Parathyroid Re-exploration

A Clinical and Pathological Study of 112 Cases

CHIU-AN WANG, M.D.*

From the Department of Surgery, Harvard Medical School and the Massachusetts General Hospital, Boston, Massachusetts

In a series of 112 patients who underwent reoperation for primary hyperparathyroidism at the Massachusetts General Hospital between 1930 and 1975, all but 10 were treated successfully. Seventy-five initial explorations had been performed elsewhere, and 37 in our hospital. A total of 110 diseased parathyroids were uncovered—89 (81%) via re-exploration of the neck and 21 (19%) via mediastinotomy. In operation via the neck, the missing glands were most frequently found in the superior posterior mediastinum at the thoracic inlet (34, or 38%) and in mediastinal exploration, in the upper anterior mediastinum (14, or 67%). There were 66 patients with adenoma, 7 with carcinoma, and 29 with primary hyperplasia. Four had a hyperfunctioning fifth gland. One patient had an intrathyroidal and one, an ectopic gland. Reoperation was unsuccessful in 10 patients. Four died, and 6 are living.

Unsuccessful exploration resulted from failure to understand the widespread distribution of normal parathyroids and the way they were displaced when diseased, error in diagnosing the pathologic entity of hyperparathyroidism at surgery, and technical incompetence.

Reoperation of the neck was generally performed first. A mediastinotomy was undertaken only if the missing gland was clearly excluded from the neck or if localization studies had demonstrated its presence beyond doubt in the mediastinum. Reoperation was rarely performed simultaneously on the neck and the mediastinum, and it was seldom indicated in asymptomatic cases with a mild degree of the disease.

EVER SINCE THE DISCOVERY of hyperparathyroidism, surgical management of the disease has been beset with many distressing unsuccessful results. Mandl's patient,[5] the first European operated on for hyperparathyroidism, continued to have the disease after what had seemed to be a successful exploration. He died of recurrent disease, most probably from primary hyperplasia, which had not been recognized. The first American patient with hyperparathyroidism, diagnosed preoperatively by DuBois and Aub, was explored seven times in the years between 1926 and 1932, before the adenoma was found in the mediastinum.[1] This unfortunate patient died of renal complications, which had developed over the 6 fateful years.

In the past four decades, while few unsuccessful explorations have been reported, it is likely that many have been performed. With routine use of the multichannel autoanalyzer, an increasing number of patients with a mild degree of the disease are being diagnosed and explored. The rate of failure is bound to rise unless surgery is restricted to those who have learned to recognize and overcome the obstacles.

Between 1930 and 1975, 712 patients with primary hyperparathyroidism were surgically treated at the Massachusetts General Hospital. In approximately 85%, no difficulties were encountered. The operation was straightforward, and hyperparathyroidism was successfully corrected. The remaining 15% were problem cases, either because the diseased parathyroid had not been found during the initial operation or because hyperparathyroidism had continued despite the removal of one or more diseased glands. The experience gained from the study of these problem cases is the subject of this paper.

Clinical Data

This study includes 112 patients who had had one or more previous unsuccessful operations for primary hyperparathyroidism. In 75, the initial surgery had

* Associate Clinical Professor of Surgery, Harvard Medical School, Visiting Surgeon, Massachusetts General Hospital.

Reprint requests: Chiu-an Wang, M.D., Massachusetts General Hospital, Boston, Massachusetts 02114.

Submitted for publication November 29, 1976.

been performed elsewhere, and in 37, at our own institution. Seventy-two were female and 40, male. Their ages ranged from 17 to 70, with an average age of 43.

Ninety-seven (87%) had unsuccessful exploration of the neck only, and 15 (13%), of the mediastinum as well (Table 1). Of the patients who had had an unsuccessful exploration of the neck, 72 had one, and 25 had two or more. Of the 15 patients with negative mediastinal exploration, 7 had one exploration of the neck, 6 had two, and two had three.

