients subsequently developed graft dependent hyperparathyroidism and the serum calcium concentration returned to normal in two (one is intermittently hypercalcemic) after partial graft resection. Total PX: total parathyroidectomy, PAG-LA (15): transplantation of 15 slivers of parathyroid tissue to the left arm, RPAG-LA (7, 8, 9): resection of 7, 8, and 9 pieces of parathyroid autograft from the left arm in the three patients.

known (prepared by QUSO-microfine silica extraction‡). Nonspecific dose values were subtracted from total dose to obtain the true dose of PTH reported.

The amino-terminal (N-PTH) assay was similar to the carboxy-terminal assay except the guinea pig antisera (GPC-I) had predominant specificity for the N-terminal portion of the PTH molecule (amino acids 1–34). One hundred microliter plasma samples were incubated with 200 μl barbital buffer (0.02 M barbital, 5% Trasylol, 0.5% bovine serum albumin, 0.01% Merthiolate, pH 8.6) containing anti-PTH antiserum (1:30,000) for three days in the cold. Then 100 μl human synthetic 1–34 ^{125}I (2,500 CPM) was added for an additional three days of incubation. Separation of antibody-bound PTH from free PTH and calculation of unknown PTH concentrations were made as with the carboxy-terminal assay; synthetic human 1–34 PTH was used for reference standard.

Results

Postoperative Evaluation

In 35 (97%) of the 36 patients, the serum calcium concentration dropped to 6.5–7.5 mg/dl within three to ten days postoperatively. In six patients, the fall in serum calcium was gradual and no supplemental calcium and vitamin D were administered. Each of the six patients currently has a serum calcium concentration between 8.3 and 10 mg/dl.

In three patients (Fig. 1) intravenous calcium gluconate was required when marked hypocalcemia developed on the fourth postoperative day. Oral replacement therapy was not given and the serum calcium concentration increased to normal following termination of intravenous therapy. Each of these patients had FHHH and subsequently developed graft dependent hypercalcemia (Fig. 1).

Two (5.6%) of the 36 patients became permanently hypoparathyroid and required replacement therapy. One of these patients had MEN I and following parathyroidectomy with autotransplantation, a total gastrectomy was performed for the Zollinger-Ellison syndrome. Even though this patient had evidence of parathyroid hormone secretion from his graft and was administered large amounts of oral calcium and vitamin D therapy, his serum calcium never rose above 8.5 mg/dl, possibly due to calcium malabsorption. The other patient had multiple endocrine neoplasia type II and developed hyperparathyroidism subsequent to a total thyroidectomy for medullary carcinoma. Parathyroid tissue was resected and frozen and the patient was subsequently grafted but there was no evidence of tissue function either clinically or biochemically. In one patient (3%), the serum calcium concentra-

‡ We are grateful to the Philadelphia Quartz Corporation, Valley Forge, PA, for providing this material.

tion did not fall postoperatively, presumably the result of an undetected supernumerary parathyroid gland. The remaining 24 patients required transient replacement therapy for 1.5 ± 2.2 months (range: 1–10 months).

A sustained differential elevation (13.7 fold ± 2.7, SEM) of PTH (grafted compared to nongrafted antecubital vein plasma) was documented in 35 (97%) patients following autotransplantation and the PTH level in antecubital vein blood from the grafted arm increased with time (Fig. 2).

Of the 21 patients undergoing first surgery for hyperparathyroidism, postoperative hypercalcemia developed in seven (64%) of 11 patients with FPH and in none of the ten patients with NFPH (Fig. 3). Of nine patients with persistent or recurrent hyperparathyroidism who were re-explored and who had parathyroid glands resected and immediately autografted, three (33%) (one with FPH and two with NFPH) developed postoperative hypercalcemia. None of the six patients who were re-explored and later autografted with cryopreserved parathyroid tissue developed hypercalcemia postoperatively (Fig. 3).

Excluding the two patients who required permanent replacement therapy and the one patient with persistent postoperative hypercalcemia, graft dependent hyperparathyroidism developed in ten (30%) of 33 patients. Eight of the patients were from the group with FPH (8/14, 57%) and two were from the group with NFPH (2/19, 11%; FPH versus NFPH, $p < 0.005$).

In five (4 with FHHH and 1 with NFPH) of the 10 patients with recurrent graft dependent hypercalcemia, approximately half of the transplanted parathyroid tissue was resected. Currently the serum calcium concentrations are normal (9.9, 9.7. 8.7 and 8.5 mg/dl) in four of these patients and borderline elevated (10.2 mg/dl) in one patient. Five of the ten patients have developed recurrent but mild hypercalcemia in the last six to nine months and will probably require partial graft resection in the future.

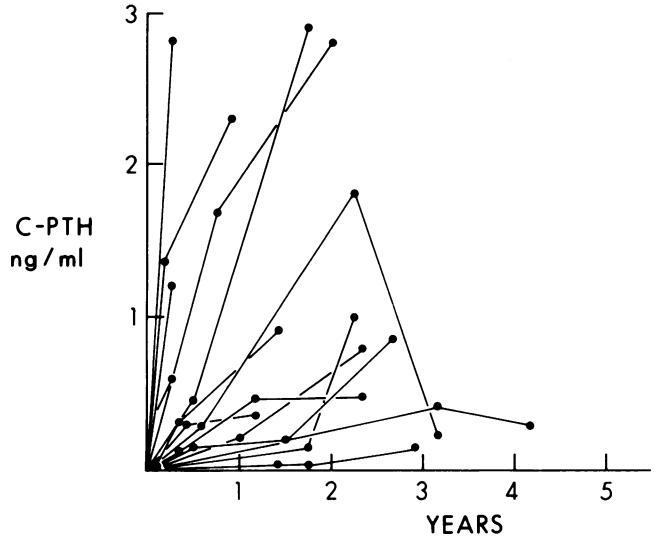

FIG. 2. Serial parathyroid hormone levels in the antecubital vein plasma of the grafted arm depicted as a function of time. All of the patients depicted had familial parathyroid hyperplasia.

