The History of Parathyroid Surgery, 1850–1996: The Excelsior Surgical Society 1998 Edward D Churchill Lecture

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I am honored to deliver the 1998 Excelsior Surgical Society/Edward D Churchill Lecture. This society was the product of military surgery during World War II in the North African and Mediterranean theaters of operation. In periods between their stressful work, surgeons in the theater were provided opportunities for exchanging ideas and promoting social graces. The second auxiliary surgical teams and other surgical officers developed new friendships and renewed old acquaintances. It was only natural that thoughts toward perpetuation of these friendships would develop after the war. The initial meeting of this society was held in October 1946 in Boston, MA. In May 1951, its name was officially changed to the Excelsior Surgical Society. Frank Simeone has reminded us that societies, clubs, and publications are the hallmark of physicians and surgeons. American medical personnel actively participated in conferences held in the Institute of Health at the University of Rome, which were later published as the *Proceedings of the Conference of Army Surgeons, Central Mediterranean Forces*. Other societies developed, ie, The Constantian Society, the Biserte County Medical Society of Tunisia, and the North Caserte Medical Society (Italy).

The Excelsior Hotels in Rome and Florence were frequent sites for these interludes, so the club was named after the Excelsior Hotel in Rome (Fig. 1). This society later established a Churchill Lecture. The initial lecture was given by Alfred Blalock, of Johns Hopkins. The first Churchill Lecture under the auspices of the American College of Surgeons was delivered by W Dean Warren, of Emory University (Fig. 2).

The Excelsior Society was founded to honor Colonel Edward Delos Churchill, who would become the one and only honorary member (Fig. 3). Early in his career, Dr Churchill distinguished himself as a pioneer in thoracic surgery. He performed and reported the first pericardiectomy in America for constrictive pericarditis, clarified the physiology and surgical anatomy of the lung, developed a rational approach to the treatment of pulmonary tuberculosis, bronchiectasis, adenoma and carcinoma of the lung, and surgery of the esophagus. Dr Churchill succeeded Edward P Richardson as the John Homans Professor of Surgery at the Harvard Medical School, a position he held until 1962.

Churchill, a surgeon's surgeon, deplored the fragmentation of surgery, believed that young surgeons should become well grounded in the principles of surgery, and advised his residents to spend at least 1 year with a master in the basic sciences during residency. Edward Churchill was indeed a surgical biologist.

> "The history of medicine is, in fact, the history of humanity itself, with its ups and downs, its brave aspirations after truth and finality, its pathetic failures. The subject may be treated variously as a pageant, an array of books, a procession of characters, a succession of theories, an expansion of hu-

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Figure 1. Excelsior Hotel, Rome, Italy.

man ineptitudes or as the very bone and marrow of cultural history."[1]

Introduction to *The History of Medicine*
Fielding H Garrison (1870–1935)

