Reproductive Endocrinology

The role of parathyroid hormone measurements after surgery for primary hyperparathyroidism

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Background. *During parathyroidectomy for primary hyperparathyroidism (pHPT), intraoperative parathyroid hormone (IOPTH) levels are used to confirm removal of all hyperfunctioning parathyroid tissue. The phenomenon of elevated parathyroid hormone (PTH) levels with normocalcemia after curative parathyroidectomy, seen in up to 40% of patients, continues to be an unexpected and unexplained finding. We therefore investigated whether postoperative PTH levels are as reliable as IOPTH levels in predicting cure after surgery for pHPT.*
Methods. *We reviewed our prospective database of consecutive patients undergoing surgery for pHPT between December 1999 and November 2004. Curative parathyroidectomy was defined as normocalcemia 6 months or longer postoperatively.*
Results. *A total of 328 patients who underwent 330 operations for pHPT had IOPTH measurements and serum follow-up calcium levels at 6 months or longer. Surgery was curative in 315 (95.5%) operations. IOPTH levels correctly predicted operative success in 98.2% (positive predictive value [PPV]. Postoperatively, the PPV of a normal PTH level at 1 week, 3 months, and 6 months was 97.1%, 97.3%, and 96.5%, respectively. Of all patients with an elevated postoperative PTH level at 1 week, 3 months, or 6 months, only 13.7%, 14.3%, and 14%, respectively, were not cured.*
Conclusions. *Normal postoperative PTH levels reliably predict operative success. However, they do not improve upon results predicted by IOPTH levels. Elevated postoperative PTH levels do not predict operative failure in most patients. We propose that PTH measurements after surgery for pHPT may be misleading, costly, and not indicated in normocalcemic patients. (Surgery 2006;140:665-74.)*

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INTRODUCTION

The only definitive treatment for primary hyperparathyroidism (pHPT) is curative parathyroidectomy, which is defined by normocalcemia after surgery. Intraoperative parathyroid hormone (IOPTH) determination has been demonstrated to be an excellent predictor of cure.[1-5] Since the initial description in 1991 by Irvin et al,[6] IOPTH has become a widely used adjunct, enabling more focused or minimally invasive parathyroidectomies to be performed. In the setting of multiple gland disease (MGD) or reoperations for recurrent or persistent hyperparathyroidism (HPT), IOPTH monitoring has proved to be helpful.[1,7-10] The positive predictive value (PPV) of IOPTH for successful parathyroidectomy, as defined by a variety of criteria, ranges from 78% to 99%, whereas the false positive rate (incorrectly predicting a successful operation) is low, ranging from 1% to 3%.[1-3,11]

Parathyroid hormone (PTH) and serum calcium measurements are frequently obtained after parathyroidectomy. After curative parathyroidectomy, 20% to 40% of patients have been reported to have elevated PTH levels despite normocalcemia.[2,12-18] The finding of an elevated PTH level following parathyroid surgery often raises great concern for

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the patient and referring physician. These patients are often subjected to additional laboratory testing, incurring additional costs and anxiety. Although many studies have explored the potential causes and natural history of this phenomenon of postoperative PTH elevation with normocalcemia after curative parathyroidectomy, few have included large numbers of patients with follow-up evaluation of serum calcium levels at 6 months or longer to establish the true significance of this phenomenon.[2,12-24]

In summary, IOPTH monitoring has been shown to predict long-term cure after parathyroidectomy in approximately 98% of cases. In contrast, the role of postoperative PTH measurements in predicting long-term cure after parathyroidectomy is less well studied. It remains unclear whether these measurements are helpful or even necessary. The aim of this study was to determine whether postoperative PTH measurements are as accurate as IOPTH levels in predicting cure after parathyroidectomy for pHPT.

METHODS

After institutional IRB approval was obtained, we reviewed the medical records of all patients in our prospective database who underwent parathyroidectomy at 1 institution (Froedtert Memorial Lutheran Hospital/Medical College of Wisconsin) between December 1999 and November 2004. A total of 450 patients underwent 455 operations for HPT. Inclusion criteria for this study were patients undergoing surgery for pHPT who had complete IOPTH monitoring information and a follow-up serum calcium level documented at 6 months or longer. Therefore, of these 455 operations, 125 (27.5%) were excluded: 13 were operations for secondary or tertiary HPT, 6 had incomplete IOPTH information, and 106 did not have a postoperative calcium value documented at 6 months or longer. The study cohort thus was composed of 328 patients who underwent 330 operations.

