



Intraoperative Urinary Cyclic Adenosine Monophosphate as a Guide to Successful Reoperative Parathyroidectomy

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Sixty patients with persistent or recurrent primary hyperparathyroidism underwent reexploration during which urinary cyclic adenosine monophosphate (UcAMP) levels were determined at half-hour intervals by radioimmunoassay. Retrospective analysis of the data allowed us to develop UcAMP criteria for surgical success. Following removal of parathyroid tissue, if an individual UcAMP level dropped 50% from the median baseline level, or if elevated levels dropped to <4.0 nmol/dl glomerular filtrate, surgery was predicted to be successful. Eight unsuccessful procedures in seven patients produced no decline in UcAMP, and the intraoperative results accurately predicted surgical failure. Fifty-three patients underwent successful procedures and in every case UcAMP fell. Ninety-eight per cent of these successful procedures were predicted by our criteria. Levels of UcAMP fell 1.5 ± 0.5 hours ($\bar{x} \pm SD$) following abnormal parathyroidectomy. In 19 of 36 successful cases diagnosed before surgery as adenoma, the operative procedure was terminated before a significant drop in UcAMP. In 16 of 17 successful cases diagnosed before surgery as hyperplasia or uncertain histology, UcAMP fell during the operation. Intraoperative determination of UcAMP is helpful in reoperative parathyroid surgery. The criteria established allow intraoperative prediction of success with remarkable accuracy. Urinary cyclic AMP is especially helpful in reoperation for multigland disease; when enough pathologic tissue has been removed, the criteria will be met and the procedure may be terminated with confidence.

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PERSISTENT HYPERPARATHYROIDISM, following cervical or mediastinal exploration for primary hyperparathyroidism, occurs in 5% to 15% of initial procedures and perhaps more frequently.¹⁻³ The subsequent care of these patients remains a challenge for the internist, radiologist, and surgeon.^{2,4-10} Success rate for reoperative parathyroid surgery has been reported to vary from 64% to 72%,⁶ 83%,⁹ 90%,² and 95%¹¹ dependent on the series and the criteria for exclusion of failures. Furthermore, parathyroid reoperations are long and tedious with higher morbidity than initial operations.

Broadus et al. reported an elevated urinary cyclic adenosine monophosphate (UcAMP) in 92% of patients with primary hyperparathyroidism.¹² Similarly, Wells et al. stated that 90% of their patients had elevated preoperative UcAMP.¹³ In a retrospective study, we initially reported that intraoperative UcAMP levels fell to normal 2 hours following successful removal of a parathyroid adenoma.¹⁴ We later extended this work in a prospective study.¹⁵ Two other groups have measured UcAMP levels during parathyroid surgery and also confirmed our results.^{16,17} However, Kaplan et al. concluded that, since most experienced neck surgeons cure 95% of patients during initial exploration, UcAMP measurements are not warranted on a routine basis. Perhaps in selected

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difficult cases (such as reoperations), the intraoperative measurement of UcAMP might be helpful.¹⁶

This study establishes criteria for intraoperative UcAMP decline to allow prediction of successful surgical outcome in reoperative parathyroid surgery and determines the subset of reoperative parathyroid patients in whom UcAMP measurements are most helpful.

Methods

We studied 60 patients undergoing reoperative surgery for primary hyperparathyroidism between April 1980 and November 1983. The 60 patients had undergone 84 prior operations for hyperparathyroidism. Eighty-five per cent of the patients had persistent primary hyperparathyroidism defined as persistent serum calcium elevations following initial surgery for primary hyperparathyroidism. The remainder had recurrent primary hyperparathyroidism, meaning that they had at least a 6-month postoperative period of normal or low serum calcium levels followed by recurrent hypercalcemia. The diagnosis of primary hyperparathyroidism was based on elevated serum concentrations of calcium and on elevated levels of parathyroid hormone, and/or elevated UcAMP. Preoperative parathyroid localization studies, including selective arteriography, computerized tomography, ultrasound, and venous sampling, were performed. Some patients did not undergo all localization procedures. Previous surgical records and pathology were reviewed and a preoperative diagnosis of adenoma, hyperplasia, or uncertain histology given. Adenoma was assigned if no abnormal glands were removed and at least one normal parathyroid gland was stated to be removed or biopsied and review of pathology with dimensions and histology confirmed normal tissue. Hyperplasia was assigned if at least two abnormal glands were stated to be removed or biopsied and review of pathology with dimensions and histology confirmed abnormal tissue. If the above criteria were not met, the preoperative diagnosis of uncertain histology was assigned.

