Chapter 137: Surgical Management of Parathyroid Disorders

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Chronic Hyperparathyroidism

Hyperparathyroidism was first recognized as a pathologic entity in 1925. In that year Felix Mandl of Vienna removed a large parathyroid tumor from his patients, "Albert" (Mandl, 1926). Albert had osteitis fibrosa cystica, a severe bone disease that had failed to respond to treatment with animal parathyroid extract and transplanted human parathyroid glands. As a last resort Mandl operated on Albert and removed a large parathyroid tumor. Albert's bone symptoms improved, and nearly 6 years passed before he had a recurrence of the disease. Mandl's first accounts were published in 1925 (Cope, 1966).

In 1926 Capt. Charles E. Martell of the United States Merchant Marines was the first patient in North America in whom hyperparathyroidism was diagnosed preoperatively. He was also the first in whom mediastinal exploration was performed successfully (Bauer and Federman, 1962; Cope, 1966). He suffered from a bone disease similar to Albert's; he sustained eight fractures, and in 6 years his height decreased by 7 inches. Between 1926 and 1932 Martell underwent six unrewarding neck explorations, three at Massachusetts General Hospital (MGH) and three elsewhere. Finally, in 1932, after he had suffered for 14 years, including 18 months of study in two metabolic wards, a large mediastinal adenoma was excised through a sternum-splitting procedure (Bauer and Federman, 1962; Churchill and Cope, 1934).

Martell withstood the procedure well; his bones began to heal, and a month later he was able to stand. However, as he was making this promising recovery, a renal calculus lodged in his ureter, and surgical intervention was required. He died fro complications about 6 weeks later.

Clinical features

Four diagnostic clues for hyperparathyroidism are well recognized. *Osteitis fibrosa cystica,* the first clue, described by von Recklinghausen in 1891, is a classic example of severe metabolic complication of hyperparathyroidism. Although bone changes with typical brown tumors have been encountered less frequently in more recent times, the diagnosis of hyperparathyroidism is still being made on the basis of bone pain caused by generalized demineralization or pathologic fractures.

Albright et al (1934b) first noted the association between hyperparathyroidism and *renal calculi.* The calculi form as a result of excessive excretion of calcium in the urine. Careful screening of patients with renal calculi frequently reveals concomitant hyperparathyroidism. Renal calculus is the most common metabolic complication of this disease.

Rogers was the first to appreciate the significance of the association of *peptic ulcer* with hyperparathyroidism (Rogers, 1946; Rogers et al, 1947). Many patients with hyperparathyroidism

suffer at one time or another from some form of gastrointestinal disorder. In some cases an ulcer is discovered by radiographic examination during the initial investigation; other patients have a history of gastric disease. The symptoms and signs of an ulcer may serve as a clue to the diagnosis of the hyperparathyroidism.

Cope et al (1957) first recognized the association of hyperparathyroidism with *pancreatitis,* which occurs in a small number of patients (Mixter et al, 1962). Is the association of these two diseases merely fortuitous or are they interdependent? Haverback et al (1960) demonstrated that by adding bovine trypsin to pancreatic juice collected from patients suffering from a wide variety of pancreatic and biliary diseases, titration of tryptic activity is possible. When a greater concentration of calcium ion is added, an equal amount of trypsin activates more trypsinogen. This observation shows that the amount of calcium ion present directly controls the activation of trypsinogen. Possibly in hyperparathyroidism the serum calcium reaches a level sufficiently high to increase the tryptic activity, which, in turn, causes acute pancreatitis.

The pseudogout syndrome with concomitant hyperparathyroidism is encountered in some patients (Wang et al, 1969). The diagnosis is based on clinical findings, radiographic evidence of chondrocalcinosis, and the presence of calcium pyrophosphate crystals in the joint fluid. The pathogenesis of chondrocalcinosis is not clear, although hypercalcemia probably potentiates the precipitation of calcium pyrophosphate crystals in the cartilages in the same way that it potentiates nephrocalcinosis in the renal parenchyma.

Other symptoms of hyperparathyroidism are often vague and nonspecific. The surgeon must therefore be aware of the diverse clinical manifestations of hyperparathyroidism and be constantly alert for the possibility of its presence. Table 137-1 lists the symptoms experienced by patients with primary hyperparathyroidism who were treated at Massachusetts General Hospital.