Reoperation

Preoperative Localization

An attempt was made preoperatively to localize the missing gland in 83 patients with cervical esophagography, in 16 patients with venous catheterization and parathormone (PTH) radioimmunoassay, and in 11, with arteriography (Table 2). The gland was successfully localized by esophagogram in 19 (23%) of the 83. In each, the gland was located in close proximity to the cervical esophagus. Its average size was 2.5 cm.

Localization studies with venous catheterization and PTH radioimmunoassay or arteriography have been used in cases with multiple unsuccessful explorations in this series. In 14 (88%) of the 16 patients who had selective venous catheterization with PTH radioimmunoassay, the gland was correctly localized; in the other two, the gland proved to be in the opposite side of the neck. In 8 (73%) of the 11 who had arteriography, the parathyroid mass was demonstrated as a tumor blush. In the other three, the gland was too small to appear in the arteriogram.

TABLE 1. *Previous Unsuccessful Operations (112 Patients)*

No. of Unsuccessful Operations	Performed Elsewhere (75)	Performed at MGH* (37)	Total
Of Neck			
1	45	27	72
2	14	5	
3	3	0	
4	2	0	25
5	0	0	
6	0	1†	
Total	64	33	97 (87%)
Of Mediastinum and Neck			
1	4	3	7
2	5	1	6
3	2	0	2
Total	11	4	15 (13%)

* Massachusetts General Hospital.

† This sea captain, Charles Martel, had 3 operations of the neck elsewhere and 3 at Massachusetts General Hospital.

TABLE 2. *Preoperative Localization*

	No. of Patients	No. of Glands Localized (%)
Cervical esophagography	83	19 (23%)
Venous catheterization and PTH assay	16	14 (88%)
Arteriography	11	8 (73%)

Some preoperative localization studies were more helpful than others, though as yet none has proved to be consistently accurate. As indicated in this study, because cervical esophagography was simple to perform and noninvasive, this technique has been routinely used and has been found to be accurate in localizing the missing gland in a selected group of patients.* In experienced hands, localization by venous catheterization with or without arteriography was more accurate than cervical esophagography, but because this procedure is time-consuming and costly, it was not used routinely in this series. If there was clear indication that the initial exploration had been inadequate and that reoperation would inevitably be needed, we did not consider it necessary to subject patients to these lengthy and taxing procedures. The majority of our patients were successfully re-explored without the aid of these studies.

Operative Findings

Site of the Missing Glands

One hundred and two patients were successfully re-explored, and a total of 110 missing glands were retrieved—89 (81%) via the neck and 21 (19%) via the mediastinum (Table 3). With the exception of 6 glands the location of which was not clearly defined, 104 were found in the following sites (Fig. 1): 34 in the superior posterior mediastinum, 21 in the anterior mediastinum, 19 in the dorsum of the upper pole and 10 behind the lower pole of the thyroid, and 13 within the thymic tongue. Five were located behind the upper esophageal wall, one at the angle of the jaw, and 1 within the thyroid. At re-exploration of the neck, the superior posterior mediastinum was unquestionably the most common site of the missing parathyroid, the upper pole of the thyroid was second, and the thymic tongue, third.

Of the 21 missing glands recovered by medias-

* In patients with markedly elevated levels of serum calcium or plasma PTH, the diseased gland was generally large and could be demonstrated as an indentation by cine-esophagogram if it was located adjacent to the esophagus.

TABLE 3. *Sites of 110 Missing Glands**

Site	Total Glands Removed
Neck	89 (81%)
Mediastinum	21 (19%)

* Eight patients with primary hyperplasia had one additional gland.

tinotomy, 19 have been recorded.[6] Fourteen (67%) were enclosed within the thymus in front of the innominate vein. Conceivably, some had originally been hidden at the thoracic inlet where they might have been retrieved via the neck. As a result of operative severance of the thymic attachment to the thyroid, however, they had slipped into the superior anterior mediastinum. The remaining 7 missing mediastinal glands (33%) were lodged caudally behind the thymus, anterior to the great vessels or the bronchus where they could obviously be removed only via a mediastinotomy (Fig. 2).