All patients completed our preoperative localization protocol consisting of neck ultrasound and sestamibi scan, as described previously.[7] Operations included minimally invasive parathyroidectomy (removal of 1 parathyroid gland through a small incision); a unilateral neck approach, involving identification of both parathyroid glands on the same side of the neck without exploring the contralateral side; or a standard bilateral cervical exploration with 4-gland identification.

Our protocol for IOPTH monitoring includes drawing blood from a peripheral vein catheter. On rare occasions, blood draws from an arterial line or internal jugular vein may be performed. IOPTH values are determined in the operating room per protocol using the QuiCk-IntraOperative Intact PTH assay, a 2-site immunochemiluminometric assay (Nichols Institute Diagnostics, San Juan Capistrano, Calif). A PTH value is determined at "baseline" (after anesthesia induction and before incision) and at "time zero" (at the time of parathyroid gland removal). Blood samples for PTH levels are then drawn at 5 minutes and 10 minutes after resection of each adenoma or enlarged parathyroid gland. Our criteria for concluding an operation is an IOPTH value at 10 minutes postresection of the last parathyroid gland that is at least 50% below the "baseline" or "time zero" value, whichever is highest, and is within the normal range of the IOPTH assay (10 to 65 pg/mL). These IOPTH criteria will be referred to as the "50% and normal" criteria.

For this study, operative success or curative parathyroidectomy was defined as normocalcemia at 6 months or longer postoperatively. Cases not meeting this standard were considered operative failures. Operative failures were placed into 3 categories depending on the time of failure: intraoperative, immediate, and delayed. Intraoperative failures were defined as cases not meeting the 50% and normal IOPTH criteria with persistently elevated postoperative calcium levels. Immediate failures were defined as cases meeting the 50% and normal IOPTH criteria but having persistent hypercalcemia first documented at the 1-week postoperative visit. Delayed failures were defined as cases meeting the 50% and normal IOPTH criteria, with normal initial postoperative calcium levels followed by hypercalcemia at follow-up 6 months or longer.

Data on demographic, surgical, and intraoperative factors were collected prospectively and included intraoperative findings and IOPTH values, parathyroid gland weight and final pathology, and postoperative PTH and calcium levels at 1 week and at 3, 6, and 12 months. All 1-week and any other postoperative PTH measurements performed at our outpatient clinic were determined by the ADVIA Centaur Intact PTH assay (Bayer HealthCare, Tarrytown, NY). Prior to September 24, 2002, the normal assay range was 10 to 65 pg/mL. Since September 24, 2002, the normal assay range is 14 to 72 pg/mL. After the 1-week postoperative visit, patients did not routinely follow-up with their endocrine surgeon. Therefore, not all patients had calcium and PTH values at the 3-, 6-, and 12-month intervals because our referring physicians performed these labs at their discretion. Patients were classified as having single gland disease (SGD)

Table I. Prediction outcomes used for analysis

Criteria	*Operative cure**	*Operative failure†*
Meet IOPTH criteria‡ or have normal postoperative PTH level	True positive (TP)	False positive (FP)
Do not meet IOPTH criteria or have elevated postoperative PTH level	False negative (FN)	True negative (TN)

IOPTH, Intraoperative parathyroid hormone; *PTH,* parathyroid hormone.
*Operative cure defined as normocalcemia at least 6 months postoperatively.
†Operative failure defined as persistent hypercalcemia at 6 months or longer after parathyroidectomy.
‡IOPTH criteria include an IOPTH value at 10 minutes postresection of the last parathyroid gland that is at least 50% below either the "baseline" or "time zero" value, whichever is highest, and is within the normal range of the IOPTH assay.

when only 1 abnormal gland was identified and removed or as having MGD when more than 1 abnormal gland was identified and removed.

