Clinic Rev Bone Miner Metab (2007) 5:75–80
DOI 10.1007/s12018-007-0002-z

Historical Perspectives on Parathyroid Surgery

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Published online: 1 September 2007

Abstract The field of parathyroid surgery is rich in history. It begins with an obscure publication by a Swedish medical student noting a distinct anatomic entity in the neck adjacent to the thyroid gland; these tiny glands would come to be known as the parathyroid glands. This was followed by the subsequent discovery of their role in calcium metabolism, once the devastating effects of hyperparathyroidism on the bones and kidneys were recognized. The first neck explorations with identification and removal of parathyroid adenomas took place in the early twentieth century. Following the initial parathyroid operations in the United States and Europe, the mid-twentieth century was dominated by extensive investigation into calcium metabolism and the effects of parathyroid hormone and by refinement of techniques in parathyroid surgery. In more recent years, the introduction of sophisticated localization studies and minimally invasive parathyroid operations continues to inspire progress in this unique and fascinating field. In this review, the sequence of events starting with the anatomic recognition of the parathyroid glands and ending with the most recent developments and advances in parathyroid surgery are described.

Keywords Parathyroid · Parathyroidectomy · PTH monitoring

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Introduction

There are few areas in medicine as filled with fascinating history as the field of parathyroid surgery. The anatomic discovery of the parathyroid glands, the evolution of the study of calcium metabolism, the recognition of the pathologic condition of excessive parathyroid hormone secretion, and the development of precise surgical techniques all interacted over time to contribute to our knowledge and understanding of parathyroid disease and how best to treat it. Furthermore, recent developments facilitating new minimally invasive approaches have propelled the realm of parathyroid surgery even further forward. This chapter begins with the recognition, over a century ago, of the parathyroid glands as a distinct anatomic entity, and walks through the subsequent discoveries across continents and time that have brought us to the understanding of parathyroid disease and the role of surgical treatment as we know it today.

First Anatomic Description of Parathyroid Glands

Unlike the thyroid gland, the parathyroid glands are, by nature of their small size and subtle appearance, not an obvious anatomic entity. Early autopsies did not identify these glands as separate anatomic structures, likely by virtue of their resemblance to perithyroidal fat and thymic tissue. The very first anatomic description was published in 1862 by Richard Owen who noted a parathyroid gland at necroscopy of an Indian Rhinoceros at the London Zoo [1]. Several years later, in the late 1870s, a Swedish medical student by the name of Ivar Sandstrom embarked on a more detailed investigation of the parathyroid glands. He studied their anatomy and histology in both animals and at human

autopsies, and published his results in a Swedish medical journal in 1879 [2–3]. At the time of these anatomic descriptions, the function of the parathyroid glands and their role in calcium metabolism was unknown.

Early Clues to Parathyroid Function

Also in the latter half of the 1800s, in parallel with the recognition of the anatomic presence of the parathyroid glands, clues to parathyroid function were emerging. Prior to the widespread recognition of the parathyroid glands as distinct anatomic structures, these observations were related to the consequences of parathyroid gland removal following thyroid surgery, with tetany noted in dogs and humans following thyroidectomy. This led to the obvious and incorrect assumption that post-operative tetany was specifically a result of thyroid removal. In fact, William Ord and Victor Horsely of London who investigated effects of thyroidectomy such as tetany and later, myxedema, attributed the muscle twitching noted post-thyroidectomy in monkeys directly to removal of the thyroid gland [4–5].