Pathology of the Missing Glands

Sixty-six of the 102 successfully re-explored patients had an adenoma and 7, a carcinoma. Twenty-nine had primary hyperplasia of which 23 were the chief-cell type and 6, the clear-cell type (Table 4).

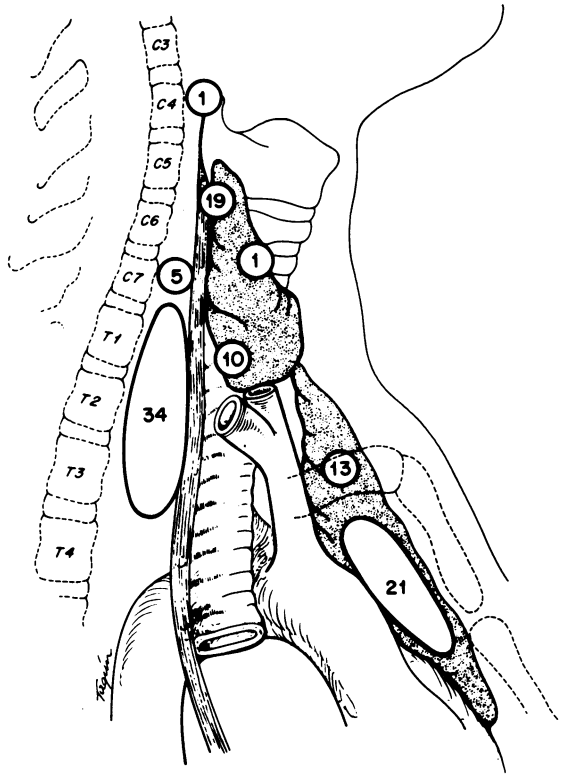

FIG. 1. Schematic representation of sites of 104 missing glands (see text).

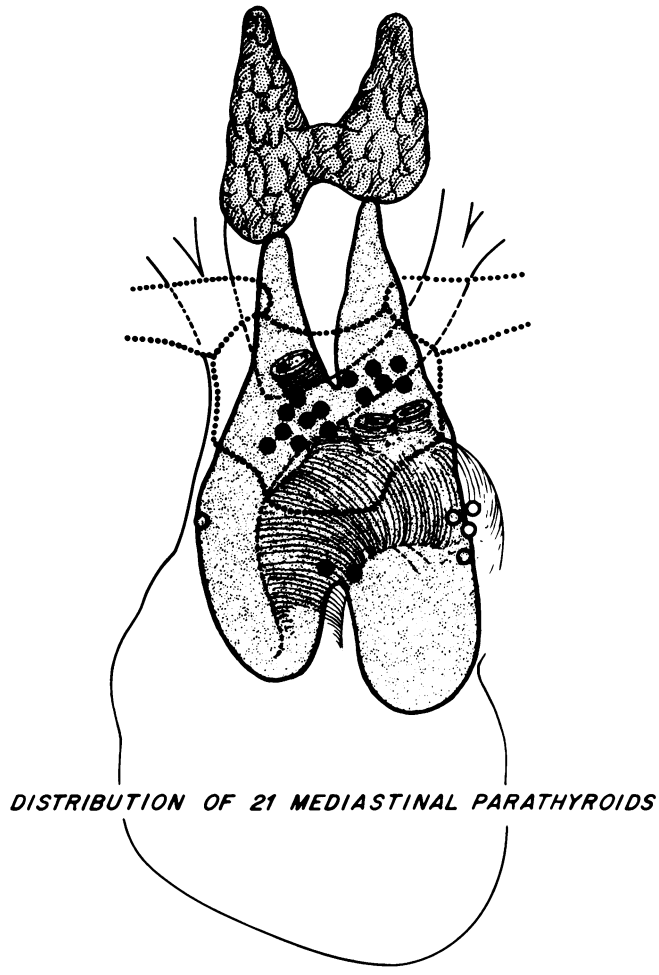

FIG. 2. Schematic representation of sites of 21 mediastinal glands. Solid dots indicate glands enclosed in thymus; open dots, those behind thymus (see text).