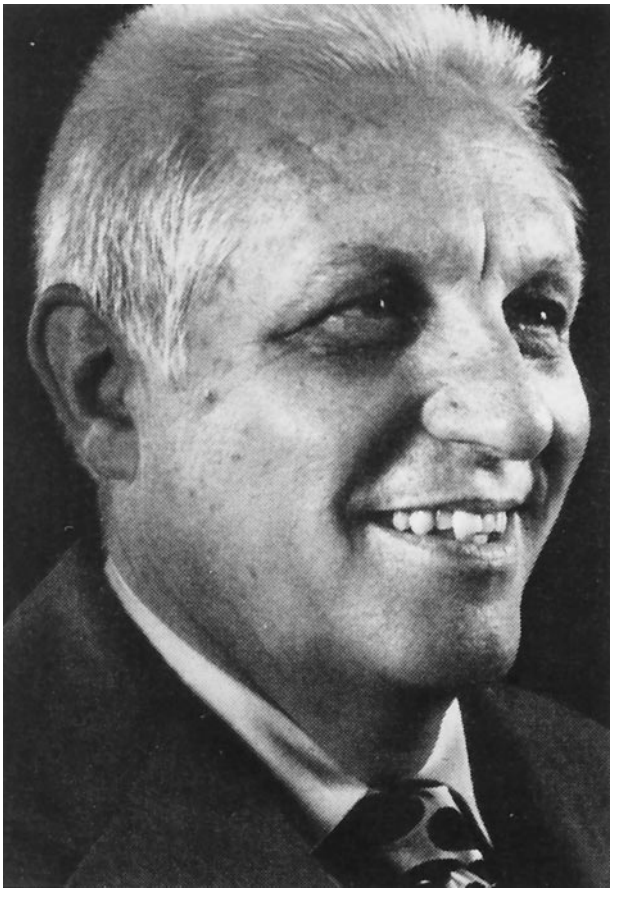

Figure 2. W Dean Warren, MD, of Emory University.

Figure 3. Edward D Churchill, MD.

The history of parathyroid surgery uniquely parallels the history of surgery, initially influenced by observations of anatomists, pathologists, and surgeons in Europe and followed by contributions of several American teams. Improved methods of communication and transportation increased the interface between investigators on both sides of the Atlantic, adding to our understanding of the parathyroid gland and the development of parathyroid surgery. Norman W Thompson[2] and Richard Wellbourn,[3] from the University of Michigan and the United Kingdom, respectively, deserve special recognition for their contributions to the history of parathyroid and endocrine surgery.

Halsted stated, "it seems hardly credible that the loss of bodies so tiny as the parathyroids should be followed by a result so disastrous."[4] I shall divide the history of parathyroid surgery into four phases:

Table 1. Significant Teams Contributing to Parathyroid Surgery

Team	Members	Discipline
Johns Hopkins	William J MacCallum	Pathology
	Carl Voegtlin	Pathology
	William Halsted	Surgery
	Herbert Evans	Medical Student
Massachusetts	Fuller Albright	Metabolism
General	Joseph Aub	Metabolism
Hospital	Benjamin Castleman	Pathology
(Harvard)	Edward Churchill	Surgery
	Oliver Cope	Surgery
Swedish	Harold A Salvesan	Biochemist
	Ivar Victor Sandström	Medical Student
Vienna:	Theodore Billroth	Surgery
Allgemeines	Felix Mandl	Surgery
Krankenhaus	Jacob Erdheim	Morbid Anatomy
	Anton von Eiselsberg	Surgery
Washington	Issac Y Olch	Surgery
University,	Henry Dixon	Medical Student
Barnes	Harold A Bulgar	Metabolism
Hospital	Samuel A Wells	Surgery

Phase I will cover the contributions of European anatomists, pathologists, and surgeons before 1925; Phase II, the search for function, in which calcium metabolism, bone disease, tetany, and primitive attempts at whole gland transplantation are studied, punctuated by initial surgical successes; in Phase III, the development of immunoassays, refined diagnostic techniques, imaging procedures, and aggressive surgery; and, finally, Phase IV, the biomolecular phase that parallels current biomolecular events as applied to the parathyroid gland and the plethora of problems presented by failed parathyroid procedures.

Contributions to the history of parathyroid surgery have been truly international. Patients, medical students, anatomists, pathologists, surgeons, and metabolic teams have made significant contributions. Several groups deserve special recognition: the Vienna group at the Allgemeines Krankenhaus, the Massachusetts General Hospital team, Johns Hopkins, the Washington University-Barnes Hospital, and the Swedish efforts (Table 1).

Patients involved with these historic developments warrant special mention: Mr Albert Gahne, the tram conductor from Vienna; Captain Charles Martell; and Mrs Elva Dawkins, of St. Louis (Table 2). Medical students made significant contributions to this saga of events: Ivar Victor Sandström, from Uppsala, Sweden (Fig. 4); Herbert Evans, of Johns Hopkins University (Fig. 5); Adolph Hanson, of Minnesota; and Henry Dixon, of Washington University (Fig. 6 and Table 2).

