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The Management of Primary Hyperparathyroidism

Michael Kleerekoper, MD*

In the hands of a skilled parathyroid surgeon, parathyroidectomy (PTX) is a curative procedure for primary hyperparathyroidism (PHPT) more than 95% of the time. Why then do we need to discuss the management of PHPT further? Why are not all patients whose diagnosis is firmly established on clinical and biochemical grounds sent to a skilled parathyroid surgeon for elective PTX? The questions that remain are really philosophical: What is meant by "cure" of PHPT? Which patients with PHPT have a disease that needs a "cure"?

During the past two decades, many patients with PHPT have had the diagnosis considered because of a chance finding of hypercalcemia on a biochemical screen, performed either as a routine measure in a well patient or as a screening test ordered for other reasons in an ill patient. Today, most patients with PHPT present in this way, rather than as the more classic patient with "stones, bones and abdominal groans."

Most consultants to whom patients with PHPT are referred develop arbitrary criteria that mandate PTX at the time of diagnosis. These include signs or symptoms directly referable to hypercalcemia, nephrolithiasis, skeletal disease, peptic ulcer disease, pancreatitis, or impaired renal function. Most physicians have a limit point for hypercalcemia above which all patients are referred for PTX. While this arbitrary criterion varies among physicians, most accept a limit of 11.5 to 12.0 mg/dl.

In the now-classic study conducted at the Mayo Clinic (1), a large number of patients with asymptomatic PHPT was followed prospectively up to 10 years after the initial diagnosis. Twenty percent of the patients were lost to follow-up during the observation period, and 20% of the patients had progression of the disease so that PTX was indicated. In retrospect, it was apparent that a substantial number of patients in whom the disease was considered to have progressed were initially misclassified and that the rate of progressive disease may be less than that which was observed. A defect in the study design was the failure to assess the effect of successful PTX on the natural history of the disease. In addition, this study was undertaken before sophisticated techniques for measuring bone mass (and the effect of PTH excess on bone mass) were available. These problems were addressed by two papers in this section of the Symposium.

The first of these, by Posen and his colleagues (pp. 154ff.), was a retrospective analysis of 128 cases which were reviewed an average of 7.8 years after "successful" PTX. This study provided some surprising and challenging observations. Although 15% of the patients had died dur-
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ing the follow-up period, death could be attributed to surgery in only one case. Whether the death rate reflects the fact that prevalence of PHPT increases with age or whether PHPT contributed to irreversible deterioration in function before surgery could not be ascertained from this study. In contrast to other studies, PTX did not appear to have an entirely protective effect against the development of nephrolithiasis. No patient who was free of stones before PTX developed stones during the postoperative follow-up. However, in the 70% of patients who had nephrolithiasis before surgery, no significant reduction occurred in the number of patients who developed recurrent stones. Successful PTX did not have an appreciable effect on hypertension present in 40-50% of the patients, nor did it restore impaired renal function. Using crude radiographic assessment, the authors found no improvement in the prevalence or degree of osteoporosis after PTX.

Neer and his colleagues from the Massachusetts General Hospital presented similar observations on 45 patients followed prospectively for three years after successful PTX. These patients all had mild, asymptomatic PHPT before surgery. The decision to operate was based on the presence of impaired renal function or, more frequently, on the presence of osteopenia (bone mineral content more than two standard deviations below expected for age, sex, and race). Two patients developed kidney stones during the follow-up period. As a group, there was no improvement in blood pressure or in renal function, nor was there any restoration of the deficit in bone mineral content. Perhaps of greater importance was the failure of PTX to slow the rate of bone loss when the group was considered as a whole, although such deceleration was observed in some patients.

Posen, et al also reported findings in 32 patients who were observed for an average of 6.6 years after unsuccessful neck exploration for PHPT. There were four deaths in this group (12.5%), one of which resulted from progressive vertebral fractures and respiratory failure, presumably a manifestation of progressive osteitis fibrosa. As was the case with the successfully treated patients, kidney stones did not occur in those patients who were free of stones preoperatively. They found no other evidence for progression of PHPT.

A noteworthy and challenging observation was the seemingly high prevalence of nonparathyroid malignancy in those patients who remained hypercalcemic after surgery. In the successfully treated group, eight of 128 (6%) developed a variety of malignancies. However, seven of the unsuccessfully treated group (22%) developed malignancy (p<0.01). There have been several reports of increased prevalence of nonparathyroid malignancy in PHPT when compared to the general population, but it has never been clearly established whether this is more than the chance occurrence of two relatively common conditions in an aging population. The observation by Posen, et al focuses attention on this potential "complication" of PHPT. If hypercalcemia, elevated PTH levels, or perhaps PHPT itself is in some way "mitogenic," it is surprising that evidence for this fact was not found in the 10-year prospective study at the Mayo Clinic. The prevalence of malignancy in a separate group of 74 patients who did not have surgery is not known but would be of interest.