At approximately the same time, Moritz Schiff of Switzerland reported his observations of fatal tetany after thyroidectomy in dogs and guinea pigs. Schiff, however, took his investigation one step further, and in 1884 noted that autotransplantation of the thyroid into the abdomen after thyroidectomy prevented tetany [1]. It is important to note that at this point in time the connection of muscular twitching and tetany to hypocalcemia had not been recognized, and few specifics were known about the function of the thyroid gland and even less about the mysterious parathyroid glands. It was not long, however, before investigators began to focus away from the thyroid and more on the tiny glands around the thyroid as the cause of post-thyroidectomy tetany. The key observations linking the parathyroid glands to tetany were made in the 1890s by a physiologist, Eugene Gley of Paris, who described the parathyroids and noted removal resulted in tetany; he published his findings in a French journal in 1891 [6], and subsequently in the Lancet in 1892 [7], thus contributing some of the earliest studies suggesting the function of the parathyroid glands. Shortly thereafter, and in parallel with Gley's observations linking parathyroid function to tetany, the association of calcium, parathyroid function, and neuromuscular irritability was taking shape on both sides of the Atlantic Ocean. In 1906, a pathologist at the University of Vienna, Jacob Erdheim, autopsied the necks of patients who died of tetany following total thyroidectomy for goiter. He suspected that parathyroid dysfunction following the thyroid surgery was the cause, and studied the effects of parathyroid removal in rats [8]. In 1909, McCallum and Voegtlin of Baltimore noted that tetany after parathyroidectomy was associated with hypocalcemia and improved not only with the administration of calcium, but also by injecting parathyroid extracts [1, 9]. Subsequently, in 1923 Harald Salvesen of Oslo established the relationship of tetany, parathyroids, and serum calcium levels [10]. The recognition that removal of the parathyroid glands caused tetany led the famous Johns Hopkins surgeon William Halsted to state in a 1907 publication: "it hardly seems credible that the loss of bodies so tiny as the parathyroids should be followed by a result so disastrous" [11–12]. Most interesting is the fact that the initial observation of tetany following thyroidectomy remains an important post-operative complication in thyroid surgery today.

Recognition of the Bone Disease of Hyperparathyroidism

Long before the parathyroid glands were discovered as anatomic structures and their connection to calcium metabolism elucidated, the entity of osteitis fibrosis cystica was recognized. It was a French pathologist from Strasbourg by the name of Friedrich von Recklinghausen who described the classic bone disease of hyperparathyroidism in 1891 [13]. At the time of his description, it was not clear what was causing this particular type of bone disease, but soon thereafter a report of a patient with von Recklinghausen's bone disease and a tumor adjacent to the thyroid was described [14], other similar patients were soon reported. These tumors were recognized as parathyroid in origin, however, in the early 1900's it was assumed that the parathyroid growth was a compensatory response to the bone disease, which was thought to be the primary pathologic process. Because of the widespread assumption that osteitis fibrosis cystica resulted in the overgrowth of the parathyroid glands, there was no reason to perform neck surgery and parathyroidectomy in a patient with von Recklinghausen's bone disease. In 1915, an Austrian pathologist challenged this assumption. Fredrich Schagenhaufer of Vienna hypothesized that the parathyroid tumor was causing the bone disease, and it was not long before his ideas were put to the test with the first parathyroid exploration in a patient with von Recklinghausen's bone disease.

Felix Mandl and Albert: The First Parathyroidectomy

Dr Felix Mandl was a surgeon in Vienna in 1925 when an interesting patient, Herr Albert, came under his care. Albert was a 37-year-old trolley car operator who was admitted to the clinic with a femur fracture. To the surprise of his physicians, x-rays showed not only the fracture, but also diffuse cystic bone disease in his pelvis and both femurs.

On further questioning, Albert reported several years of bone pain and general malaise, and laboratory studies revealed elevated serum calcium levels. Still experimenting with the assumption that parathyroid growth was a compensatory response to the destructive bone disease seen in Albert and others, Mandl treated his patient with a parathyroid extract known as "parathyreoidin tablets" [15], and even attempted to transplant fresh parathyroid from an accident victim into his patient [1]. Needless to say, treatment with additional parathyroid hormone was not effective in improving Albert's condition.