Pathology

Adenomas

An adenoma causes primary hyperthyroidism in about 83% of patients. The diagnosis of an adenoma can be confirmed only by the presence of a second, normal gland or of a small remnant of normal tissue from the involved gland (Castleman and Roth, 1978).

Adenomas vary greatly in size and shape. The largest gland in the MGH series weighed 49 g and the smallest, 100 mg. The adenoma may be ellipsoid, round, or oval (Fig. 137-1). Its shape is invariably affected by its location. In the superoposterior mediastinum where there is ample room to accommodate its expansion, it is shaped like a pear or a teardrop suspended by a vascular pedicle from one or more branches of the inferior thyroid artery. An adenoma located in the space behind the upper pole of the thyroid frequently lies within the thyroid capsule where it is flat because the thyroid capsule compresses it. Within the thymus gland or thymic tongue the adenoma is often round. An adenoma is well encapsulated, smooth, and readily resectable.

The color of the adenoma in situ is characteristically beefy red. It appears orange-brown following resection, whereas the normal gland is yellowish tan or yellowish brown. Histologically, chief cells are predominant. Occasionally a few stromal fat cells and intracellular fat granules are present.

Primary hyperplasia

Primary hyperplasia of clear cells or chief cells is the second most common pathologic entity of primary hyperparathyroidism. Thirteen percent of the patients with hyperparathyroidism in the MGH series had hyperplasia. *Clear cell* hyperplasia was first reported in the 1930s (Churchill, 1933; Albright et al, 1934a). Macroscopically the parathyroid gland is chocolate or dark brown. Its shape is often irregular with pseudopodal projection. Microscopically the gland consists entirely of large clear cells (Fig. 137-2). The incidence of this type of hyperplasia has declined in recent years (Wang et al, 1982).

Chief cells hyperplasia was first described by Cope et al in 1958, and the incidence has been increasing in recent years. Grossly and microscopically, chief cell hyperplasia is indistinguishable from an adenoma. In both entities the cellular components of the gland are predominately chief cells (Fig. 137-3). The single reliable diagnostic feature of primary hyperplasia is the presence of more than one diseased gland. For this reason the otolaryngologist - head and neck surgeon must search for a second gland if one diseased gland is found. It is vitally important to identify and prove by biopsy at least one other hyperplastic gland. The presence of a second diseased gland is generally sufficient evidence on which to base the diagnosis or primary hyperplasia. Conversely, if the second gland is normal, the diagnosis is adenoma, not primary hyperplasia.

Primary hyperplasia can be differentiated from adenoma by the density test (Wang and Rieder, 1978). This simple test can be performed at surgery. It is based on the difference in density between normal and diseased parathyroid tissue (Fig. 137-4). Whereas the normal parathyroid tissue floats in a mannitol solution with a density range between 1.049 and 1.069, the diseased tissue invariably sinks. If both tissues sink within this density range, the diagnosis is primary hyperplasia without exception even if the gland is of average size or only slightly enlarged. The density test provides a valuable clue in the differentiation of primary parathyroid hyperplasia from neoplasia.

Not all hyperplastic parathyroid glands are the same size, and hence size alone is not a reliable indicator of normalcy of a parathyroid gland. In fact, in most cases of primary hyperplasia the upper glands are much larger than the lower (Fig. 137-5). Castleman and Roth (1978) found that in about 50% of patients, only one or two glands were significantly enlarged; and the others were only slightly enlarged or nearly normal in size. Such lack of uniformity in the size of the parathyroid glands has often led to an incorrect diagnosis of double or triple adenomas rather than primary hyperplasia.

Carcinomas

Parathyroid carcinomas are a rare cause of hyperparathyroidism. Of the first 1000 cases of hyperparathyroidism treated at the MGH, only 28 (3%) were caused by parathyroid carcinomas. The clinical manifestation of hyperparathyroidism resulting from a parathyroid carcinoma is indistinguishable from that caused by benign parathyroid enlargement. Either pathologic entity may cause metabolic complications, such as renal calculi or bone disease. Some patients have both renal calculi and bone disease, although these manifestations are generally more severe in patients with parathyroid carcinomas than in those with a benign parathyroid disorder.