Of the 66 patients with an adenoma, 51 required re-exploration of the neck and 15, a mediastinotomy. In each of the 7 patients with a carcinoma, the tumor was recovered from the neck at re-exploration. Of the 29 patients with primary hyperplasia, 23 underwent reoperation of the neck and 6, a mediastinotomy. Six patients had the multiple endocrine syndrome.

Supernumerary and Ectopic Glands

Four patients had a hyperfunctioning fifth gland which was located in the mediastinum in three and behind the cervical esophagus in one. Three of the diseased glands were adenomas, and in one, hyperplasia was the cause of failure in the initial operation.

Each of two patients had an ectopic gland. In one, the gland was intrathyroidal, located within the left thyroid lobe. The other, located behind the angle of the right side of the jaw and associated

TABLE 4. *Pathological Classification of 102 Patients*

	No. of Patients	Excision via Neck	Excision via Mediastinum
Adenoma	66	51	15
Carcinoma	7	7	0
Hyperplasia*	29	23	6

* Twenty-three chief-cell; 6 clear-cell; 6 multiple endocrine syndrome.

with a pad of thymic fat, was likely to be an inferior gland, secondary to developmental arrest.

Results

Complications

Forty-seven patients, nearly half of those in our series, developed transient hypocalcemia with a serum calcium of 8 mg % or lower on the second or third postoperative day, but the symptoms often were mild. These patients rarely required prolonged calcium therapy.

In 20 other patients, two or more normal parathyroid glands had been excised either accidentally or intentionally, and severe hypocalcemia became evident in the immediate postoperative period. In 3 patients, intensive calcium and Vitamin D therapy was needed for a period of more than a year and a half. Because hypocalcemia is likely to become protracted in a patient in this group who had had a benign lesion, the preferred treatment was subtotal ablation of the diseased gland, leaving a small remnant of the hyperfunctioning tissue *in situ* (approximately 75 mg) to obviate the risk of permanent hypoparathyroidism.

Injury to the recurrent laryngeal nerve occurred in 3 patients who subsequently recovered spontaneously.

Unsuccessful Reoperation

In 10 of the 112 patients, the diseased gland was not found at reoperation, and the outcome was considered a failure (Table 5). Four of the 10 died of the disease, and 6 are living. Postmortem examination of the four who died showed an adenoma in the carina in the first, in front of the pulmonary artery in the second, and behind the aortic arch in the third, but none in the fourth patient. All four patients had undergone three or more unrewarding explorations. The disease was relatively mild in the 6 living patients; they were asymptomatic and are currently being treated medically.

Discussion

From this study, it seems clear that ultimate success in the management of patients with continuing hyperparathyroidism depends on the surgeon. He alone must recognize where the mistake lies and how to correct it.

Causes for Unsuccessful Parathyroid Exploration

Of the three causes of unsuccessful parathyroid exploration, by far the commonest was the failure of the surgeon to understand the normal location of the parathyroid glands and the way the glands may be displaced when they become diseased. Despite the wide spread of possible sites, the parathyroid gland generally falls in a fairly definite pattern of distribution, sharing its origin embryologically with the thyroid and the thymus. The adult upper gland (Parathyroid IV) is frequently confined to the lateral posterior surface of the thyrocricoid junction, or the dorsum of the upper pole, and the adult lower gland (Parathyroid III) is located at or near the lower pole of the thyroid or within the thymic tongue. Rarely, the parathyroid gland may be found in an ectopic location.[9] This embryologic relationship of the parathyroid, the thyroid, and the thymus explains why the location of many parathyroid glands is predictable. Failure to appreciate this relationship constitutes the main cause of unsuccessful exploration in many patients. Nineteen of the 110 glands, for example, were overlooked at the dorsum of the upper pole of the thyroid, 10 behind the lower pole of the thyroid, and 13 within the thymic tongue at the thoracic inlet.