Operative outcome, IOPTH, and postoperative PTH values were analyzed to determine accuracy in predicting operative cure (Table I). True positive (TP) was defined as the correct prediction of operative cure; true negative (TN) was defined as the correct prediction of operative failure; false positive (FP) was defined as the incorrect prediction of operative success; and false negative (FN) was defined as the incorrect prediction of operative failure. Positive predictive value (PPV), the ability to predict a curative operation, was defined as TP cases divided by the sum of TP and FP cases. The negative predictive value (NPV), the ability to predict operative failure, was defined as TN cases divided by the sum of TN and FN cases. All PPVs and NPVs were determined using the definition of a curative parathyroidectomy as normocalcemia at least 6 months postoperatively.

Statistical analysis. Descriptive statistics were used to summarize the data. To investigate how IOPTH and postoperative PTH levels predicted a curative operation, PPVs and NPVs were generated. To compare the PPV of our IOPTH criteria to that of the postoperative PTH levels at 1 week, 3 months, and 6 months, 95% confidence intervals of the difference of each pair comparison were performed. Statistical analysis was performed using SAS software (SAS, ver 9; SAS Institute, Cary, NC).

RESULTS

Of the 328 pHPT patients studied, 254 (77%) were female and 74 (23%) were male. The median age at diagnosis was 57 years (range, 17 to 91). The median preoperative calcium concentration was 11.1 mg/dL (range, 9.1 to 13.8 mg/dL) and PTH level was 111.6 pg/mL (range, 41 to 630 pg/mL). Twenty-four (7.3%) cases were reoperations for pHPT. Of the 330 operations, SGD was found in 287 (87.0%), MGD in 41 (12.4%), and no parathyroid glands were identified in 2 patients. Curative parathyroidectomy was performed in 315 (95.5%) cases.

Prediction of operative cure. Of the 330 operations, 287 met the 50% and normal IOPTH criteria. Of these 287 operations, 282 (98.2%) were normocalcemic at 6 months or longer postoperatively (TP cases). Therefore, the ability of our IOPTH criteria to predict a curative operation (PPV) was 98.2%, as shown in Table II.

Of the 330 operations, postoperative PTH levels were obtained in 290 (88%) cases at 1 week, 153 (46%) at 3 months, and 157 (47.6%) at 6 months. As shown in Table II, normal PTH levels at various time points after surgery also predicted operative cure quite accurately. The PPV of a normal postoperative PTH level at 1 week, 3 months, and 6 months was 97.1%, 97.3%, and 96.5%, respectively. The 95% confidence intervals of the difference between the PPV of our IOPTH criteria and the PPV of the postoperative PTH level at 1 week, 3 months, and 6 months revealed that normal postoperative PTH levels are equivalent to the 50% and normal IOPTH criteria in predicting a curative operation.

Operative failures. There were a total of 15 failed operations, which are summarized in Table III. Four failures had MGD, of which none had multiple endocrine neoplasia (MEN). Of the 15 failures, 5 met the 50% and normal IOPTH criteria to conclude an operation (FP cases, Cases no.11 to 15), whereas 10 did not (TN cases, Cases no.1 to 10).

The 5 FP cases represent 3 immediate failures and 2 delayed failures. The 3 immediate failures all underwent parathyroidectomy with IOPTH values that met our criteria to conclude an operation. However, postoperative 1-week calcium values were elevated, which persisted at 1-year follow-up for all 3 patients. At 1-year follow-up, PTH values were normal in 1 patient, elevated in 1 patient, and unknown in the third patient.

Table II. Ability of IOPTH criteria and normal postoperative PTH levels to predict operative cure

Lab value	*Ability to predict cure (PPV; %)**
50% and normal IOPTH criteria	98.2*
Normal postoperative PTH level	
1-week	97.1
3-month	97.3
6-month	96.5

IOPTH, Intraoperative parathyroid hormone; *PPV,* positive predictive value; *PTH,* parathyroid hormone.
*The 95% confidence intervals of the difference between the PPV of our IOPTH criteria and the PPV of the postoperative PTH level at 1 week, 3 months, and 6 months revealed that normal postoperative PTH levels are equivalent to the 50% and normal IOPTH criteria in predicting a curative operation.

The 2 delayed failures underwent parathyroidectomy, had IOPTH values that met our criteria to conclude an operation, and had normal 1-week calcium values. However, in 1 patient, follow-up calcium value at 6 months was elevated (10.8 mg/dL) with a normal PTH value. In the second patient, follow-up calcium value at 1 year was minimally elevated (10.6 mg/dL) with an elevated PTH value.

