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Results of Reoperation for Persistent and Recurrent Hyperparathyroidism

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Between August 1975 and January 1981, 106 patients thought to have persistent or recurrent hyperparathyroidism underwent a total of 108 parathyroid re-explorations at the National Institutes of Health. These 106 patients had a total of 175 previous operations for hyperparathyroidism (156 cervical and 19 mediastinal). Nephrolithiasis (54% of patients) and bone disease (24% of patients) were the predominant symptoms. Arteriographic examination and selective venous sampling provided highly accurate localizing results in 33% of the patients, and were of some help in 64%. The final diagnoses after reoperation and re-evaluation were: single-gland disease in 58 patients, primary nonfamilial hyperplasia in 19 patients, familial hyperplasia in three patients, multiple endocrine neoplasia (MEN) Type I in ten patients, MEN Type II in two, parathyroid carcinoma in four patients, secondary hyperplasia in three patients, and familial hypocalciuric hypercalcemia (FHH) in two patients. The diagnosis was in doubt in five patients. In the 95 patients with unequivocal hyperparathyroidism, not due to parathyroid carcinoma, surgery eliminated hypercalcemia in 91 (96%). Two patients died after operation, one of disseminated candidiasis, and one patient, with an immunodeficiency, of sepsis. Five patients developed temporary, and one permanent, recurrent nerve damage; 41% of the patients were hypocalcemic, at the time of discharge from the hospital.

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THE FIRST "SUCCESSFUL" parathyroidectomy for hyperparathyroidism by Mandl in 1931 was rapidly followed by a recrudescence of symptoms and unsuccessful reoperation.[12] Persistent hyperparathyroidism, following an unsuccessful cervical or mediastinal exploration for primary or secondary hyperparathyroidism, remains a challenge for the internist and surgeon.[1,7,10,13,15,16] This report analyzes a consecutive series of 108 reoperations in 106 patients by one surgeon.

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Materials and Methods

From August 1975 to January 1981, 106 patients thought to have persistent or recurrent hyperparathyroidism underwent 108 reoperations at the National Institutes of Health. The patients were admitted to the Clinical Center of the National Institutes of Health, mainly under the Metabolic Diseases Branch; on some occasions, patients with multiple endocrine neoplasia were admitted to other services.

All patients underwent standard preoperative testing to confirm the diagnosis and to exclude other causes of hypercalcemia. All available pathologic material from prior operations was reviewed. This included operative reports, gross pathology report and histologic sections. Once the patient was thought to have hyperparathyroidism and to have symptoms and signs sufficient to warrant re-exploration, invasive localization studies were then initiated.[5] Patients were defined as having persistent disease if, following their prior operation, no fall in calcium occurred, or the transient postoperative fall in the serum calcium level was not maintained for six months. Patients were defined as having recurrent

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TABLE 1. *Patient Group*

	Number of Patients	Mean Age (Range)	Female: Male
Persistent Disease	97	46.5 (12–77)	57:40
Recurrent Disease	9	50.1 (33–64)	7:2

disease if, after a period of at least six months normo- or hypocalcemia, they again became hypercalcemic. Of the patients referred following prior unsuccessful surgery, approximately 50% came to reoperation.[14] The main reason for not offering reoperation was paucity of symptoms, although the diagnosis of familial hypocalciuric hypercalcemia (FHH)[14] and treatment by catheter embolization,[6] were other reasons.

Results

The majority of patients were of middle age, with a preponderance of females (Table 1). The 106 patients had undergone 175 previous cervical or mediastinal operations for their hyperparathyroidism (Table 2) (42 patients had two or more prior procedures). During these procedures, 37% of the patients had some form of surgery on the thyroid gland (Table 3). No abnormal parathyroid tissue was found in these thyroid specimens. It was confirmed, by histologic review, that 138 parathyroid glands had been previously removed and a further 60 had been biopsied. The histopathologic diagnosis of these removed glands is given in Table 4. Of great concern were the major disparities between the surgeon's operative description of the site and nature of the tissue removed, and the pathologist's documentation of what was received in the pathology department.

All patients coming to reoperation were symptomatic (Table 5). The predominant symptoms were nephrolithiasis and bone disease. Up to 20% of the patients had proximal muscle weakness which, on occasion, was sufficiently severe as to require aid in walking. Neuropsychiatric symptoms included four patients who had been obtunded by hypercalcemic crises. Arteriographic examination and selective venous sampling for localization were rigorously pursued, and data from both provided excellent localization in 33% of the patients (Table 6), compared with a previously reported 39%.[2] One or both studies were correct in 64% of the patients.