A detailed flow sheet of our reexploration was recorded on a form that listed the site of exploration in half-hour intervals, the times of removal of tissue specimens, and the histologic diagnosis for frozen tissue sections. Intraoperative UcAMP levels were determined at half-hour intervals by radioimmunoassay using the Gammaflow (Squibb, Princeton, NJ) system.^{15,18} Urine was collected at half-hour intervals by draining the urinary volume for 25 minutes and collecting the sample the last 5 minutes each half-hour period. Urinary cyclic AMP is expressed as nanomoles per deciliter of glomerular filtrate (obtained by multiplying the ratio of UcAMP to urine creatinine, in nanomoles per milligram, by serum creatinine, in milligrams per deciliter). The normal range

is 1.2 to 3.6 nmol/dl glomerular filtrate (GF), and in this study we defined normal as <4.0 nmol/dl GF.¹⁹ Results of UcAMP determinations were sent to the operating room as soon as available, generally within 5 to 15 minutes of sample collection.

Midway through the study we analyzed the intraoperative UcAMP results and developed tentative criteria to predict successful surgical outcome. In some cases toward the end of the study, the operating surgeon used these criteria to decide to terminate the surgical procedure. The final criteria stated here were formulated from a retrospective review of the entire 60 patients attempting to achieve high accuracy with no false-positives in the shortest time possible following removal of parathyroid tissue. Following removal of parathyroid tissue (proven on frozen section), if an individual (one) UcAMP level dropped 50% from the median baseline level (levels at half-hour intervals prior to removal of parathyroid tissue), or if elevated levels dropped to <4.0 nmol/dl GF, surgery was predicted to be successful. Surgical outcome was defined as successful if calcium levels fell to normal or less for at least 14 postoperative days. A doubling in UcAMP excretion above median baseline level was designated as a "peak."

Data are presented as mean \pm standard error of the mean unless otherwise specified.

Results

Fifty-three patients underwent successful surgical procedures, and seven patients underwent eight unsuccessful procedures. Of the 53 patients who underwent successful surgery, 21 required postoperative vitamin D and calcium at discharge, 13 required only calcium, and 19 required no medication. In the seven patients with failed surgical procedures, the preoperative diagnosis was hyperplasia or unknown in all patients. One unsuccessfully treated patient subsequently was proven to have parathyroid carcinoma, which required two operative procedures. In the 53 patients with successful surgery, the preoperative diagnosis was adenoma in 36 and uncertain histology or hyperplasia in 17.

Urinary cyclic AMP at the start of surgery was elevated in 55 of 60 patients (92%, \bar{x} = 8.2 \pm 0.8 nmol/dl GF). Eight unsuccessful surgical procedures in seven patients demonstrated no decline in UcAMP level despite removal of parathyroid tissue, and the intraoperative results accurately predicted surgical failure (Fig. 1). One patient's UcAMP levels dropped transiently slightly less than 4.0 nmol/dl GF, but he did not have parathyroid tissue removed so that represented baseline variation. Fifty-three patients underwent successful procedures, and in every case UcAMP levels fell. Ninety-eight per cent of successful surgical procedures (all but one patient)