Prediction of operative failure by IOPTH values. Of the 330 operations, 43 did not meet the 50% and normal criteria to conclude an operation. However, only 10 (23.2%) of these 43 operations were proven to be actual failures (TN cases). Therefore, the ability of the 50% and normal IOPTH criteria to predict a failed operation (NPV) is only 23.2% (Table IV). Of the 33 patients who did not meet our IOPTH criteria but were normocalcemic at 6 months or longer postoperatively (FN cases), 23 (70%) did not undergo further neck exploration. All 23 demonstrated a 50% drop in IOPTH levels at 10 minutes after resection and had IOPTH values in, or close to, the normal range at time points later than 10 minutes after resection. The remaining 10 patients (30%) underwent further neck exploration, and 3 of the 10 had additional parathyroid glands removed.

Prediction of operative failure by postoperative PTH values. Elevated postoperative PTH levels at various time points did not predict operative failure well (Table IV). At 1 week, 51 patients had elevated PTH levels. Only 7 of these 51 patients (13.7%) would prove to have failed operations (TN cases). In other words, an elevated postoperative PTH level at 1 week predicted failure (NPV) in 13.7% of cases. Similarly, the ability of an elevated postoperative PTH level at 3 months and 6 months to predict failure was 14.3% and 14%, respectively.

This finding that elevated postoperative PTH levels do not predict operative failure well is illustrated in a different fashion in the Fig 1. This graph shows the percent of cured patients who had elevated postoperative PTH values at various time points. Of the cured patients with documented postoperative PTH values, 15.9% (44/276) had elevated PTH values at 1 week, 25% (36/144) had elevated PTH values at 3 months, and 25.2% (37/147) had elevated PTH values at 6 months.

Table V summarizes the postoperative PTH trends in all 330 parathyroidectomies that had documented postoperative calcium values at 6 months or longer. As discussed previously, of the 287 operations that met our IOPTH criteria, 5 proved to be failures (immediate or delayed). Of the remaining 43 cases that did not meet our IOPTH criteria, 10 proved to be failures (intraoperative). Among these 15 failures, the postoperative PTH levels fluctuated between elevated and normal values.

Similarly, evaluation of the 315 curative parathyroidectomies, regardless of whether they met our IOPTH criteria, revealed that postoperative PTH levels could be elevated initially and remain elevated, normalize, or fluctuate over time. Furthermore, if the initial 1-week postoperative PTH was normal, subsequent PTH measurements could remain normal or elevate over time. Although we do not have values on every patient at every time point, our data demonstrate that postoperative PTH values fluctuate over time and do not predict failure well.

DISCUSSION

This study was composed of 328 patients who underwent 330 operations for pHPT and had doc-

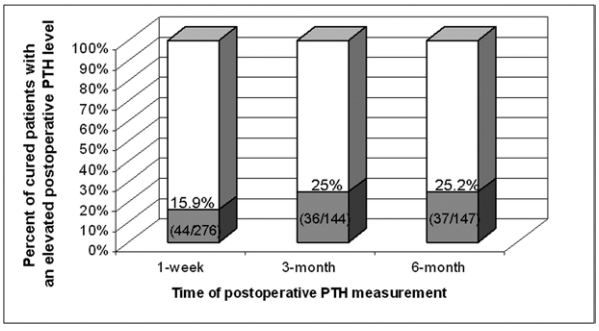

Fig 1. Percent of surgically cured patients with an elevated PTH value at 1 week, 3 months, or 6 months postoperatively. *PTH,* parathyroid hormone.