The characteristic features of a parathyroid carcinoma are the significant elevations of the serum calcium and parathyroid hormone (PTH) levels. Although making the diagnosis of a parathyroid carcinoma preoperatively is seldom possible, one must suspect a parathyroid carcinoma on the basis of symptomatology when the serum calcium level exceeds 14 mg/100 mL and the PTH rises three to four times higher than the normal range (Holmes et al, 1968; Wang and Gaz, 1985).

The macrosopic features of a parathyroid carcinoma are unmistakable. The malignant tissue is grayish white and has a stony consistency. An intense local reaction often exists around the carcinoma, with evidence of local invasiveness. The recurrent laryngeal nerve, the esophagus, and the trachea are frequently invaded. Microscopically the presence of fibrosis, trabeculation, and mitoses intermingled with large pleomorphic chief cells is pathognomonic of a parathyroid carcinoma (Fig. 137-6).

Diagnostic assessment

Diagnosing hyperparathyroidism is not always easy and at times can be extremely difficult. Traditionally hypercalcemia was presumed to be a sine qua non diagnostic feature of hyperparathyroidism (Avioli, 1958; Keating, 1961). This assumption, however, is no longer tenable because hypercalcemia is frequently encountered in patients with malignancy, both with and without osseous metastasis. According to Lafferty (1966), metastatic bone disease and multiple myeloma account for more than half the cases of hypercalcemia, whereas pseudohyperparathyroidism is responsible for only 15% and primary hyperparathyroidism for only 20%. Hypercalcemia occurs in patients who have a hematologic malignancy or bone metastases of a solid tumor, such as of the lung, pancreas, bone, ovary, breast, kidneys, and prostate (Galasko and Burn, 1971; Myers, 1960; Powell et al, 1973). Furthermore, the factors contributing to hypercalcemia are not clear (Mundy et al, 1984). Eliminating malignancy as an underlying cause of hypercalcemia can be one of the most difficult diagnostic undertakings. For this reason diseases other than primary hyperparathyroidism must be included in the differential diagnosis of hypercalcemia.

The serum calcium level fluctuates in both health and disease. In patients with hyperparathyroidism the serum calcium level may be normal or even below the normal value.

In massive ulcer hemorrhage, fulminating acute pancreatitis, severe burns, or extreme malnutrition, the total serum calcium level is reduced secondary to the excessive loss of the protein-bound fraction of calcium. Under these circumstances the diagnosis of primary hyperparathyroidism may be masked. Thus the serum calcium determination, with allowance for the protein loss, becomes of utmost importance. As a rule of thumb, 1 mg of calcium may be allowed for each gram of protein loss. For example, if the serum calcium level is 10 mg/100 mL in a patient with a total protein level of 5 g/100 mL, the corrected serum calcium value is 11 mg/100 mL. This patient is hypercalcemic and is suspected of having primary hyperparathyroidism.

By contrast, the diagnosis of hyperparathyroidism is usually considered tenuous in the absence of hypercalcemia. Cope et al (1961) explored 17 patients with renal calculi who had consistently normal serum calcium levels but low phosphorus values. They found no abnormal parathyroid glands in any of these patients. In many patients the primary defect appears to be in the kidney, which accounts for the excretion of a huge amount of calcium phosphate in the urine. This constitutes a separate disease entity, namely, idiopathic hypercalcuria, which is unrelated to hyperparathyroidism. Cope (1961) concluded that exploration is seldom a satisfactory method of differentiating primary hyperparathyroidism from idiopathic hypercalcuria.

The introduction of radioimmunoassay for parathyroid hormone has simplified the diagnosis of hyperparathyroidism (Potts, 1980). If plasma parathyroid hormone levels are consistently elevated, the diagnosis of hyperparathyroidism is presumed. In some malignancies, however, the parathyroid hormone may be slightly elevated and in about 20% of asymptomatic patients with hyperparathyroidism proven by surgery, the PTH is barely above the upper limits of normal (Neer, 1984). Thus the diagnosis of hyperparathyroidism based on the measurement of parathyroid hormone alone can be questionable.

Despite the difficulties encountered in the differential diagnosis, a persistently elevated serum calcium level with a concomitantly elevated PTH level is probably the most reliable evidence for the diagnosis of hyperparathyroidism.