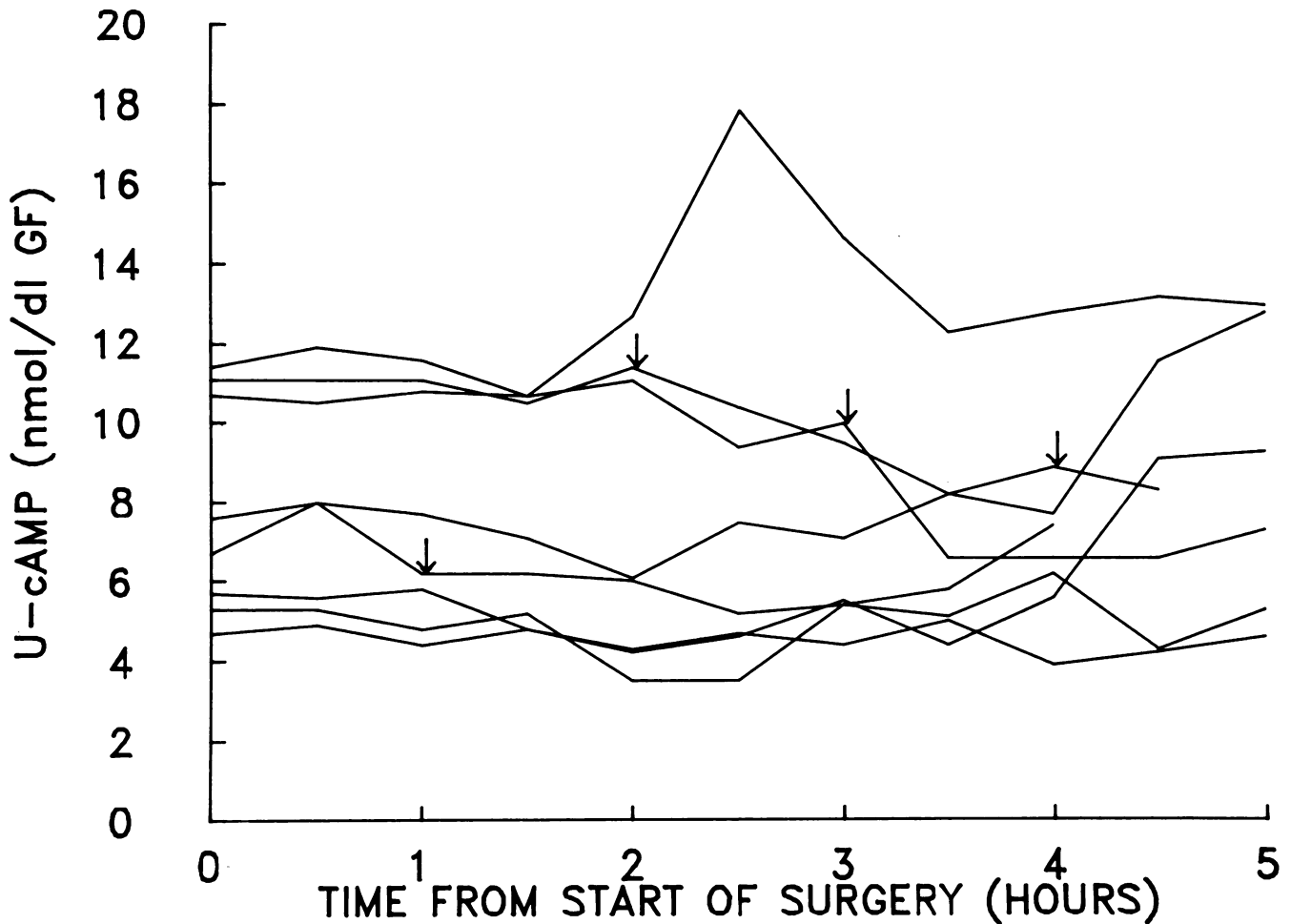


FIG. 1. Urinary cyclic adenosine monophosphate (UcAMP) levels are plotted against time from start of surgery for patients with known unsuccessful surgery. The inverted arrow indicates the time that parathyroid tissue was removed. Only the initial 5 hours are plotted, but most procedures continued for 8 to 10 hours with similar data. The initial UcAMP levels are elevated in all patients. The criteria for successful parathyroidectomy were not met following excision of parathyroid tissue in any patient. Therefore, UcAMP levels accurately predicted unsuccessful outcome in all patients.

were accurately predicted by our criteria. The single patient who had successful surgery but was not correctly predicted by intraoperative UcAMP levels had a low level of UcAMP (3.4 nmol/dl GF) before surgery and the decline following removal of abnormal tissue was only 23% (Fig. 2). It took 1.5 ± 0.5 ($\bar{x} \pm SD$) hours following parathyroidectomy for UcAMP criteria to be met. "Peaks" of UcAMP occurred in only two (4%) successfully treated patients, and it coincided with the removal of the abnormal gland in both cases.