Table III. Characteristics of 15 operative failures

Case no.	*Age/gender*	*Previous parathyroid surgery*	*IOPTH criteria met*	*Comments*
1	74/F	No	No	940-mg adenoma removed.
2	71/F	No	No	135-mg adenoma removed; inferior glands not identified.
3	51/F	No	No	4 normal glands identified and biopsied; no glands removed.
4	51/F	No	No	No glands identified after thymectomy and bilateral neck exploration.
5	42/M	Yes	No	Total removal of 3 glands (200 mg, 490 mg, 200 mg), and right thyroid lobectomy.
6†	64/F	Yes	No	Parathyrocytosis, possible parathyroid cancer.
7†	64/F	Yes	No	Parathyrocytosis, possible parathyroid cancer.
8	54/F	No	No	3 normal glands identified and biopsied; fourth not identified; no glands removed.
9	54/F	No	No	Removal of 2 glands and left thymectomy; 2 remaining normal glands identified and biopsied.
10	65/F	No	No	3-gm adenoma removed.
11	58/F	No	Yes	678-mg adenoma removed.*
12	63/F	No	Yes	4-gland hyperplasia; 3 removed.*
13	65/F	No	Yes	125-mg adenoma removed.*
14	63/F	No	Yes	746-mg adenoma removed; hypercalcemic at 1 year.*
15	57/F	No	Yes	2.8-gm adenoma removed; hypercalcemic at 6 months.*

IOPTH, Intraoperative parathyroid hormone; *F,* female; *M,* male.
*See text for details.
†Cases no.6 and 7 represent the same patient.

Table IV. Ability of IOPTH criteria and elevated postoperative PTH levels to predict operative failure

Lab value	*Ability to predict failure (NPV; %)*
50% and normal IOPTH criteria is not met	23.2
Elevated postoperative PTH level	
1-week	13.7
3-month	14.3
6-month	14

IOPTH, Intraoperative parathyroid hormone; *PTH,* parathyroid hormone; *NPV,* negative predictive value.

umented IOPTH values and postoperative serum calcium levels at 6 months or longer. Curative parathyroidectomy was defined as normocalcemia at 6 months or longer postoperatively. Defining a cure after parathyroidectomy is dependent on an adequate follow-up period. The follow-up time in published clinical papers is variable, ranging from days to years postoperatively. The postoperative 6-month calcium value is generally used to define persistent or recurrent HPT. Patients with an elevated calcium level up to 6 months postoperatively are thought to have persistent HPT due to inadequate initial parathyroidectomy; those with recurrent HPT have normocalcemia for at least 6 months after surgery, followed by hypercalcemia some time thereafter. We therefore decided to include only patients with documented follow-up of 6 months or longer in our study, realizing that an even longer time period would be optimal. In 1 study with a mean follow-up of 10 years after parathyroidectomy for pHPT, approximately 5% of patients developed recurrent hyperparathyroidism.[25]

Our results revealed that the 50% and normal IOPTH criteria predict operative success well, with a PPV of 98.2%. This value is in agreement with other studies.[1-3] Furthermore, by using our IOPTH criteria, the ability to predict failure is poor, with a NPV of only 23.2%. As discussed previously by our group, we continue to use our stringent IOPTH criteria specifically to increase our ability to find MGD and get better curative results.[7] We believe

Table V. Trend of postoperative PTH levels at 1 week, 3 months, and 6 months in 330 parathyroid operations

Postoperative PTH levels			*No. with hypercalcemia at ≥6 months*	*Failure type**
1-week (n)	*3-month (n)*	*6-month (n)*		
Elevated (51)	Elevated (14)	Elevated (7)	3	2 A; 1 B
		Normal (3)	0	
		Unknown (4)	2‡	2 A
	Normal (9)	Elevated (4)	0	
		Normal (4)	0	
		Unknown (1)	0	
	Unknown (28)	Elevated (7)	1	1 A
		Normal (3)	0	
		Unknown (18)	1§	1 C
Normal (239)	Elevated (24)	Elevated (10)	1	1 A
		Normal (9)	0	
		Unknown (5)	0	
	Normal (100)	Elevated (7)	1	1 A
		Normal (63)	2	1 B; 1 C
		Unknown (30)	0	
	Unknown (115)	Elevated (7)	0	
		Normal (27)	2	1 A; 1 B
		Unknown (81)	1§	1 A
Unknown† (40)	Elevated (4)	Elevated (0)	0	
		Normal (2)	0	
		Unknown (2)	0	
	Normal (2)	Elevated (0)	0	
		Normal (1)	0	
		Unknown (1)	0	
	Unknown (34)	Elevated (1)	0	
		Normal (2)	0	
		Unknown (31)	1§	1 A