Finally, Dr Mandl explored the neck in July 1925 and removed a $21 \times 15 \times 12$ mm parathyroid with dramatic clinical improvement. His operation and results were presented at the Viennese Medical Society in December 1925 [16] and he subsequently published an account of the operative findings and histology of the removal gland:

> "The operation was performed under local anesthesia and was started on the left side. The left thyroid lobe was mobilized. First a small nodule was removed, demonstrating fatty tissue. Suddenly, in the rim between larynx and esophagus, a dark, partly grayish nodule separate from the thyroid was located in the inferior parathyroid position close to the inferior thyroid artery and between its branches, adhering to the left recurrent nerve. The tumor required a sharp dissection to free it from the trachea and the nerve. While grasping the tumor, the voice of the patient became hoarse. A ligature placed earlier on one of the many branches of the artery was subsequently removed and the voice became clear again. During the bilateral exploration, three additional structures were identified macroscopically as the three remaining normal glands, one on the left and two on the right side" [15–16]

Following the operation, Albert's condition markedly improved. He was discharged from the hospital, and x-rays several months later documented healing of the bones. Albert did well clinically until approximately 7 years later, when his hypercalcemia recurred; a subsequent neck exploration did not uncover additional enlarged parathyroid glands and he eventually died of renal failure. An extensive autopsy was performed and no additional parathyroid tissue was found; the cause of his recurrence remains unknown to this day.

The Case of the Sea Captain Charles Martell

Across the Atlantic Ocean, at the Massachusetts General Hospital (MGH) in Boston, a similar patient underwent a neck exploration in 1926; the team at MGH was not aware at that time of the operation performed in Vienna by Felix Mandl one year earlier. The story of the first parathyroid exploration in the United States begins in the early 1920's, when Joseph Aub and Walter Bauer, both professors of medicine at Harvard, began a series of detailed studies on lead poisoning. Patients with lead poisoning were noted to have lead deposits in bone, elevated serum lead levels, and severe colic. Calcium administration caused the precipitation of lead in the bones, and withdrawal of calcium and subsequent lowering of serum calcium levels drew lead out of bone and into the serum from where it was excreted into the urine and feces; a so-called "de-leading regimen" [17]. The studies of Aub and Bauer coincided with those of James Collip of the University of Alberta in Edmonton, Canada. Dr Collip and his collegues, in 1925, were producing a purified form of parathyroid hormone (PTH), and had studied its metabolic effects in dogs [18]. They noted that PTH caused calcium resorption from bone, thus increasing calcium levels in the blood and excretion in the urine. The group at MGH began using Dr Collip's purified PTH in order to facilitate the removal of lead from the bones and in doing so noted the effects of PTH in their human patients [19–20]. A professor of medicine in New York City, Eugene duBois of Cornell and Bellevue Hospital, learned of Aub and Bauer's findings regarding the effects of PTH. In January 1926, a patient by the name of Charles Martell came under Dr. duBois' care. The patient, a former sea captain and merchant marine, had diffuse and severe bone disease. duBois made the astute observation that Captain Martell's metabolic profile was similar to the patients treated at MGH with PTH injections, that is, an elevated serum calcium, low-serum phosphate, and increased urine calcium. duBois referred Captain Martell to the MGH, where he was noted to have what was postulated as severe, advanced HPT with bone pain, fractures, osteoporosis, kyphosis, hypercalcemia, and hypophosphatemia. Neck exploration was recommended by the team of medical doctors, and in May 1926, Dr Edward Richardson, then the chief of surgery at MGH and an experienced thyroid surgeon, performed a neck exploration. No adenoma was found, and Captain Martell's disease persisted and progressed. He subsequently underwent several more failed explorations until finally in 1933 an enlarged parathyroid gland was removed from the mediastinum. He developed post-operative tetany and an impacted kidney stone and died shortly thereafter [21].