Management

The surgical management of hyperparathyroidism must be based on the pathologic entities of the disease. If the diagnosis of an adenoma is confirmed, excision of the diseased gland is all that is required. If primary hyperplasia is confirmed by the presence of more than two diseased glands, a resection of three and part of the fourth gland is mandatory. Total parathyroidectomy with autotransplantation has been advocated (Wells et al, 1976), but this approach should be reserved for patients in whom a subtotal resection is neither advisable nor feasible. The incidence of permanent hypoparathyroidism is high if routine total parathyroidectomy is done by inexperienced surgeons (Wang et al, 1977).

The management of a parathyroid carcinoma is entirely different from that of adenoma and requires aggressive yet meticulous surgery. An en bloc resection including the excision of

a wide margin of normal tissue is needed. Care must be taken to avoid violation of the tumor capsule or spillage of the tumor cells. With anything less than the most scrupulous care in handling, the disease will be inevitably recur. Routine radical dissection of the neck, however, is not recommended, because the disease often spreads by local extension, sparing the cervical lymph nodes until a later date (Wang and Gaz, 1985).

Indications for surgery

Patients with metabolic complications of hyperparathyroidism such as renal calculi, bone disease, ulcers, and pancreatitis should have surgery because these complications tend to become worse. As the disease progresses, ultimately the patient may die. Thus surgery is clearly indicated in patients with one or more of the metabolic complications of hyperparathyroidism.

Patients who are asymptomatic and have no metabolic complications pose an entirely different problem. No hard and fast rule exist concerning whether or not these patients should undergo surgery, although the current trend seems to favor early surgical intervention (Attice and Khafit, 1976; Heath et al, 1980; Scholz and Purnell, 1981). In approximately 25% of asymptomatic patients the disease will progress, and they will develop some form of metabolic complications within 5 years (Scholz and Purnell, 1981).

Although surgery is a preventive measure against the development of complications, those opposing surgery believe that in some of these patients the disease will remain asymptomatic and may even regress. Thus surgery may be postponed at least temporarily or until signs of progressive disease become apparent (Gaz and Wang, 1984). Surgical intervention is not indicated in patients in whom the disease is mild and asymptomatic. It is advised only for those whose disease is relatively severe. If the serum calcium level is consistently elevated in the range of 11 mg/100 mL, if the PTH is inappropriately higher than normal, if the 24-hour urinary calcium excretion exceeds 150 mg, or if evidence of deteriorating renal function or loss of bone mass exists, surgery should be seriously considered. These criteria are admittedly arbitrary, but they take into account the difficulty one may encounter in determining the diseased gland, which may be only slightly larger than normal, or in making a pathologic diagnosis when the gland is only slightly diseased. For this reason surgery or asymptomatic patients should be highly selective and individualized and never undertaken indiscriminately.

Preoperative localization

Parathyroid glands are rarely palpable. In the neck they are obscured by the thyroid or the trachea or are in the tracheoesophageal groove where they are difficult to detect. When they are located deep in the mediastinum, they are beyond the reach of the finger.

Opinions differ about the role of preoperative localization in the surgical management of patients with hyperparathyroidism. Considerable controversy has existed over whether preoperative localization studies should ever be used. The consensus of opinion is that although some of the studies are extremely useful, they are indicated only in patients who have had

previous hyperparathyroid surgery. In these cases accurately localizing the gland reduces operative time, risk from anesthesia, and morbidity. Because the success rate for locating the gland in parathyroid surgery for a primary case is as high as 95% ni the hands of an experienced surgeon, little justification exists for the routine use of preoperative localization studies (Russell and Edis, 1982; Graham et al, 1980).

Those who favor the use of preoperative studies point out that a single hyperfunctioning parathyroid adenoma is the cause of hyperparathyroidism in over 80% of patients, and expeditious excision of the adenoma can be accomplished if the adenoma is accurately localized. Exploration of the contralateral side of the neck is not needed. Most patients can go home on the third postoperative day. This approach is used at Massachusetts General Hospital.

Many procedures have been devised in the quest for a sensitive means of localization. High-resolution, real-time ultrasonography is now used in place of cine-barium swallow, which was used for many years. Because many patients are asymptomatic, the diseased parathyroid glands are relatively small and can seldom be localized by cine-esophagram. Ultrasonography, however, can pinpoint a diseased gland as small as 0.5 cm. The sensitivity of ultrasonography is about 80%; the specificity is 95% (Reading et al, 1982; Simeone et al, 1981).