PTH, parathyroid hormone.
*Failure type: A = *intraoperative*, defined as cases not meeting the 50% and normal IOPTH criteria with persistently elevated postoperative calcium levels; B = *immediate*, defined as cases meeting the 50% and normal IOPTH criteria but having persistent hypercalcemia first documented at the 1-week postoperative visit; C = *delayed*, defined as cases meeting the 50% and normal IOPTH criteria, with normal initial postoperative calcium levels followed by hypercalcemia at 6 months or longer.
†Unknown, defined as no documented PTH value.
‡One patient underwent reoperation at 6 months and was subsequently cured; the other has persistently mild hypercalcemia at 1 year with an elevated 3-month PTH value but no documented subsequent PTH values.
§No documented 6-month PTH values but elevated 1-year PTH and calcium values.

that, since IOPTH criteria has such a poor NPV, it should not be used alone as a criteria to predict a failed operation. We emphasize that the prediction of a noncurative operation should incorporate not only the IOPTH criteria values but also IOPTH values at later time points after resection, as well as intraoperative findings, patient history and previous surgeries.

As illustrated in Table II, we demonstrate that normal postoperative PTH levels at various time points predict operative success well, with PPVs ranging from 96.5% to 97.3%. However, they do not improve upon results predicted by our IOPTH criteria (PPV = 98.2%). Furthermore, this study demonstrates that elevated postoperative PTH values do not mean operative failure in the majority of patients (Table IV).

Finally, we demonstrate that postoperative PTH levels fluctuate over time. Of the cured patients with documented postoperative PTH values, 15.9% had elevated 1-week PTH values, 25% had elevated 3-month values, and 25.2% had elevated 6-month PTH values. These findings are in agreement with other studies that have demonstrated that up to 40% of patients after curative parathyroidectomy have documented elevated postoperative PTH levels despite normocalcemia, and that these levels may increase, stabilize, or normalize over time.[2,12-24]

The biologic significance and pathophysiology of this phenomenon remain to be elucidated. This

phenomenon has been reported to be associated with older age, female gender, higher preoperative PTH levels, larger parathyroid adenomas, vitamin D deficiency, decreased renal function, increased bone turnover, SGD, and peripheral resistance to PTH.[2,12-15,17-21,24] We are currently investigating these possible predictors of this phenomenon in our patient population. Given the high percentage of our patient population with vitamin D insufficiency (52%) and the possible contribution of vitamin D deficiency to this phenomenon, we routinely check a preoperative 25-OH vitamin D level. If there is evidence of vitamin D insufficiency, we replenish vitamin D stores, if possible, preoperatively.

Elevated postoperative PTH levels after curative parathyroidectomy are thought to be largely transient (less than 1 year).[16,17,19] However, several studies with longer follow-up have demonstrated that this phenomenon may persist long term.[2,14,18,20] Although the development of persistent or recurrent HPT has been demonstrated to be less than 5% in these patients,[2,14,17,18,20,23] the possibility of persistent or recurrent HPT must be entertained in this patient population.[15,16,18,20,24] These patients may have abnormal parathyroid glands remaining but have not yet manifested hypercalcemia. The true clinical significance of this phenomenon will not be understood until prospective studies with long-term follow-up are conducted in a systematic fashion. However, until these studies are completed, we believe that routine measurements of PTH levels in patients who are normocalcemic after parathyroidectomy are not indicated clinically.

In summary, normal postoperative PTH levels reliably predict cure after parathyroidectomy for pHPT, but they do not improve upon results predicted by IOPTH criteria. Furthermore, elevated postoperative PTH levels do not predict operative failure in the majority of patients. Given these findings, we believe that PTH measurements after surgery for primary HPT may be misleading, costly, and not indicated in normocalcemic patients. We therefore propose the following algorithm. A calcium level should be obtained postoperatively at 1 to 2 weeks. If normal, it should be repeated at 6 months and then yearly. If the calcium level is elevated at any time point, we recommend checking a PTH level. We believe that this approach will decrease patient and clinician anxiety, decrease costs, and still lead to the timely detection of persistent or recurrent HPT.

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DISCUSSION

Dr Christopher R. McHenry (Cleveland, Ohio): The phenomenon of elevated PTH levels and normocalcemia postoperatively in patients who have been cured of their hyperparathyroidism is common and is now an expected consequence of curative parathyroidectomy. Dr Mittendorf reported our experience in 2002 and documented a 20% incidence of what has now been termed "postoperative secondary hyperparathyroidism."