Early Parathyroid Surgery at the Massachusetts General Hospital

Despite the unfortunate outcome of Captain Charles Martell, the lessons from his case were not lost on the

physicians at the Massachusetts General Hospital who cared for him. During the 1930s, Aub and Bauer's studies of calcium metabolism and parathyroid gland function were continued under the leadership of Fuller Albright, a Harvard professor of medicine and an endocrinologist. Dr. Albright and his associates identified patients with the classic bone disease of HPT and referred them for neck exploration. Basic parathyroid anatomy was not well understood, however, and after failed neck explorations in two patients, an appeal was made by Bauer and Albright to the chief of the surgical service, Edward Churchill, who had succeeded Dr Richardson, to remedy the situation. In fact, the team of medical doctors had ceased from referring patients they suspected had parathyroid tumors to the surgical service for neck exploration. Dr Churchill readily agreed that further study was needed prior to subjecting more patients to unsuccessful explorations. He then enlisted the apprenticeship of an MGH surgical resident, Dr Oliver Cope, and the two embarked on a journey of discovery to which we owe much of today's knowledge of parathyroid anatomy and surgical technique. The story of their studies is well told by Dr Cope himself at his presidential address to the Boston Surgical Society on Dec 13, 1965, the text of which was subsequently published in the New England Journal of Medicine in 1966 [17]. As Dr Cope tells the story:

> "I shall always remember and shall always be grateful to Dr Churchill for the ground rules laid down by him when he first asked me whether I should care to join him in the parathyroid assignment. He discerned then, before the fact, that the success of parathyroid surgery must lie in the ability of the surgeon to know a parathyroid gland when he saw it, to know the distribution of the glands, where they hide, and also to be delicate enough in technique to make use of this knowledge. He told me I must go to the post-mortem room, dissect out the parathyroid glands, come to know what they looked like and find out their distribution and anatomic relations. He said further, when he was satisfied that I knew, then I might have the privilege of operating on the first patient" [17].

As instructed, Oliver Cope dutifully undertook autopsy studies to learn the anatomy and appearance of the parathyroid glands. Cope undertook these studies with the assistance of a resident pathologist, Dr Benjamin Castleman, who helped confirm by histology if the tissues dissected by Cope were in fact parathyroid tissue. One year and 30 post-mortem examinations of the neck and mediastinum later, Dr Churchill decided Cope was ready for his first case. A patient with the classic bone disease of HPT underwent a neck exploration, performed by Cope and supervised by Churchill. An adenoma was successfully removed, but as described by Dr Cope in his 1966 presidential address, it was in Dr Churchill's critique of his technique that the true and lasting lessons were found. Dr Churchill commented that Dr Cope's technique was rough, and that the younger surgeon was too rushed and impatient. He recommended traction sutures on the thyroid, instead of sharp hooks, which tended to bloody the field. Small cotton pledgets replaced large, unwieldy sponges, and Dr Churchill suggested replacing the large autopsy scissors with a smaller delicate pair [17]. This emphasis on meticulous and careful technique continues to dominate the approach to parathyroid exploration today.

The Growth of Parathyroid Surgery

By the mid-1930s, several more cases of patients with von Recklinghausen's bone disease underwent parathyroid exploration in the United States and Europe [1, 22, 23] and by the mid 1900s it was not an uncommon operation. Initially, hyperparathyroidism was recognized only in patients who had the classic bone disease. As more and more patients were evaluated, Fuller Albright noted that several patients had renal stones as well, and it was not long before patients with kidney stones were also undergoing successful removal of parathyroid adenomas. For the next several decades, primary HPT presented as a symptomatic disease and patients referred for parathyroidectomy were in the more advanced stages with clinical manifestations such as "stones, bones, groans, and moans, " conveying in a traditional medical school mnemonic the side-effects of nephrolithiasis, bone loss, abdominal, and neuropsychiatric symptoms. With the introduction in the late 1960s of the serum biochemical multichannel autoanalyzer detecting asymptomatic hypercalcemia, the referral patterns for patients with primary HPT underwent a radical change [24]. In the early 1970's, as more and more patients were detected and diagnosed, the incidence of primary HPT increased dramatically [25].