If successful PTX is without obvious benefit in patients with mild PHPT, has anything new been learned since the Mayo Clinic study of patients who were not operated? Neer and his colleagues reported their three-year study of a small number of such patients. Like the Mayo Clinic experience, the drop-out rate was relatively high (12%), an occurrence which must be carefully considered whenever a decision to follow a patient with PHPT is undertaken. During a three-year period, the Boston group detected no significant progression of the disease, as evidenced by serum calcium and inorganic phosphate levels, urine calcium excretion, renal function, and bone mineral content. Several anecdotal reports exist of patients with established mild PHPT who developed sudden marked rises in serum calcium while under observation. Since at present no way of predicting this rare, life-threatening complication is known, every attempt must be made to ensure continuous observation of all patients with PHPT who do not undergo elective PTX at the time of initial diagnosis.

Wells and Leight (pp. 152 ff.) described the type of surgery required for patients with PHPT, highlighting their experiences at Duke University in North Carolina and Washington University in St. Louis. Most surgeons prefer to identify all four parathyroid glands at the time of initial neck exploration. The surgeon should rely on his or her own skill at identifying parathyroid tissue and resect those glands that appear macroscopically enlarged (≥50 mg). At the time of surgery, the role of the pathologist is to confirm that resected tissue is indeed parathyroid, and the surgeon should not rely on the descriptive terms "parathyroid adenoma" and "parathyroid hyperplasia".

Of 350 patients observed over a five-year period, 68% had a single enlarged gland, 22% had two or three enlarged glands, and 10% had four enlarged glands. During a four-year follow-up, PHPT did not recur in any patient with single gland enlargement and recurred in only one patient with two or three gland enlargement.
Patients with four gland enlargement have been managed by total parathyroidectomy and autotransplantation of tissue in the forearm muscle. The incidence of graft failure was less than 5%. Of patients with four gland enlargement, 36% had familial hyperparathyroidism. The incidence of recurrent hypercalcemia in patients with four gland enlargement without familial hyperparathyroidism was 15%.

There remains a group of patients with PHPT in whom elective surgery would normally be recommended, but because of other medical considerations they are at too great a risk for elective surgery. There is also a growing group of patients for whom surgery is recommended but who decline surgical intervention. Bilezikian (pp. 159 ff.) from Columbia University outlined medical alternatives for these patients. General principles of management include maintaining adequate hydration and avoiding immobilization and thiazide diuretics. There is limited evidence that restriction of dietary calcium is of benefit. However, if one demonstrates increased intestinal absorption of calcium or elevated 1-25 dihydroxy cholecalciferol levels, dietary restriction of calcium might be beneficial.

Drug therapy to inhibit parathyroid secretion (e.g., beta-adrenergic-blockade and histamine receptor antagonists) or to inhibit the action of PTH on bone (e.g., estrogens, calcitonin, diphosphonates) has not been helpful in most centers. However, scattered case reports exist of a short-term reduction in serum calcium with some of these drugs. Estrogens have the most potential benefit, particularly in postmenopausal women with PHPT. While the serum calcium may not be normalized by administration of estrogen, the rate of bone loss may be decreased.

**Summary and Conclusions**

If performed by a skilled parathyroid surgeon, elective parathyroidectomy is a simple, safe, and effective means of curing PHPT in more than 95% of cases. No equally effective medical therapy exists for this disease, although the administration of estrogens to postmenopausal women with PHPT holds promise of decreasing the rate of bone loss. Many patients, perhaps the majority, derive no clinical benefit from having their disease “cured” by PTX. What is not currently available from the data, either in the published literature or in the material presented at this Symposium, is the means to predict accurately at the time of diagnosis which patient is likely to develop complications if not cured. To the classic list of “stones, bones, and abdominal groans” that complicates PHPT must be added a possible increased occurrence of non-parathyroid malignancy in untreated patients. If close observation during follow-up after diagnosis can be assured, only a small number of patients will develop major complications (such as life-threatening hypercalcemia) if left untreated. Careful observation must remain an important caveat, since two prospective studies have documented a 12% and 20% drop-out rate during three and 10-year follow-up periods, respectively.

**References**