A parathyroid gland seldom remains in one place, tending to move about, particularly when it is diseased. One located outside the capsule of the thyroid—the extracapsular gland—tends to be displaced into an area where it encounters the least resistance, most commonly the superior posterior mediastinum. In this series, 34 missing glands were recovered in this location. Similarly, a diseased parathyroid gland within the

TABLE 5. *Unsuccessful Reoperations (10 Patients)*

Case Number*	No. of Operations	Result	Pathology	Site
1	3 (2N, 1M)†	Died	Adenoma	At carina‡
2	3 (3N)	Died	Adenoma	In front of right pulmonary artery‡
3	3 (2N, 1M)	Died	Adenoma	Behind aortic arch‡
4	4 (2N, 2M)	Died	···	Not found‡
5	3 (2N, 1M)	Living	···	Unknown
6	4 (3N, 1M)	Living	···	Unknown
7	2 (2N)	Living	···	Unknown
8	2 (2N)	Living	···	Unknown
9	2 (2N)	Living	···	Unknown
10	2 (1N, 1M)	Living	···	Unknown

* Case numbers 1 through 6 had initial procedure elsewhere and 7 through 10, at Massachusetts General Hospital.
† N, neck; M, mediastinum.
‡ At postmortem examination.

thymic tongue can easily disappear behind the clavicle and sink into the superior anterior mediastinum. This unique characteristic of the parathyroid is rarely appreciated and accounts for the fact that the diseased glands may be readily recovered in some patients and completely missed in others.

The next cause for unsuccessful parathyroid exploration was error in diagnosing the pathologic types of hyperparathyroidism at surgery. As evidenced by 29 patients in this series with primary hyperplasia, hyperparathyroidism had continued despite excision of one or more diseased glands at the initial operation. Intraoperative differentiation of primary hyperplasia from adenoma is not always easy, but it can be done.[3,10] If the macroscopic features of the second gland are clearly normal, the enlarged gland is likely to be a neoplasm, commonly an adenoma.* Excision of the adenoma is all that is needed for cure because the third and fourth glands are generally free of the disease and need not be sought. Double adenomas, if they ever exist, are rare. We have not encountered a case in the last 500 patients with primary hyperparathyroidism treated here.† In contrast, if the second gland is also diseased, the pathologic process must surely involve all the other glands, and the diagnosis is obviously primary hyperplasia. Resection of only one or even two glands is seldom adequate; the removal of three or more may be required. In theory, then, the ideal surgical approach to hyperparathyroidism should be based on the pathologic diagnosis,[8] but if the surgeon is doubtful of the diagnosis, he must by all means search for the remaining parathyroids.

The third cause for lack of success in the surgical correction of hyperparathyroidism is technical incompetence. In more than half the unsuccessful cases, the initial diagnosis of parathyroid tissue later was proved at histological examination to be that of a lymph node or of fat or thyroid tissue. In less than half these patients had two and very rarely, three glands been identified and confirmed.

That surgery of hyperparathyroidism is demanding should go without saying but bears reiteration. A bloodless field, meticulous technique and above all, knowledge of the anatomy of the normal parathyroids and their pattern of distribution are essential to a successful exploration.[2,9]

* Carcinoma is rare and, in general, can be recognized by its stony hard consistency, its whitish-gray color, and its tendency to invade locally.

† The diagnosis of double adenoma in a Massachusetts General Hospital series of 13 patients prior to 1958 subsequently proved to be primary hyperplasia in 6 and has not been conclusively substantiated in the other 7.