We considered the UcAMP criteria to be met if following removal of parathyroid tissue an individual (one) UcAMP determination either dropped 50% below the median baseline level, or dropped to <4.0 nmol/dl GF (if the median baseline level was greater than 4.0 nmol/dl GF). Often in the recovery room (3–6 hours after removal of abnormal parathyroid tissue), an individual level might be greater than 4.0 nmol/dl GF (Fig.

2). This mild "rebound" occurred in the illustrative patient (Fig. 3). We do not think that this indicates unsuccessful outcome, and it does not appear to predict postoperative vitamin D or calcium requirements.

In the 36 patients successfully treated surgically with a preoperative diagnosis of adenoma, 19 patients (53%) had a significant drop in UcAMP prior to completion of surgery. While in the 17 patients (one patient did not significantly decline UcAMP) successfully treated surgically with a preoperative diagnosis of uncertain histology or hyperplasia, 16 had a significant drop in UcAMP prior to completion of surgery. This indicates that UcAMP determinations had the potential for utility in 94% of patients with a preoperative diagnosis of hyperplasia or unknown etiology, while it only had the potential for utility in 53% of the patients with a diagnosis of adenoma. Furthermore, in seven of the patients with hyperplasia or uncertain histology, surgery

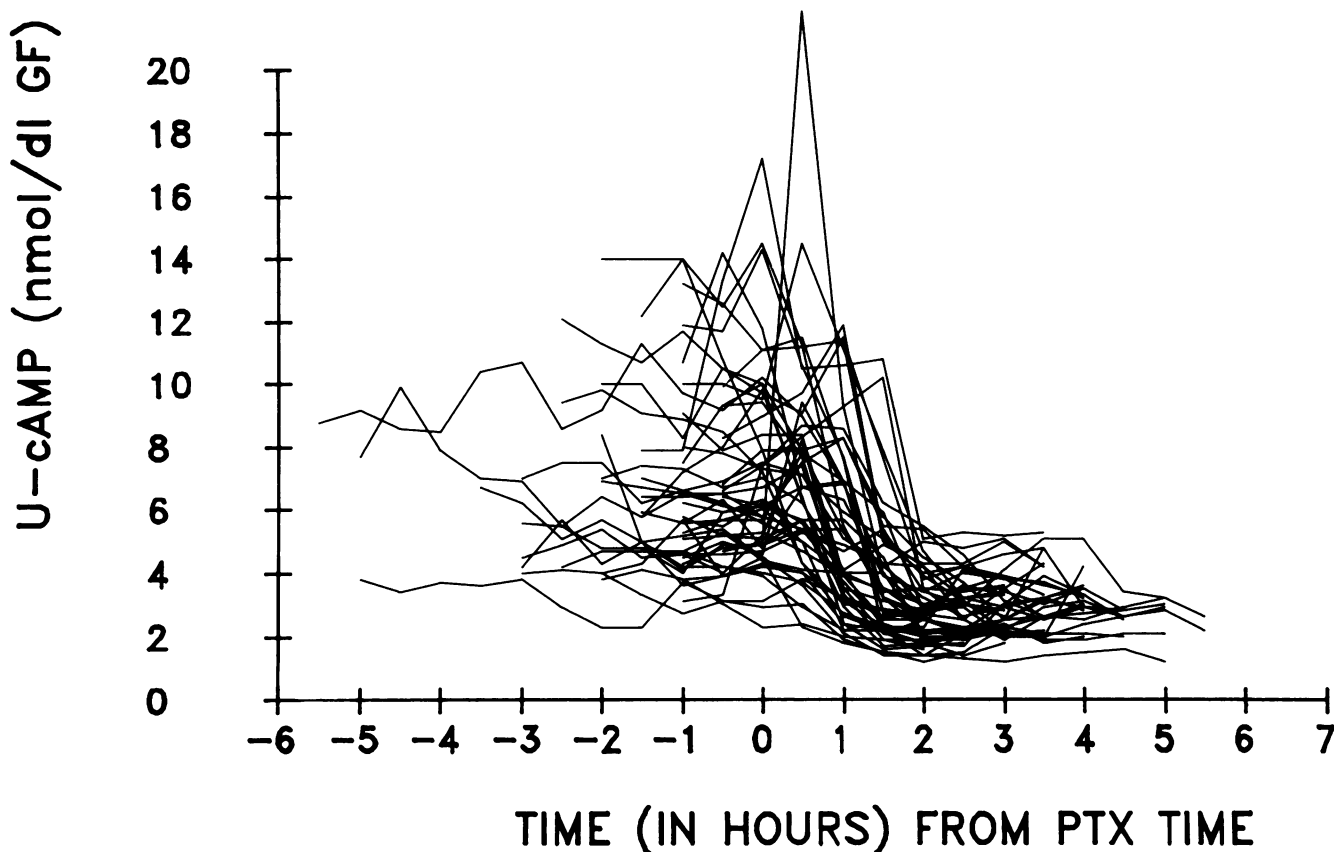


FIG. 2. Urinary cyclic adenosine monophosphate (UcAMP) levels are plotted against time from abnormal parathyroidectomy (PTX TIME) for all patients who had successful surgery. The UcAMP criteria for successful parathyroidectomy (see text) was met in 52 of 53 patients within 1.5 ± 0.5 hours ($\bar{x} \pm SD$). Therefore, UcAMP levels accurately predicted successful outcome in 98% of these patients.

was terminated only because the UcAMP level fell; the surgeon was unable to identify any other parathyroid tissue.