Recently, a duo-imaging procedure with both technetium (^{99m}Tc) and a thallium (^{101}T) has been introduced to be used as an alternative to ultrasonography. Although it is too early to predict the role of this procedure in localization, it appears to be promising (McKusick et al, 1984; MacFarlane et al, 1984).

Computerized tomography (CT) is useful for locating a parathyroid gland deep in the mediastinum, if the parathyroid mass is larger than 1 to 2 cm (Stark et al, 1983).

Selective venous catheterization and arteriography are two highly sophisticated invasive localization procedures that have been used primarily for complicated reoperative cases (Brennan et al, 1982; Doppman, 1976). They are useful in many cases, but they are time consuming and not without risk. Moreover, because these studies are often very expensive, they must be used with discretion.

Location of the parathyroid glands

In managing patients with hyperparathyroidism the surgeon's primary concerns are to find and excise the diseased parathyroid. The exact location of the diseased gland and the extent of surgery required must be determined.

The parathyroid gland has a unique embryologic relationship with the thyroid and the thymus glands (Norris, 1937; Weller, 1933). The upper, or adult superior, parathyroid gland shares a common primordium in the fourth branchial pouch with the lateral thyroid, which subsequently fuses with the median thyroid gland. Thus the upper parathyroid gland and the thyroid gland are close together. Occasionally an upper parathyroid gland is embedded within the

parenchyma of the thyroid gland, thus becoming an intrathyroidal parathyroid. A diseased intrathyroidal parathyroid gland may appear as a solitary "cold" thyroid nodule by radioactive iodine scanning. A diseased parathyroid of this type was the cause of failure of parathyroid exploration in six patients in the first 1000 cases of the MGH series. Understanding this unique embryologic relationship is important. When an adult upper parathyroid gland is missing at the time of the cervical exploration, an intrathyroidal parathyroid must be suspected (Fig. 137-7). A thyroid lobectomy is necessary to exclude such a probability.

The lower, or adult inferior, parathyroid gland originates within the thymus in the third branchial pouch. As this complex descends caudally, the lower parathyroid gland often becomes dissociated from the thymus and is located in the lower part of the neck, usually in the vicinity of the lower pole of the thyroid. An occasional lower parathyroid gland continues its course with the thymus into the mediastinum. Therefore, the lower gland has a much wider distribution than the upper one. The unique embryologic relationship between the lower parathyroid and the thymus gland explains why the lower parathyroid gland is more difficult to find than the upper gland.

Occasionally a patient has more than four parathyroid glands. This supernumerary gland, whether fifth or sixth, is frequently associated with the thymus (Wang et al, 1979). Embryologically this gland is likely to be a lower one and may be located anywhere in the neck or occasionally, in the mediastinum (Fig. 137-8). Such a gland has been the cause of failure of parathyroid exploration in a small percentage of cases.

Despite the diversity in their embryologic development and widespread distribution, the parathyroid glands often can be found quite readily because they generally follow a fairly constant anatomic pattern (Gilmour, 1938). According to Wang's 1976 study of parathyroid dissection, over 98% of the normal parathyroid glands are confined to the neck; only 2% are situated deep within the mediastinum. Most (77%) upper parathyroid glands are located at the posterior aspect of the cricothyroid junction; 22% are in the dorsum of the upper thyroid pole. Less than 1% are in an ectopic position (Fig. 137-9). Forty-two percent of the lower parathyroid glands are found in and around the lower pole of the thyroid; 39% are within the thymic tongue. Rarely, a lower parathyroid gland is located behind the pharynx or the angle of the jaw (Fig. 137-10).

Theoretically, based on their anatomic distribution, the parathyroid glands should be easy to find; unfortunately, this is not so. When the parathyroid glands become enlarged and diseased, they rarely remain in one place. Many of the parathyroid glands are displaced downward into the superoposterior or superoanterior mediastinum where they may easily disappear from sight. Because of this pathologic displacement, the surgeon often misses the diseased glands at the time of exploration.

Extent of surgery

The extent of surgery depends on the cause of the hyperparathyroidism (Wang, 1966). Primary hyperparathyroidism results from an excess of parathyroid hormone secreted by a neoplasm, an adenoma, a carcinoma, or primary hyperplasia. The adenoma is the most common cause (Table 137-2). This disease involves only one or part of one gland. The second most common entity is primary hyperplasia, a disease that invariably involves all four and sometimes five glands. Less common than either the adenoma or primary hyperplasia is carcinoma, which, like an adenoma, involves only one gland. The so-called double adenomas, if they ever existed, are extremely rare. Early in the experience of Massachusetts General Hospital 13 patients were classified as having double adenomas, but these were subsequently confirmed to be primary hyperplasias because the disease involved more than two glands. We have not encountered a single case of double adenoma in the last 800 cases of hyperparathyroidism.