Recent Evolution of Parathyroid Surgery: From 4-gland Exploration to Focused Parathyroidectomy

From 1940 to 1980s, the surgical approach in patients with primary HPT was essentially the same as that used on Albert and Charles Martell in the earlier part of the century. No pre-operative localization studies were performed in an attempt to localize the abnormal gland(s). Indeed, no reliable radiologic studies for such a purpose were available. The traditional operative approach was a neck exploration through a standard transverse cervical incision with

identification of all four parathyroid glands. Abnormally enlarged glands were removed, and normal-appearing glands were identified and often sampled by biopsy and frozen section histology when deemed appropriate by the operating surgeon. Using this approach, the success rate among surgeons experienced in parathyroid surgery was, and still is, on the order of 95% for the treatment of primary hyperparathyroidism [26–27].

In the 1980s, however, parathyroid surgery evolved once more. A focused neck exploration with identification and resection of the abnormal gland only was proposed as an alternative to the 4-gland exploration. This idea was based on the fact that the majority of cases of primary HPT are caused by enlargement of a single gland. The introduction of focused parathyroid explorations was dependent on advancements in two specific areas of parathyroid surgery: pre-operative localization and intraoperative PTH monitoring. Tc-99 m sestamibi and high-definition ultrasound were introduced in the 1980s and both have been shown to be highly accurate in the localization of abnormal parathyroid glands preoperatively, especially in cases of single adenomas [28–29]. The widespread acceptance of preoperative localization studies provides one component of unilateral explorations. The intraoperative PTH assay provides another key component, allowing the surgeon to determine in the operating room whether all hypersecreting parathyroid tissue has been removed prior to terminating the procedure. The intraoperative PTH assay was first introduced to the surgical community by a group led by the well-known MGH endocrine surgeon Dr CA Wang. At the ninth annual American Association of Endocrine Surgeons (AAES) meeting in 1988, the MGH group presented a report of 13 patients who underwent parathyroid resection with measurement of PTH intraoperatively. They demonstrated that with a 15 min, radioimmunoassay directed at two binding sites on the PTH protein (IRMA), normalization of PTH could be demonstrated immediately following parathyroid resection [30]. Soon thereafter a group from Paris reported a series of 45 patients who underwent focused explorations using the IRMA assay [31]. In 1999, Dr. George Irwin, an endocrine surgeon at the University of Miami, described in his presidential address to the AAES his personal interest in the assay and how it came about as the result of a frustrating case of persistent hyperparathyroidism following a standard bilateral exploration. Irwin strongly believed that the ability to measure parathyroid hormone secretion intraoperatively would have avoided the initial operative failure. He successfully re-operated on the patient, this time using the intraoperative PTH assay, and noted a significant drop in the PTH after removal of an intrathyroidal parathyroid adenoma [32]. Since then, Irwin and his colleagues at the University of Miami have published several reports of cases using preoperative localization and intraoperative PTH to facilitate focused explorations [33–35]. The ultimate effectiveness of focused explorations will depend on demonstrating long-term cures comparable to that of bilateral neck surgery. Such long-term data is currently lacking and other authors have demonstrated inaccuracies in reliance on rapid intraoperative PTH measurements [36].

Conclusions

There indeed have been impressive advances in parathyroid surgery, beginning with the discovery of the parathyroid glands by a medical student, continuing with the surgeons on both sides of the Atlantic Ocean who embarked on the first parathyroid explorations in courageous attempts to cure what was then a devastating disease, to the current era of constant advancement and evolution. Ongoing investigation in the areas of pre-operative localization, intraoperative PTH monitoring, and parathyroid cryopreservation continue to stimulate progress and change. There is still controversy and debate among parathyroid surgeons and endocrinologists with regards to many areas of parathyroid surgery, for example, whether or not the focal parathyroid explorations will lead to an increase in late recurrences, and if patients with “asymptomatic” hyperparathyroidism should undergo surgery. What is perhaps most impressive, however, is not what is changing in parathyroid surgery, but what has stayed the same. Referring back to the descriptions of Dr Felix Mandl and Dr Oliver Cope, the careful and meticulous dissection, the understanding of the appearance and anatomy of the parathyroid glands, and their dedication to ultimately providing a cure for patients suffering from the uncontrolled growth of these often evasive and still mysterious glands: these principles of parathyroid surgery have stood the test of time.

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