Table 2. Patients and Medical Students

Name	Location
Patients	
Captain Charles Martell	New York, NY
Albert Gahne	Vienna, Austria
Elva Dawkins	St Louis, MO
Medical students	
Ivar V Sandström	Uppsala, Sweden
Henry Dixon	St Louis, MO
Adolph Hanson	Minneapolis, MN
Herbert Evans	Baltimore, MD

PHASE I

Let us return to the latter part of the 19th century. Enter Medical Student #1: Sandström, a 25-year-old medical student at the University of Uppsala, working as a summer research assistant in 1887, observed a new gland while dissecting the neck of a dog, which led to his classic monograph entitled,

Figure 4. Ivar V Sandström, Uppsala, Sweden.

"On a New Gland in Man and Fellow Animals."[5] He had found this gland on the thyroid of a dog, cat, rabbit, ox, and horse and noted "the existence of a hitherto unknown gland in animals that has so often been a subject of anatomical examination and called for a thorough approach to the region around the thyroid gland in man." Sandström's dissection of 50 human bodies confirmed his findings in animals. In this detailed manuscript, he described the color, protean shapes, and positions of the gland, and performed microscopic studies on fresh autopsy specimens using several staining techniques.

Sandström was aware of the variability of their location and further observed, "Although the glands were generally united with the thyroid by means of soft connective tissue, they were often movable against its capsule. Many of the glands are well-defined fat lobules separated from the thyroid gland capsule. To each gland there are one or more small arteriole branches from the inferior thyroid artery, and in the interstitial tissue there are often considerable fat cells and may be so numerous that the parenchyma of the gland appears only here and there in the spaces between the fat cells."

Sandström suggested the use of the name "glandulae parathytreoidae" and acknowledged "two authors who seemed to have traced the glands in question, although I do not want thereby to deny the possibility that even others may have observed them before me." It seemed otherwise to be unknown in the literature at that time. His manuscript, with carefully detailed gross and microscopic drawings, was rejected by German editors because of its length—early evidence that editors never change. His manuscript would be published later in Swedish in an Uppsala medical journal. Two abstracts published in the 1880 German yearbooks saved this important work from being unrecognized. Sandström did not receive the acclaim he deserved during a short lifetime, later committing suicide.

Remak (Fig. 7), a microanatomist and embryologist who initially described the three primary germ layers (ecto-, meso-, and endoderm), also described the parathyroid as a small gland in association with the thymus that was clearly not a lymph node, but never again made mention of this structure.[6] Virchow, called the greatest pathologist of the 19th century and referred to as "the Pope of Medicine," also may have identified the parathyroid gland in a single specimen emphasizing that this was not an accessory thyroid gland, lymph node, or any other structure with which he was familiar.[7]

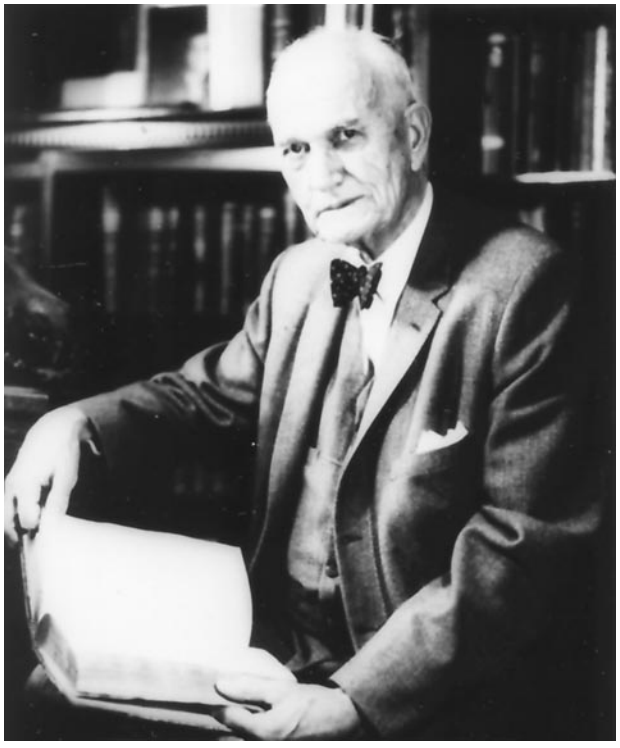

Figure 5. Herbert Evans, Johns Hopkins University.