Discussion

Since our first report of total parathyroidectomy and autotransplantation in patients with primary parathyroid hyperplasia, concern has been voiced regarding its use.[8,10] It was questioned whether the incidence of recurrent hyperparathyroidism or of hypoparathyroidism was sufficiently high following three and one-half gland parathyroidectomy to merit consideration of an alternative technique. It was feared that many patients would experience prolonged hypocalcemia postoperatively and that parathyroid graft failure would frequently occur. It was also felt that should a supernumerary parathyroid gland be present, its management would be complicated by the existence of functioning parathyroid tissue at the transplant site. Our data show that these concerns are largely unwarranted. Parathryoid tissue can be successfully autografted in virtually all patients and there is a very low incidence of late graft failure. In only two (5.6%) of the 36 patients did the parathyroid autograft fail to maintain the host in a normocalcemic state and one of these had a functioning parathyroid graft as determined by PTH measurements but remained hypocalcemic despite supplementation with large amounts of vitamin D and calcium. In the other patient there apparently was a technical error in freezing and the grafted tissue did not function.

The length of replacement therapy is no more than four to six weeks in most patients and nine (27%) of 33 patients with functioning grafts never required oral vitamin D or calcium supplementation. The apparent length of time for vascular ingrowth and graft function to develop is approximately 10–20 days following implantation. This observation closely parallels our previous studies in experimental animals.[18] The presence of an undetected fifth gland can be inferred from the absence of the characteristic hypocalcemia developing immediately after parathyroidectomy.

With time there appears to be a progressive increase in the PTH level measured in antecubital vein blood emanating from the grafted arm. Furthermore, ten (33%) of the 33 patients with functioning grafts have already developed graft dependent hypercalcemia. Recurrent hypercalcemia has occurred in 100% of our patients with familial hypocalciuric, hypercalcemic hyperparathyroidism. These problems can be

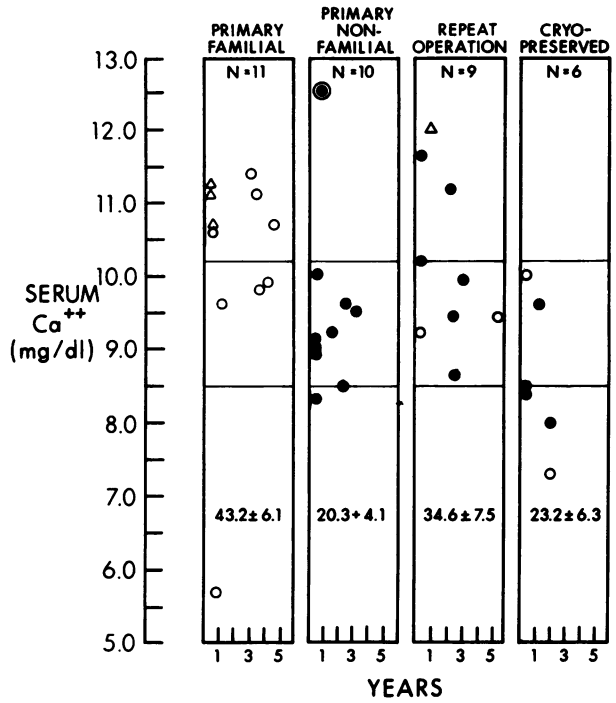

FIG. 3. Serum calcium concentrations (mg/dl) of patients with primary hyperparathyroidism due to generalized parathyroid hyperplasia who were undergoing parathyroidectomy and autotransplantation. The open triangles = patients with familial hypocalciuric, hypercalcemic hyperparathyroidism. Open circles: patients with MEN I or MEN II. Closed circles: patients with nonfamilial parathyroid hyperplasia. Circle within a circle: the patient with persistent postoperative hyperparathyroidism. N: number of patients in each group and the numbers in the lower part of each column denote the average length of follow-up ± SEM (in months) since parathyroid grafting.

relatively easily corrected by resecting a portion of the autografted parathyroid. All five patients with graft-dependent hypercalcemia who were treated by partial graft resection became normocalcemic; however, one is currently intermittently hypercalcemic.

If parathyroid autografts had not been performed in the 15 patients re-explored for hyperparathyroidism, they would have been rendered aparathyroid. The method for cryopreserving parathyroid tissue allows a margin of safety whereby the surgeon may observe the course of the patient following parathyroid gland resection and then autograft tissue if it becomes obvious that the patient is aparathyroid. The length of time following reoperation at which patients should be maintained on replacement therapy before transplanting cryopreserved tissue is at present unclear. All of our patients have been grafted between two and six months following parathyroidectomy.

The technique of parathyroid autotransplantation with or without cryopreservation offers great utility to the surgeon in treating patients with primary hyperparathyroidism. Our results suggest that it may provide the optimal therapy in subjects with familial hyperparathyroidism and in patients undergoing re-exploration for persistent or recurrent hyperparathyroidism.

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