Table 137-2. Pathologic entities of primary hyperparathyroidism in the first 1000 patients at MGH 1930-1980.

Pathology	**No of patients**	**Percent**
Adenoma	832	83
Hyperplasia	127	13
Clear-cell	106	
Chief-cell	21	
Carcinoma	28	3
"Double adenomas"*	13	1

* Provisional diagnosis.

Mediastinal exploration

Parathyroid surgery is usually relatively straightforward. Success may be expected in 95% or more of the cases (Russell and Edis, 1982; Satava et al, 1975). In about 5% of patients, however, the diseased gland is located deep in the mediastinum (Wang, 1977). Exploration of the neck in these cases is obviously insufficient and mediastinostomy is required.

Mediastinal exploration is seldom performed at the same time as the initial cervical operation. Because of the stamina and long hours that may be required to perform a thorough cervical exploration, Cope (1941) advised a staged mediastinal operation. If performed simultaneously with the initial cervical operation, mediastinal exploration can prove to be overwhelming and too fatiguing. Consequently, the search for the diseased glands will be cursory rather than thorough and the results correspondingly disappointing. Furthermore, the initial diagnosis in some patients may well be erroneous in which case exploration of the mediastinum is obviously pointless. Thus a two-stage exploration has become the practice in most large

centers. In an exceptional case, such as acute parathyroid crisis, exploration of the neck and the mediastinum by a one-stage cervicomediastinal approach is occasionally considered mandatory.

A partial or complete sternotomy generally provides adequate access for the mediastinal exploration (Wang, 1977; Wang and Guyton, 1983). Because most mediastinal parathyroid glands are located within the thymus (Fig. 137-11), it should be the first place to search. A small number of mediastinal parathyroid glands are located deep in the anterior mediastinum (Fig. 137-12). They are wedged between the pleural reflection and the pericardium on the left and the pleura and the great vessels on the right. In one patient a parathyroid adenoma was located in the posterior mediastinum at the level of the carina. The key to successful mediastinal exploration is a meticulous, systematic search. The space in front of and behind the great vessels should be thoroughly explored. The remnant of the thymic tongue in the neck and the carotid sheath should also be examined (Wang and Guyton, 1983).

Postoperative course

Postoperatively the serum calcium may take one of three courses. First, it may plummet to a normal level within 24 hours. This dramatic response occurs after successful removal of an adenoma or carcinoma. The patient experiences significant hypocalcemic symptoms, including paresthesia of the fingers, toes, and lips. Circumoral pallor occurs, which is apparently associated with positive Chvostek's or Trousseau's sign. These features reflect a state of subclinical hypoparathyroidism in which the suppressed parathyroid glands have not as yet resumed their normal function. A physiologic parathyroprivia exists. The intensity of the symptoms and signs and the rapidity of the fall of the serum calcium level are directly proportionate to the severity of the disease. If the patient has little or no involvement of the skeletal system, hypocalcemia is transient and self-limiting, and exogenous calcium supplementation is seldom needed. However, if the patient has significant skeletal demineralization, as demonstrated by an elevated serum alkaline phosphatase level or by radiographic evidence of bone resorption, the fall of the serum calcium is even greater and the symptoms are more intense (Fig. 137-13). Under these circumstances, hypocalcemia is often protracted, and the patient requires intense therapy with calcium and vitamin D. Ultimately, hypocalcemia will revert to normocalcemia.

Second, after the excision of two diseased hyperplastic glands, the serum calcium remains at the preoperative level or falls slightly (Fig. 137-14). A postoperative course with persistent hypercalcemia is almost certainly caused by residual primary hyperplasia. More of the remaining hyperplastic tissue must be resected before the serum calcium will return to a normal level. Patients with primary hyperplasia rarely show any signs or symptoms of marked hypocalcemia after a subtotal parathyroidectomy unless they have extensive bone disease. No physiologic parathyroprivia exists as would occur in patients after the removal of a parathyroid adenoma or carcinoma. After subtotal resection, the remnant of hyperplastic tissue often sustains calcium homeostasis. Hardly any need exists for supplemental calcium. This subtle but unequivocal distinction in the postoperative response of the serum calcium level to surgery is an aid in differentiating hyperplasia from neoplasia.