Richard Owen, from the Hunterian Museum of

Figure 6. Henry Dixon, Washington University.

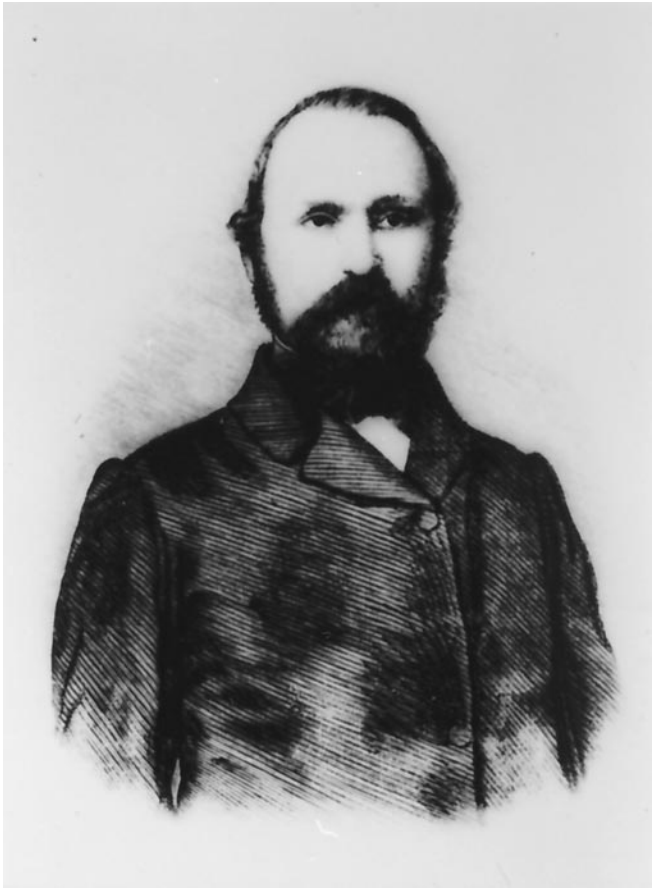

Figure 7. Robert Remak, MD.

the Royal College of England and Hunterian Professor of Anatomy, had reported before the Zoological Society of London in 1850 his observation made at autopsy after the death of a great Indian rhinoceros in the London Zoo. Cave, a comparative anatomist, suggested in 1953 the eponym "the glands of Owen." Owen's description of the parathyroid was very short: "a small, compact, yellow glandular body was attached to the thyroid at the point where the veins emerge.[8]

PHASE II: SEARCH FOR FUNCTION

What role did tetany play in the historic development of the parathyroids? In 1879, postoperative tetany was first described by Anton Wolfer in a patient on whom Theodor Billroth had performed his first total thyroidectomy. This patient recovered after 3 weeks of extremity convulsions. Tetany was attributed to hyperemia of the brain from the total thyroidectomy. This was the beginning of the detoxification theory. Nathan Weiss, another Billroth student, collected 13 cases of tetany, 8 of which followed total thyroidectomy performed by Billroth.[9]

The first connection between the parathyroid glands and tetany was made by French physiologist Eugene Gley, who initially observed a relationship between tetany and the parathyroid glands. He began to unravel the mysteries of parathyroid function. Working with rabbits and rats, Gley observed that these animals developed tetany and died when their thyroid and parathyroid glands were removed. A selective parathyroid injury model alone also caused tetany. His report (1891) was immediately appreciated by European thyroid surgeons.[10]