Following reoperation at the NIH and reinvestigation where appropriate, the final diagnoses on clinicopathologic grounds were as illustrated in Table 7. The predominant diagnosis in this selected group of patients remained single-gland adenomatous disease, presumptively missed at the time of first operation. Hyperplasia, either occurring in primary form or as part of a multiple endocrine neoplasia syndrome, occurred in 32% of the patients, compared with the 55% of patients who had adenomas. As the diagnosis of familial hypocalciuric hypercalcemia (FHH) became more familiar, this diagnosis began to be increasingly suspected.[14] A diagnosis of FHH was suspected in five patients and confirmed in two. Three others are suspected of having FHH, but family members are unable to be screened. Two patients are now thought to have nonparathyroid hypercalcemia.

In the treatment of these patients, 108 operations were performed (Table 8), combined mediastinal and cervical exploration being performed at the same time in 22. Two patients underwent two operations, while two patients with parathyroid carcinoma each underwent diagnostic laparotomy to confirm metastatic disease, and thoracotomy for resection of pulmonary nodules, respectively. One hundred seventeen abnormal parathyroid glands were removed (Table 9). Of the five patients (Table 4) thought to have had a total of six "adenomas" removed at previous operations, one patient was suspected of having FHH, while the other four had multiple gland disease (three with primary hyperplasia, one with MEN I). Two patients in the recurrent group had an adenoma removed and a normal gland biopsied at the time of reoperation. Both had at least one normal gland removed previously. One patient was presumed to have had an inadequate adenoma resection, and the other to have had the adenoma infarcted at the time of initial surgery. Neither has had a recurrence at one and six years follow-up, respectively.

The abnormal tissue was found in the mediastinum following sternotomy in 20 patients (16 adenomas, one

TABLE 2. *Previous Surgery for Hyperparathyroidism*

Patients	Cervical	Mediastinal	Total
Persistent disease	139*	18	157
Recurrent disease	17	1	18
All patients	156	19	175

* Figures are the number of prior explorations by site.

TABLE 3. *Prior Thyroid Surgery*

	Total Lobectomy	Partial Lobectomy	Bilateral Subtotal	Total Thyroidectomy
Persistent disease	14	12	9	2
Recurrent disease	2	—	—	—
All patients	16	12	9	2

TABLE 4. *Parathyroid Glands Previously Removed or Biopsied*

	Removed—Histology				Biopsied—Histology			
	Ad	Ca	Hyp	N	Ad	Ca	Hyp	N
Persistent disease	5	2	65	53	—	—	17	39
Recurrent disease	1	2	7	3	—	—	2	2
All Patients	6	4	72	56			19	41

Histopathological diagnoses on basis of referred material.
Ad: adenoma.
Ca: carcinoma.
Hyp: hyperplasia.
N: normal.

carcinoma, three hyperplasia), and both cervical and mediastinal in two patients (both hyperplasia). In two patients, following an unrewarding sternal splitting medistinal exploration, abnormal tissue was identified in the neck.

Persistent hypercalcemia was encountered in ten patients immediately after operation (Table 10). A further patient had persistent hypercalcemia following recurrence and then reoperation at the NIH. At a second reoperation, abnormal tissue was again removed from this patient. After the second operation her serum calcium level has remained at 10.8 mg/dl. It should be emphasized that this patient now has had six documented abnormal parathyroid glands removed and remains with mild hypercalcemia. Of those patients who remain hypercalcemic, the diagnosis of hyperparathyroidism is in considerable doubt in five (Table 11), and two have had the diagnosis of FHH confirmed. Two other patients with persistent disease had carcinoma, one of whom died within six months of his reoperation. An additional patient with parathyroid carcinoma was profoundly hypocalcemic for many months after pulmonary resection requiring vitamin D and calcium supplementation, before recurring with further metastatic disease in the lung, which was unresectable.

Of those patients with unequivocal hyperparathyroidism, but not carcinoma, the short-term success rate is 95.7% (91 of 95). With follow-up periods longer than six months, this success rate remains identical, with one recurrence and two previously uncured patients having developed normocalcemia, one on minimal oral phosphate supplementaion (serum calcium level 10 mg/dl) and one following total gastrectomy for Zollinger-Ellison syndrome (serum calcium level: 9.4 mg/dl). The success rate in curing hypercalcemia by parathyroid exploration, regardless of the subsequent cause of the hypercalcemia, was 86%.

Postoperative hypocalcemia requiring calcium and Vitamin D supplementation occurred in approximately 50% of patients (Table 12). This was prolonged, requiring the maintenance on calcium and vitamin D supplements at the time of discharge from the hospital in approximately 41% of the patients.