To further illustrate the utility of intraoperative UcAMP determination, we would like to briefly describe one patient. He had a previous neck exploration for primary hyperparathyroidism. Two glands were found, a normal gland was biopsied, and an abnormal gland was removed. Pathology was confirmed. He had persistent hypercalcemia and renal stones. At reexploration we removed one localized abnormal parathyroid gland and found no other parathyroid tissue. One parathyroid gland was not accounted for, but the procedure was terminated only because UcAMP levels fell significantly 1 hour after removal of the abnormal gland (Fig. 3). At 1.5 hours after surgery, he had a UcAMP >4 nmol/dl GF, but this was considered inconsequential. Six months after surgery, he is normocalcemic receiving no medications.

Discussion

In a previous retrospective study of 21 patients with primary hyperparathyroidism¹⁴ and a prospective study

of an additional 20 patients,¹⁵ we found that UcAMP excretion dropped rapidly after successful parathyroidectomy. The specificity of this response was shown by no decline in UcAMP excretion in five patients with unsuccessful parathyroid surgery and persistent hypercalcemia.^{14,15}

The current prospective study establishes UcAMP criteria for successful parathyroidectomy. The median of the baseline levels prior to removal of tissue is chosen to disregard massive elevations of UcAMP levels that may occur during operative dissection of the gland ("peaking"). This actually occurred in only four per cent of the patients, but it had occurred in 30% previously.¹⁵ Ninety-two per cent of the patients had elevated baseline UcAMP levels, which agrees well with our previous results¹⁵ and the reports of others.^{12,13} In these patients with elevated baseline levels, the criteria for successful parathyroidectomy were met if one UcAMP level dropped below 4 nmol/dl GF or if it declined 50% from the median baseline level. In the five patients with normal baseline UcAMP levels, successful surgery criteria was only a 50% decline from the median baseline level. Using these criteria, successful parathyroid surgery was