Vassale and Generali also reasoned that tetany could result from parathyroidectomy and further observed that excision of both the thyroid and parathyroid glands in animals caused tetany. They concluded that the parathyroidectomized animal was a poisoned animal, further affirming the detoxification theory. The detoxification function of the parathyroid would remain active conceptually for 25 or more years. Gley, Vassale, and Generali cautioned surgeons to treat these glands with care when operating on the thyroid gland.[11]

Jacob Erdheim, from the University of Vienna, destroyed the parathyroid glands in rats with cautery, confirmed the experimental work of Gley, and made original observations about chronic parathyroid insufficiency. Erdheim studied the parathyroid glands at autopsy in all patients who died with bone disease. He reported (1907) that the parathyroid glands were enlarged in a number of severe bone diseases such as osteomalacia, osteitis fibrosis cystica, etc. Erdheim was the first to associate bone disease with abnormalities of the parathyroid glands, although his conclusion that their enlargement resulted from compensatory hyperplasia was erroneous. Erdheim continued to believe that the bone changes were primary and not related to an excess of parathyroid secretion. As an influential pathologist during this era, his opinions had great influence.[12]

Before these observations Frederich von Recklinghausen (Fig. 8), professor of pathology at Strasbourg, described seven patients with bone disease in a Festschrift for Virchow. At least one of these patients had osteitis fibrosis cystica. The eponym of

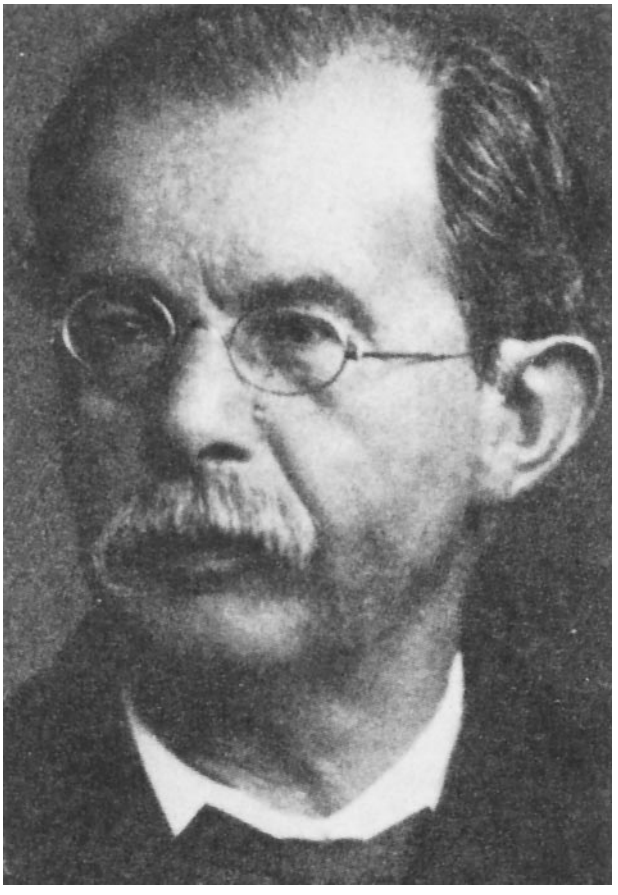

Figure 8. Frederick von Recklinghausen (1823–1910).

von Recklinghausen's disease has been used for decades and associated with hyperparathyroidism, even though the author apparently possessed minimal knowledge about that disease.[13] In 1903 the first report of a patient with bone disease associated with a large parathyroid tumor was published by Askanazy, who speculated that it might be a parathyroid tumor.[14]

Observations of tetany after parathyroidectomy and thyroidectomy were of great interest to surgeons and led to important discoveries regarding parathyroid function. In the early part of the 20th century, several investigations related to the parathyroid glands were published in the continued search for the cause(s) of tetany, the composition of parathyroid extract, and efforts at transplantation. At the Johns Hopkins Hospital, pathologist William J MacCallum (Fig. 9) reported his first study of their function in 1903, describing tumors of the parathyroid gland and the relief of tetany in experimental animals with parathyroid extract. He considered those glands neutralizers of a circulating toxin. MacCallum would later conclude that the parathyroid glands exert some control over calcium metabolism.[15]

Figure 9. William J MacCallum, MD.