Operative Complications

There were two deaths within 30 days of reoperation, the first death occurred in a patient who was admitted to the hospital obtunded in hypercalcemic crisis, on high dose corticosteroids, who subsequently had a mediastinal parathyroid gland removed, became profoundly hypocalcemic, but died of what proved to be widely disseminated candidiasis from tricuspid valve endocarditis. The presumption was that the combination of prolonged obtundation, multiple central venous lines, antibiotics and high-dose corticosteroids, all contributed to the development of the candida endocarditis and subsequent disseminated disease.

A second, massively obese patient with nephroli-

TABLE 5. *Predominant Symptoms*

	Per Cent Renal	Per Cent Gastrointestinal	Per Cent Muscular	Per Cent Bone	Per Cent Neurologic
Persistent disease	51	19	20	27	8
Recurrent disease	77	0	33	44	0
All patients	54	17	21	29	8

TABLE 6. *Localization Studies*

	Arteriography and Selective Venous Sampling				
	Per Cent AGL Correct	Per Cent VGL Correct	Per Cent One or Both Correct	Per Cent Both Correct	Per Cent Neither Correct
Persistent disease	43	50	64	31	37
Recurrent disease	55	55	64	33	33
All patients	45	52	63	33	36

AGL: arteriogram localization.
VGL: venous sampling localization.

TABLE 7. *Final Clinicopathological Diagnosis*

	Persistent	Recurrent	Both
Adenoma	56	2	58
Primary hyperplasia	16	3	19
Familial hyperplasia	2	1	3
MEN I	9	1	10
MEN II	2	0	2
FHH	2	0	2
Parathyroid carcinoma	2	2	4
Secondary hyperplasia	3	0	3
Other (see table 9)	5	0	5
Total patients	97	9	106

thiases, hypertension and hyperprolactinemia, died of staphlococcal septicemia, following successful parathyroid reoperation. This patient was known, prior to surgery, to have a poorly characterized combined immunodeficiency.

At least 12 patients were referred with vocal cord paralysis from recurrent nerve damage. Two were referred with in-dwelling tracheostomes. Following surgery at the authors' institution, there were five temporary and one permanent nerve pareses, and one patient with a previously paralyzed cord, required a temporary tracheostome. The carotid artery was injured during reoperation in two patients, requiring intraoperative repair. No long-term sequelae occurred from the injury. One patient developed a Horner's syndrome. There were two wound infections, one requiring local drainage, and two wound hematomas. There was one clinically insignificant, but radiologically suggestive, pulmonary embolism.

Discussion

The true occurrence of persistence or recurrence following operation for hyperparathyroidism is unknown. In single studies in one institution, there is a 3.7–5% incidence of persistent hypercalcemia in patients undergoing primary exploration by experienced surgeons.[13,15] Recurrence occurred in 33% of 21 patients with multiple endocrine neoplasia or familial hyperparathytroidism, but in only 0.4% of 242 patients without these entities.[4] In a review of 3,788 cases from the literature, the incidence of recurrence was 51 or 1.34%.[1] In a further report, an 18% incidence of persistence or recurrence was found in 110 patients operated on at a single institution.[11] If the failure rate of first operations is 5% in experienced hands, then a strong argument can be made to dissuade the less experienced surgeon from approaching these problems.

It is clear that diagnosis is central. The presence of the FHH syndrome should be diligently searched for, as it occurs in 9% of patients referred with persistent hypercalcemia.[14]

The present prevalence of multiple-gland disease—37/99 patients (37%)—is much higher than would be expected in a normal population undergoing a first procedure, but is consistent with the expectation that persistence and recurrence would be more common in patients with multiple-gland disease. Clearly, patients

TABLE 8. *Reoperative Surgery at NIH*

	Cervical*	Mediastinal†	Other	Total
Persistent disease	93	21	1‡	115
Recurrent disease	7	3	1§	11
All patients	100	24	2	126

* Twenty-two patients had both cervical and mediastinal procedures synchronously.
† Requiring sternotomy.
‡ Liver biopsy.
§ Pulmonary resection.

TABLE 9. *Glands Removed at the Time of Reoperation*

	Removed—Histology			
	Ad	Ca	Hyp	N
Persistent disease	57	2	47	3
Recurrent disease	2	2	7	1

Ad: Adenoma.
Ca: Carcinoma.
Hyp: Hyperplasia.
N: Normal.