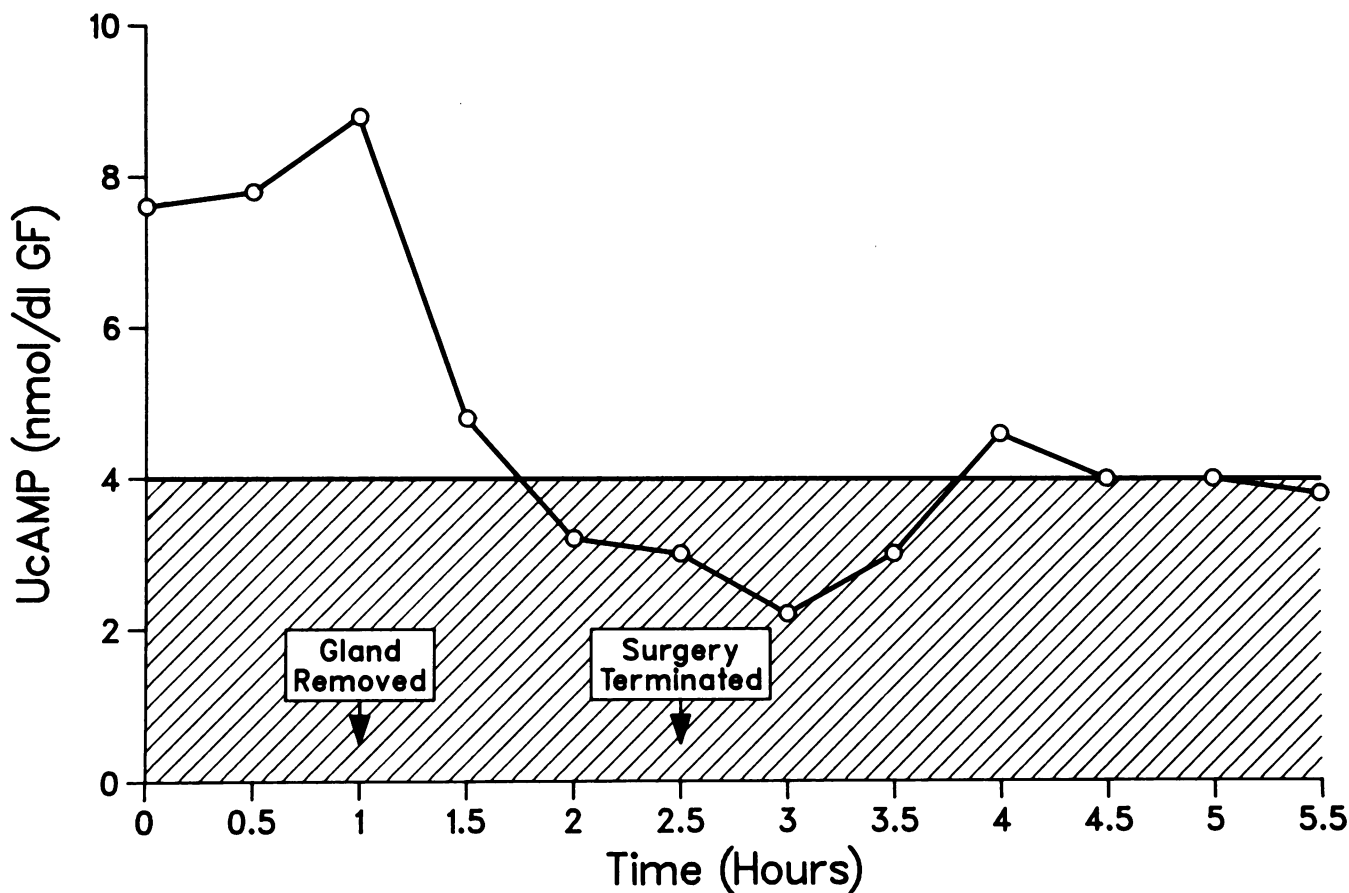


FIG. 3. Illustrative patient with multigland parathyroid disease who had one abnormal gland removed and one normal gland biopsied previously. Urinary cyclic adenosine monophosphate (UcAMP) levels are plotted against time from start of surgery. The normal range is given by the hatched area (<4.0 nmol/dl GF). Initial UcAMP levels are elevated. Parathyroid tissue is removed at 1 hour. No additional parathyroid tissue is recovered, but UcAMP criteria are met at 2 hours. Surgery is terminated at 2.5 hours despite not accounting for one gland.

correctly predicted in all but one patient who ultimately had successful surgery. One false-negative response occurred, and that patient had low pre-resection UcAMP levels.