MacCallum and Carl Voegtlin demonstrated that postparathyroidectomy tetany could be corrected by a parathyroid extract or by injection of calcium but not potassium or sodium. They further demonstrated a decrease in tissue calcium in tetany, hyperexcretion of calcium in the urine and feces, and increased urinary excretion of nitrogen. MacCallum and Voegtlin identified the cause of tetany as hypocalcemia resulting from insufficient parathyroid secretion, not the detoxification theory.[16]

In a classic experiment, MacCallum, using dialysis, removed calcium from blood, injected it into tetanic animals, and observed that these animals remained tetanic when compared with animals given normal blood. These results verified his theory that parathyroid tetany resulted from the lack of blood and tissue calcium. In his 1917 textbook of pathology, MacCallum stated that "metabolism and tetany have been studied with unsatisfactory results and nothing definitely illuminating the situation has been found." Not until 1924 was MacCallum convinced that his experimental studies were valid and that tetany was a direct result of calcium deficiency.[17]

Halsted, working at the Johns Hopkins Hospi-

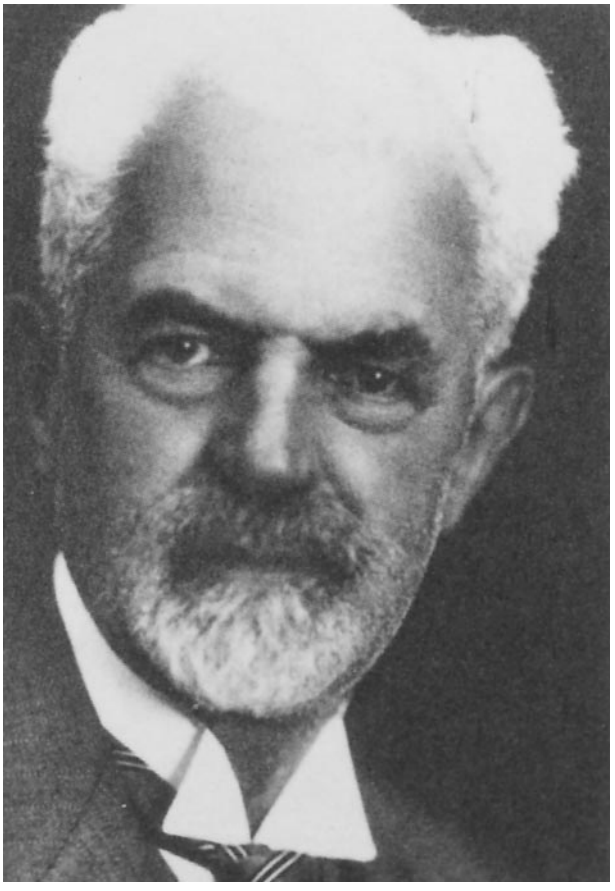

Figure 10. Anton von Eiselsberg, MD.

tal, described patients with chronic hypoparathyroidism and the acute onset of this disease after thyroidectomy. Halsted had used a crude parathyroid extract and calcium chloride by injection since 1907 to treat these patients.[18]

Carlson and Jacobson, repeating the experiments of MacCallum and Voegtlin, confirmed that calcium suppressed the symptoms of tetany in parathyroidectomized animals.[19] In 1912 WF Koch observed the presence of methylguanidine in the urine of parathyroidectomized tetanic dogs. He reasoned that digested proteins taken into the body had toxic effects after parathyroidectomy and that parathyroid secretion appeared to be concerned with the anabolic processes closely related with the building of these nucleins.[20]