The exact pathophysiology has yet to be elucidated but is likely a compensatory response to "relative hypocalcemia." This is important to recognize because elevated postoperative PTH levels generate anxiety and concern in both patients and their referring physicians, who think this is indicative of persistent hyperparathyroidism. It is now nice to know we can send a copy of Dr Yen's paper to allay the anxiety of our referring physicians.

Dr Yen, your results are well analyzed and I agree with your conclusion that postoperative PTH measurements do not improve upon results predicted by intraoperative PTH, and, thus, postoperative PTH measurements are not indicated in normocalcemic patients. This will help avoid unnecessary and costly laboratory testing.

Is it necessary that the PTH level fall into the normal range as a criterion for concluding your operation? The problem with this criterion is that the half-life of intact PTH is 3 to 5 minutes and, as a result, patients with a baseline or pre-excision PTH level greater than 300 will not have a PTH decline into the normal range by ten minutes. That means you have either to wait an additional 18 minute turn-around time for a repeat PTH level or continue your exploration. Was this the explanation for the 33 patients with false negative intraoperative PTH levels and the low negative predictive value for your intraoperative PTH?

Can you comment on the explanation for normalization of serum calcium in the 2 cases that you documented in your manuscript that were felt to be failures by the surgeon that ultimately were not? These included one patient who had all 4 of their glands identified and biopsied, but none resected, and a second patient who had a bilateral neck exploration and a cervical thymectomy with no parathyroid glands identified. Both patients had postoperative PTH levels that normalized.

Have you reoperated on the 5 patients who had false positive intraoperative PTH? If so, what was the pathology?

In your manuscript, you report that using intraoperative PTH alone predicted failure of operation in only 23% of patients, but, when combined with surgeon judgment, the ability to predict failure increased to 80%. What specifically was it about the surgeon judgment that improved your ability to predict failure?

Dr Charles E. Lucas (Detroit, Mich): Dr Yen, you convinced us that the postoperative elevation in PTH is not critical when the calcium is normal. This will allay some of the insecurity and paranoia for those of us who do less of these operations than you do. It also demonstrates, in this subset of patients, that the trigger mechanism for the release of PTH is no longer the ionized calcium. The most important issue for me is the cause of this phenomenon. What do you think is the mechanism that leads to the elevated PTH in these patients? What other signaling process are going on? Is it related to bone? Is it related to other illnesses? Rather than not measure the PTH in these patients, I think we should measure them routinely and find out what other signaling is operative.

Dr Carmen Solorzano (Chicago, Ill): How many patients did you operate on that had normocalcemic hyperparathyroidism? For example, there are some patients that have calcium levels of 10.3, 10.5, that don't reach above the upper limit of normal who have elevated PTH, around 100 or so. Some surgeons are operating on those patients. How do you follow these patients postoperatively and what do you consider a cure if they have persistently elevated parathyroid hormone.

I also echo the comments of Dr McHenry about requiring your intraoperative PTH hormone to drop within the normal limit. That is going to increase the number of false negatives. I want to know what you did with those patients. Did you end up waiting for 20 minutes? Or did you try to find more abnormal glands? How did waiting predict the ultimate result?

Lastly, did you find any factors preoperatively or intraoperatively that predicted an increased PTH postoperatively, for example vitamin D 25-OH level, size of the adenoma, the surgical approach that you took—whether it was a focused approach or exploring both sides of the neck? Did you put some of these patients on vitamin D postop because that has been shown to decrease the PTH postoperatively?

Dr E. Christopher Ellison (Columbus, Ohio): I had a question about the methodology for the parathyroid hormone assay. First, was it done in the same lab at all time points postoperatively? And second, what control measures were put into place to assure the accuracy of the test? Could it be that some of these fluctuations simply reflect variability in the assay?

Dr Thomas E. Stellato (Cleveland, Ohio): We are seeing elevations of PTH with normal calcium levels in a small subset of our bariatric patients after gastric bypass. We think that this is at the expense of the bone, that they are maintaining the calcium levels at the expense of their bone. These patients are requiring additional calcium despite the normal calcium levels. Why are you seeing these elevations in PTH levels? What do you think that PTH is responding to?