Third, the serum calcium level may remain elevated after removal of all four parathyroid glands, but no evidence of hypocalcemia appears as would occur after inadvertent excision of or injury to one or more of the parathyroid glands during a thyroidectomy. In such a case a hyperfunctioning supernumerary parathyroid gland probably causes the hypercalcemia. Hypercalcemia will persist no matter how many normal glands are excised. The hyperfunctioning supernumerary gland must be excised before the serum calcium will revert to the normal range.

Complications

Occasionally serious complications occur. For example, a renal calculus may crumble as it forces its way down thus precipitating acute renal colic. Ureteral calculus has caused acute obstruction in patients as early as the second day after surgery and as late as several months postoperatively. Most small calculi will pass spontaneously although occasionally cystoscopic or even operative removal is required.

Infection of the urinary tract accompanied by gram-negative septicemia is potentially a serious threat, and measures must be taken to guard against its occurrence. For this reason urinary catheterization should be used only when necessary. Most patients can void spontaneously without difficulty. Should a urinary tract infection develop, the bacteria flora must be identified, and sensitivity to the antibiotic must be determined before treatment is initiated.

Pancreatitis occasionally occurs during or after surgery, which greatly compounds management. As the serum calcium level plummets precipitously to the tetanic range, so does the level of magnesium (Fig. 137-15). Intensive replacement therapy is essential for both, particularly to correct the severe hypomagnesemic state. Primary hyperparathyroidism is often associated with a negative magnesium balance because of increased urinary loss. After surgical correction of hyperparathyroidism, the plasma magnesium level falls. The calcemic and phosphaturic effects of parathormone are magnesium dependent; hypocalcemia in the severely hypomagnesemic state is caused by PTH unresponsiveness and is corrected only by magnesium replacement (Estep et al, 1969).

Reoperation

The operative difficulties are formidable, the failure rate is high, and the outcome unpredictable for a second parathyroid procedure. Of three possible causes of unsuccessful parathyroid surgery, by far the most common is the surgeon's failure to understand the anatomic distribution of the normal parathyroid glands and the way the glands may be displaced when they become diseased. A second cause is an error in the diagnosis of the pathologic entity of the disease at the time of the initial surgery. In primary hyperplasia, hyperparathyroidism often persists if only one or two glands have been excised. Excision of three or more glands is needed for cure. The third cause for unsuccessful exploration is technical incompetence. In more than half of the unsuccessful cases referred to Massachusetts General Hospital, the tissue diagnosed as parathyroid in the initial operation proved to be lymph node, fat, or thyroid tissue. In fewer

than half of the referred patients examined only one or, very rarely, two glands had been identified at the initial exploration. The exploration was clearly inadequate.

Before reoperation three questions must be answered affirmatively: (1) Is the diagnosis of hyperparathyroidism unequivocal and has pseudohyperparathyroidism been excluded? (2) Is the disease severe enough to justify a reoperation? (3) Is the patient a reasonably good surgical risk to undergo the procedure?

Preoperative localization is essential in an attempt to pinpoint the missing gland. Noninvasive studies such as the high-resolution real-time ultrasonography or duo-imaging procedures with thallium scanning should be tried first. If these tests are not revealing, one or more of the invasive procedures such as arteriography or selective venous catheterization study may be helpful. The success of localization depends on the size and location of the missing gland, as well as on the radiologist's experience.

Because 80% or more of the missing glands are located in the neck, unless clear evidence shows that the missing gland is mediastinal, neck exploration should be repeated first (Wang, 1976).

In the reoperation of the neck a lateral approach is best when entering the tracheoesophageal groove (Wang and Guyton, 1983). (1) It is usually found in the superoposterior mediastinum, where it has been displaced caudally from the cricothyroid junction. It is tucked behind the trachea and the cervical esophagus at the thoracic inlet. (2) The gland may be wedged between the lateral wing of the thyroid cartilage and the upper pole of the thyroid, in which case it is invariably located within a fibrosed, indurated, surgical capsule of the thyroid. It can be readily uncovered by taking down the upper pole of the thyroid. (3) The gland may be in the cervical thymic tongue behind the sternothyroid muscle at the thoracic outlet. (4) The gland may be in the lower pole of the thyroid, either close to the thyroid lobe or displaced slightly laterally. (5) In a few cases the diseased glands are uncovered in the retropharyngeal space or submerged in the crevices of the thyroid where they may be mistaken for a thyroid nodule. (6) In a small number of patients the missing gland is located behind the angle of the jaw.