Conclusion

To Reoperate or Not to Reoperate

In his eagerness to find the missing gland, the surgeon frequently wants to reoperate on his patient. In general, this is understandable, but not every patient needs the reoperation. If the disease is relatively mild and unaccompanied by metabolic complications, reoperation is not warranted. In fact, a patient with asymptomatic hyperparathyroidism seldom requires an operation and perhaps should not have been operated on in the first place. At the Massachusetts General Hospital, a patient is generally managed medically if the serum calcium level is consistently below 11 mg %, if the plasma parathormone level is undetectable or only slightly elevated, and if the 24-hour-urinary calcium is less than 150 mg. These parameters indicate a mild degree of hyperparathyroidism which is seldom lifethreatening. Furthermore, the missing diseased gland is generally small in these patients and often difficult to find at reoperation. Cases have been well documented that patients with asymptomatic and mild hyperparathyroidism have lived for years without progression of the disease.[4,7]

Reoperation: the Neck, the Mediastinum, or Both

Statistically, very few patients require a mediastinotomy because a mediastinal parathyroid is rare.[9] The majority of the missing glands in our series (81%) were retrieved via the neck where they had been overlooked at the initial operation. Many missing mediastinal glands (67%) were located high in the superior anterior mediastinum, and they might have been retrieved by the same route. It is well, therefore, to defer this procedure until the neck has been thoroughly searched. Four patients in this series underwent exploration first of the neck, then of the mediastinum, and finally, of the neck again where the missing gland was recovered. Mediastinal exploration could have been spared in these four patients had the first exploration of the neck been thorough.

The surgeon may also be guided by the previous operative findings and the localization studies. An inadequate initial exploration of the neck, as evidenced by the finding of only one or even two normal glands, should necessitate reoperation of the neck, unless localization studies clearly demonstrate the presence of a mediastinal parathyroid tumor. In this event, further surgery of the neck is seldom needed.

It is generally preferable to perform a mediastinotomy as a separate operation. Simultaneous exploration of the neck and mediastinum is exhaust-

ing and often ends in only a cursory examination of both.

If thorough search for the missing gland fails repeatedly, it is better for the surgeon to accept defeat than to pursue another fruitless attempt. A medical regime may be a reasonable alternative therapy.

References

1. Bauer, W. and Federman, D. D.: Hyperparathyroidism Epitomized: The Case of Captain Charles E. Martell. Metabolism, 11:21, 1962.
2. Cope, O.: The Story of Hyperparathyroidism at the Massachusetts General Hospital. N. Engl. J. Med., 274:1174, 1966.
3. Cope, O., Keynes W. M., Roth, S. I., and Castleman, B.: Primary Chief-cell Hyperplasia of the Parathyroid Glands. Ann. Surg., 148:375, 1958.
4. Kosinski, K., Roth, S. I., and Chapman, E. H.: Primary Hyperparathyroidism with 31 Years of Hypercalcemia. JAMA, 236:590, 1976.
5. Mandl, F.: Therapeutischer Versuch bei Ostitis Fibrosa Generalisata Mittels Exstirpation Eines Epithelkorperchentumors. Wien. Klin. Wochenschr., 50:1343, 1925.
6. Nathaniels, E. K., Nathaniels, A. M., and Wang, C. A.: Mediastinal Parathyroid Tumors: A Clinical and Pathological Study of 84 Cases. Ann. Surg., 171:165, 1970.
7. Purnell, D. C., Scholz, D. A., Smith, L. H., et al.: Treatment of Primary Hyperparathyroidism: A Prospective Clinical Study. Am. J. Med., 56:800, 1974.
8. Wang, C. A.: Surgery of the Parathyroid Glands. Adv. Surg., 5:109, 1971.
9. Wang, C. A.: The Anatomic Basis of Parathyroid Surgery. Ann. Surg., 183:271, 1976.
10. Wang, C. A. and Rieder, S. V.: Intraoperative Differentiation of Parathyroid Hyperplasia from Neoplasia by Density Test. (in press)