Dr Tina W. Yen: Dr McHenry's first question refers to our intraoperative parathormone (IOPTH) criteria to conclude an operation. Our criteria are an IOPTH level at 10 minutes postresection of the last parathyroid gland that not only is at least 50% below the baseline value but is also within the normal range of the IOPTH assay. These criteria are more stringent than the "50% drop" criteria that are used at other centers. As previously shown by our group, we have chosen to adhere to these stringent criteria because we can identify more patients with multiple gland disease, and therefore increase our cure rate in patients with multiple gland disease. Given these more stringent criteria, it is true that our false negative rate (10%) is higher than most studies.

With respect to the 33 false negative cases that we did identify, cases that did not meet our IOPTH criteria to conclude an operation but ultimately were cured, 23 (70%) did not undergo further neck exploration. All 23 demonstrated a 50% drop in IOPTH levels at 10 minutes after resection and had additional IOPTH values past the 10-minute postresection mark that either fell into or were close to the normal assay range. As Dr McHenry previously mentioned, these patients had very elevated preoperative PTH levels that just took longer to fall into the normal range after resection. The remaining 10 patients (30%) underwent further neck exploration, and 3 had additional parathyroid glands removed.

Two patients were presumed failures at the conclusion of their operations but were normocalcemic at 6 months. In one patient, 4 glands were identified that were normal in size and on biopsy. The second patient underwent a bilateral neck exploration and cervical thymectomy. No parathyroid glands were identified. The presumed reason why these 2 patients became normocalcemic is that, during their operation, the arterial supply to the hyperfunctioning glands was disturbed, resulting in infarction of the hyperfunctioning glands.

With respect to the 5 false positive cases, cases that met IOPTH criteria to conclude an operation that were ultimately failures, none of these patients underwent reoperations. With follow-up ranging from 6 months to 5 years, all 5 have very mild hypercalcemia.

Dr McHenry's last question refers to our IOPTH criteria's low negative predictive value of only 23%, meaning that only 23% of cases that did not meet our IOPTH criteria were actual failures. This is largely due to our stringent IOPTH criteria. In the manuscript, we explained that the ability to predict a failed operation could be increased to 80% by integrating the IOPTH criteria with intraoperative findings and patient history. So patients that don't meet our IOPTH criteria and in whom we identify only normal glands or perhaps don't identify all glands, we know that they have disease left behind, and we have left the operating room knowing we haven't cured these patients and presume that they will remain hypercalcemic.

Drs Lucas, Solorzano, and Stellato asked about the mechanism responsible for the phenomenon of elevated PTH levels despite normocalcemia after curative parathyroidectomy. This area has been fairly well studied. As Dr McHenry alluded to, it is thought to be a response to relative hypocalcemia due to possibly several reasons, including vitamin D deficiency, decreased renal function, increased bone turnover, and peripheral resistance to PTH. The resulting relative hypocalcemia may be the driving force for an elevated PTH level transiently postoperatively. I agree with Dr Lucas' comment that PTH levels

should continue to be measured for research purposes. However, until the true biologic significance of the phenomenon of elevated PTH levels in the setting of normocalcemia is determined, the routine measurement of PTH levels in patients who are normocalcemic after parathyroidectomy is not clinically indicated.

Dr Solorzano's question about whether we looked at various factors that could be predictive of which patients will have elevated PTH levels postoperatively despite normocalcemia is actually something that we are currently studying and will hopefully present in the near future. As Dr Solorzano alluded to, presumed factors include higher preoperative PTH levels, single gland disease, and larger adenomas that are being removed.

Dr Solorzano asked about the role of vitamin D supplementation. In Milwaukee, about 50% of our patients are vitamin-D deficient. So it is our policy to check 25-OH vitamin D levels preoperatively; if they are low, we try to supplement them either preoperatively or postoperatively. This is a standard practice for us. Finally, we do not routinely offer an operation to patients who are normocalcemic but have elevated PTH levels.

Dr Ellison's question addresses the methodology of the postoperative PTH assay. At least all of our 1-week postoperative PTH levels are drawn at our institution. Our lab uses the ADVIA Centaur intact PTH assay, which is a 2-site sandwich immunoassay. In September 2002, the normal range of the assay changed. I do not know what control measures are used to assure the accuracy of this assay. However, it is certainly possible that some fluctuations in PTH results may be attributable to the assay performance.