TABLE 10. *Postoperative and Subsequent Hypercalcemia*

Patient	Diagnosis	Hypercalcemia: Immediate	Hypercalcemia: At 6 Months
1, 2	FHH	+	+
3–7	Not Primary Hyperparathyroid	+	+
8	MEN I	+	−
9	MEN I	+	+
10	Primary Hyperparathyroidism	+	+
11	Primary Hyperparathyroidism	+	−
12	Parathyroid Carcinoma	−	**
13	Familial Hyperparathyroidism (first NIH reoperation, 3rd operation)	−	+
13a	Familial Hyperparathyroidism (2nd NIH reoperation, 4th operation)	+	+
14	Parathyroid Carcinoma	+	*
15	Parathyroid Carcinoma	+	+

* Died.
** Subsequently recurred and died.
FHH: Familial hypocalciuric hypercalcemia.

TABLE 11. *Results of Subsequent Evaluation of Five Patients Thought Not to Have Primary Hyperparathyroidism*

Patient	Presumptive Diagnosis	Serum Calcium Meq/L	Plasma PTH mg/ml	GFR ml/min. 1.73m²	Normo-alcemic Relatives	Urine CAMP nm/100 mIGF	Calcium: Creatinine Clearance
3	Abnormal vitamin D metabolism, hyperabsorption, intermittent hypercalcemia	5.20	UD	100	NT	1.0	0.035
4	Unknown	5.28	0.20	70	NT	2.37	0.038
5	Unknown	6.85	0.48	22	NT	2.50	0.114
6	Probable FHH	5.45	UD	60	3	3.75	0.011
7	Probable FHH	5.38	0.54	86	5	6.78	0.007
Primary Hyperparathyroidism		≥5.3	>0.24	>100	—	>3.6	0.01-0.04

GFR: glomerular filtration rate.
UD: undetectable.
NT: none tested.

with persistence are more likely to be seen at a referral center.

The management of patients with persistent or recurrent disease varies widely. The present series addresses only those patients who are symptomatic; we do not recommend surgical re-exploration for the patient with mild disease following prior exploration.

The use of invasive localization studies is a subject of some controversy and should be reserved for the patient who will require reoperation.[2] The generalized application of invasive localization studies is still to be defined.[10] In the hands of an experienced angiographer, complications will be rare and the morbidity rate will approach zero.[2,5,16] The results of invasive localization studies in this update of our experience are comparable, but not as good (33% vs 39% excellent localization; 63% vs 75% suggestive localization), as have been previously reported.[2] Although the reason for this is not clear, we believe the patient population to have become more complicated with time. Forty per cent of our patients have had two or more prior surgical explorations, and one-third have had some thyroid ablation. The noninvasive studies such as ultrasound[8,9] and barium swallow,[15] advocated by othes have not, in the authors' experience, been of much value.[1,2]

The success of reoperation in the present series (95% in patients with proven hyperparathyroidism) compares favorably with the 64% (mediastinal) 72% (cervical)[10] and 90%[15] reported elsewhere. The high prevalence of abnormal glands in the mediastinum in this series—22/95 patients (23%)—compares with the 19%,[15] 25%,[11] and 15%[10] of other reoperative series.

TABLE 12. *Postoperative Hypocalcemia*

	Left Hospital on Ca++/Vit D	In Hospital on Ca++/Vit D
Persistent disease	38 (39%)	50 (52%)
Recurrent disease	5 (56%)	5 (56%)
All patients	43 (41%)	55 (52%)

It is clear that, as reoperative surgery is not without considerable risk, every attempt should be made to resolve the problem at the time of first exploration. It appears that prolonged exploration in inexperienced hands results in a high incidence of recurrent nerve damage. Severe postoperative hypoparathyroidism following reoperation is common and occurs transiently in 40-50% of the patients.[1,10,15] The latter complication, however, is preferable to persistent disease, as it may be treated pharmacologically or by immediate or delayed autografting.[1,3,17]

We would like to conclude that symptomatic, severe hyperparathyroidism can be a life-threatening illness, which requires aggressive attempts to confirm the diagnosis. We believe invasive localization studies in the hands of an experienced radiologist and endocrinologist to be safe and of value, and especially indicated where the initial operations has been performed by a surgeon experienced in parathyroid surgery.

Despite the fact that surgical re-exploration can be hazardous and, on occasions unrewarding, the authors' results show that re-exploration of the symptomatic patient is successful in 96% of the patients with proven hyperparathyroidism not due to parathyroid carcinoma. Hypoparathyroidism is common, however, following reoperation and can be managed by autotransplantation, the indications for which are still undergoing evaluation.[1,3,17]

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