In every patient with unsuccessful surgery, UcAMP levels accurately predicted failure. No false-positive responses occurred, *i.e.*, UcAMP did not fall enough to meet the criteria without removal of sufficient abnormal parathyroid tissue to render the patient normocalcemic. If we include our two prior reports, we have studied over 100 patients with no false-positive responses.^{14,15}

The average time required for UcAMP to return to normal after abnormal parathyroidectomy is 1.5 hours. Excess parathyroid hormone release during manipulation of the abnormal gland may delay decline of UcAMP. It is important to obtain a fresh urine aliquot at half-hour intervals and not the entire volume of urine that drained during the half-hour period. One only needs 5 ml to run an assay. By obtaining a fresh sample each half hour, we think the decline will occur earlier. If UcAMP remains elevated at 2 hours following removal of parathyroid tissue, the surgical procedure should not be

terminated. Either the parathyroid tissue removed was normal, or abnormal tissue was incompletely removed; nevertheless, the procedure will be unsuccessful if terminated, and the patient will remain hypercalcemic.

Several limitations of intraoperative UcAMP level determinations should be noted. A significant decline in intraoperative UcAMP levels will accurately predict that the patient is no longer hyperparathyroid; that is, elevated serum calcium levels will decline. These UcAMP changes will not accurately predict if the patient will be hypocalcemic or normocalcemic, if he or she will need vitamin D or calcium replacement, if he or she will need these medications transiently or permanently, or if he or she will develop recurrent primary hyperparathyroidism in the future. These intraoperative UcAMP level changes will only predict that he or she will no longer have persistent primary hyperparathyroidism. Finally, these measurements are not possible in patients with significant renal impairment, creatinine clearance <25 ml/min.¹²

Because our success rate with cryopreserved autologous parathyroid grafts is only 50%,^{7,20} it would be beneficial

to know at the time of reoperative parathyroid surgery which patients will develop permanent hypoparathyroidism. Fourteen per cent of our patients have received cryopreserved autografts.²⁰ We have been unable to use intraoperative UcAMP determinations to distinguish these patients from the remainder of patients who undergo successful surgery. If we could distinguish them, we would advocate fresh parathyroid autografts that will work in 90% to 100% of patients.²¹ Postoperative permanent hypoparathyroidism with vitamin D dependence and possible vitamin D-related nephrotoxicity is important to avoid.

Reoperative parathyroid surgery in patients with multigland disease is more difficult than in patients with simple adenomas. If the surgeon is confident of a preoperative diagnosis of adenoma (one or more normal glands biopsied or excised and no pathologic glands identified), then he or she simply removes the abnormal gland. Adenomas are usually bigger, easier to localize radiographically, and easier to find surgically than multiple hyperplastic glands.² This was also our experience in approximately 50% of the patients with a preoperative diagnosis of adenoma, because we could confidently end the procedure prior to fall of UcAMP levels. However, patients with multigland disease or uncertain histology presented the greatest challenge. In this report, all patients who had unsuccessful surgery had a preoperative diagnosis of hyperplasia or uncertain histology. In 16 of 17 patients with this preoperative diagnosis, UcAMP levels fell significantly prior to conclusion of the procedure. In seven patients, the surgeon ended the procedure only because UcAMP levels fell. In these cases when the parathyroid pathology is unclear, the UcAMP excretion is a valuable *in vivo* assay for function of abnormal parathyroid tissue. When sufficient abnormal parathyroid tissue has been removed, the levels will drop, and the procedure can be terminated.

In an age of expensive technology, we are obliged to consider the cost-benefit ratio of monitoring intraoperative UcAMP excretion in patients with primary hyperparathyroidism undergoing reoperation. In patients undergoing repeat neck exploration with a preoperative diagnosis of adenoma, intraoperative UcAMP determinations are not necessary. However, in patients undergoing neck reexploration with hyperplasia or in whom the location and number of glands to be resected are unknown, rapid intraoperative UcAMP determinations are helpful. The risks of the determinations are small (bladder catheterization). The UcAMP results are available immediately and, using the guidelines developed here, the surgeon can accurately predict a successful outcome within 1.5 hours of tissue removal. This appears to be especially helpful in patients undergoing reoperation with multigland disease or hyperplasia, because when enough pathologic tissue has been removed, the levels

will drop significantly and the procedure may be terminated with confidence despite having not biopsied all glands.