When the missing gland is finally found, the operator's natural impulse is to excise it, but to do so would be unwise. Unless one or more normal glands are left, the missing gland may be the only gland that was not touched in the previous exploration. Keeping a small remnant of benign tissue in situ is essential. Autotransplantation of the excised glandular tissue may be required in a few cases. Cryopreservation of a piece of the tissue may be necessary. If this is done, it will be possible to determine if autotransplantation is really necessary and also if the excised tissue is benign or malignant before it is implanted.

Acute Hyperparathyroidism

Clinical features

In the majority of patients hyperparathyroidism runs a chronic course, and years pass before the clinical manifestations become apparent. Occasionally, however, acute hyperparathyroidism occurs that requires immediate treatment. The patient complains of intense bone pain accompanied by nausea, retching, and often bilious vomiting. The serum calcium level rises rapidly from a relatively low level to 14 mg/100 mL or higher, with a concomitantly increasing elevation of the blood urea nitrogen (BUN) and the creatinine levels. The patient can become oliguric or anuric, quickly lapse into a coma, and die. Acute hyperparathyroidism is also known as *acute parathyroid poisoning* and *parathyroid crisis* (Albright and Reifenstein, 1948; Lowenberg and Ginsberg, 1932).

The clinical manifestations of acute hyperparathyroidism are indistinguishable from those of hypercalcemia caused by a malignancy or pseudohyperparathyroidism, and the diagnosis of acute hyperparathyroidism is not always easy to make. A careful and thorough clinical assessment is extremely important. In acute hyperparathyroidism the PTH is almost always markedly elevated. In over 70% of cases there is evidence of subperiosteal resorption of the phalanges or the loss of lamina dura of the teeth. If these findings are evident, the diagnosis is confirmed (Wang and Guyton, 1979). Pseudohyperparathyroidism and acute hypercalcemia arising from a malignancy, however, are not always curable, whereas acute hyperparathyroidism is. Therefore every effort must be made to exclude pseudohyperparathyroidism and to prepare the patient for prompt surgical intervention.

Management

Acute hypercalcemia must be vigorously treated with saline infusion, furosemide, and electrolyte replacement solution (Neutra-phos), and, if necessary, mithramycin. Many patients respond favorably to this therapeutic regimen, and the serum calcium level falls dramatically within 24 to 48 hours. As massive saline infusion therapy is continued, interstitial edema increases, rendering the operative search for the parathyroid glands extremely difficult. Operating no later than 3 to 4 days after the patient has been clinically well prepared is preferable.

Surgery

Acute hyperparathyroidism is one of the few endocrine surgical emergencies, and prompt surgical intervention is imperative. Because the diseased gland is generally large, finding it at surgery is relatively easy. If preoperative localization by ultrasonography or CT scan is revealing, surgery can be carried out expeditiously. Over 90% of the patients have an adenoma, and excision of the diseased gland is generally adequate for cure. In those rare instances when primary hyperplasia causes the disease, excision of more than one gland is required.

Postoperative course

The postoperative course is often gratifying. Most of the symptoms will disappear within 24 hours after surgery. The serum calcium level generally falls slowly, taking 4 to 5 days to return to normal (Fig. 137-16). In this type of patient the large calcium pool in the interstitial tissue space will take time to dissipate. Of the 27 patients with acute hyperparathyroidism treated at MGH between 1930 and 1982, 25 lives after undergoing immediate surgery; 2 who did not have surgery died (Wang and Guyton, 1979). Prompt surgery is the only effective treatment of the disease.

Summary

Considerable progress has been made in the last 60 years in the diagnosis and treatment of hyperparathyroidism, although much still remains to be learned about the natural history of the parathyroid disorders. The surgeon must know not only where to look for the parathyroid glands but also how to differentiate a diseased from a normal gland. He must also understand the pathophysiology of the disease in order to determine how extensive the surgery should be.