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References

- Brennan MF. Reoperation for suspected hyperparathyroidism. *Clinical Surgery International*, vol 4. Surgery of the Thyroid and Parathyroid Glands. New York: Churchill-Livingston, 1983; 168-176.
- Wang CA. Parathyroid re-exploration. *Ann Surg* 1977; 186:140-145.
- Martin JK, Van Heerden JA, Edis AJ, et al. Persistent postoperative hyperparathyroidism. *Surg Gynecol Obstet* 1980; 151:764-768.
- Beazley RM, Costa J, Ketcham AS. Reoperative parathyroid surgery. *Am J Surg* 1975; 130:427.
- Wells SA, Doppman JL, Bilzkeian JP, et al. Repeated neck exploration in primary hyperparathyroidism: localization of abnormal glands by selective thyroid arteriography, selective venous sampling and radioimmunoassay. *Surgery* 1973; 74:678-686.
- Edis AJ, Sheedy PF, Beahrs OH. Results of reoperation for hyperparathyroidism, with evaluation of preoperative localization studies. *Surgery* 1978; 84:384-391.
- Saxe AW, Spiegel AM, Marx SJ, Brennan MF. Deferred parathyroid autografts with cryopreserved tissue after reoperative parathyroid surgery. *Arch Surg* 1982; 117:538-543.
- Saxe AW, Brennan MF. Strategy and technique of reoperative parathyroid surgery. *Surgery* 1981; 89:417-423.
- Brennan MF, Doppman JL, Marx SJ, et al. Reoperative parathyroid surgery for persistent hyperparathyroidism. *Surgery* 1978; 83:669-676.
- Saxe AW, Brennan MF. Reoperative parathyroid surgery for primary hyperparathyroidism caused by multiple-gland disease: total parathyroidectomy and autotransplantation with cryopreserved tissue. *Surgery* 1982; 91:616-621.
- Brennan MF, Marx SJ, Doppman J, et al. Results of reoperation for persistent and recurrent hyperparathyroidism. *Ann Surg* 1981; 194:671-676.
- Broadus AE, Mahaffey JE, Bartter FC, Neer RM. Nephrogenous cyclic adenosine monophosphate as a parathyroid function test. *J Clin Invest* 1977; 6:771-783.
- Wells SA Jr, Leight GS, Ross AJ. Primary hyperparathyroidism. *Curr Probl Surg* 1980; 17:398-463.
- Spiegel AM, Marx SJ, Brennan MF, et al. Urinary cAMP excretion during surgery: an index of successful parathyroidectomy in patients with primary hyperparathyroidism. *J Clin Endocrinol Metab* 1978; 47:537-542.
- Spiegel AM, Eastman ST, Attie MF, et al. Intraoperative measurements of urinary cyclic AMP to guide surgery for primary hyperparathyroidism. *N Engl J Med* 1980; 303:1457-1460.
- Kaplan EL, Fang VS, Sugimoto J, Fredland A. Serum calcium, parathyroid hormone, and urinary cyclic adenosine monophosphate after parathyroidectomy. *Surgery* 1982; 92:822-826.
- Kohri K, Kataoka K, Yachiku S, et al. Changes in cyclic AMP and electrolytes after parathyroidectomy in primary hyperparathyroidism. *Clin Endocrinol* 1983; 18:371-376.
- Brooker G, Terasaki WL, Price MG. Gammaflow: a completely automated radioimmunoassay system. *Science* 1976; 194:270-276.
- Madvig P, Young G, Marcus R. Assessment of adenosine 3',5' monophosphate excretion and an oral calcium tolerance test in the diagnosis of mild primary hyperparathyroidism. *J Clin Endocrinol Metab* 1984; 58:480-487.
- Norton JA, Santora A, Marx S, et al. Function of cryopreserved human parathyroid tissue (abstract). *Clinical Disorders of Bone and Mineral Metabolism*. Detroit, 1983.
- Niederle B, Roka R, Brennan MF. The transplantation of parathyroid tissue in man: development, indications, technique, and results. *Endocrine Reviews* 1982; 3:245-279.