In 1921, Boothby, in summarizing the existing knowledge of the parathyroid gland, stated, "there is evidence that their functions in some way are concerned with calcium, methylguanidine metabolism or with both."[21]

Dolev summarized these confusing investigations in an article entitled, "A Gland in Search of a Function: The Parathyroid Glands and the Explanations of Tetany." Dolev concluded, "In the history of endocrinology the theory of detoxification by the endocrine glands has always arisen, but the experimental facts have always proven it to be wrong."[22] Investigators continued to be divided on the function of the parathyroid glands. Harold A Salvesan, a Swedish biochemist, was convinced that all symptoms after parathyroidectomy were from calcium deficiency, and he questioned methylguanidine as a causative factor.[23]

On this side of the Atlantic, Lester Dragstedt, a young physiologist who later would become a renowned surgeon, was the last great advocate of the theory of autointoxication and authored three papers on this subject in the mid-1920s.[24]

To what extent did parathyroid transplantation play a role in the development of parathyroid surgery and function of the parathyroid glands?

The first attempted transplantation of parathyroid glands was performed by Anton von Eiselsberg (Fig. 10), a pupil of Theodor Billroth, in 1892, approximately 1 year after Gley's report. Eiselsberg, a professor of surgery at the Allgemeines Krankenhaus, performed autografts in cats by transplanting half of the thyroid and the parathyroid gland between the rectus fascia and peritoneum; for up to 1 month the animals showed no evidence of tetany. Histologic studies demonstrated neovascularization of the transplant had occurred.[25] During the next two decades a number of surgeons experimentally grafted the thyroid and parathyroid glands and found that death resulted from tetany if all parathyroids were removed.

Biedl and Leichner independently transplanted parathyroid glands into the spleen and other tissues in a variety of animals demonstrating histologically viable parathyroid tissue and gave a detailed description of functional results after a followup of 5 months.[26,27] Pfeiffer and Mayer were the first to demonstrate clinical success with autografted parathyroid tissue, in 1907. During this same time frame numerous surgeons claimed success with allografts.[28]

Halsted's clinical observations of patients with chronic hypoparathyroidism prompted him to be-

gin transplantation using dogs. His experiments with transplants of parathyroid glands into the thyroid at heterotopic locations led him to propose the Law of Deficiency: "the autotransplantation of parathyroid glands is only successful in animals in which a deficiency of greater than one-half has been created. In no instance has autotransplantation succeeded without the creation of such a deficiency."

This law was widely accepted and not disproved for almost 30 years. Halsted proved that even one transplanted parathyroid gland could be life-saving. He reminded his colleagues that "we made the startling and hardly believable observation that the life of a dog may be maintained by a particle of parathyroid tissue only one-quarter of a millimeter in diameter and distinguished by tetany after its removal." Halsted used intravenous calcium gluconate to treat tetany in experimental animals in clinical cases after thyroidectomy. Halsted consistently emphasized injury prevention during thyroidectomy.[18]

PHASE III: IMMUNOASSAYS, IMAGING, AND AGGRESSIVE SURGERY

Enter Medical Student #2: Halsted (Fig. 11) and Herbert M Evans, a medical student at Hopkins, defined the blood supply to the parathyroid glands using vascular cast injections. They demonstrated the exact source and position of the blood supply to these glands from fresh specimens supplied by MacCallum. Halsted and Evans noted that each gland was supplied by a single delicate end artery and that there were no capsular collaterals. The inferior thyroid artery was the principal blood supply to both the inferior and superior glands in more than 90% of cases. Halsted emphasized that the inferior thyroid artery, not its branches, should be ligated proximal to the end artery supplying the parathyroid glands. They further stressed that the occurrence of tetany after thyroidectomy was less often from parathyroid excision than from interference with the circulation of the parathyroid glands.[29]

The evolving role of parathyroid extract further clarified the function of these glands and calcium metabolism. Several investigators were convinced, even without studying hormonal preparations, that the parathyroid glands controlled calcium metabolism. Salvesan long believed the symptoms of tetany

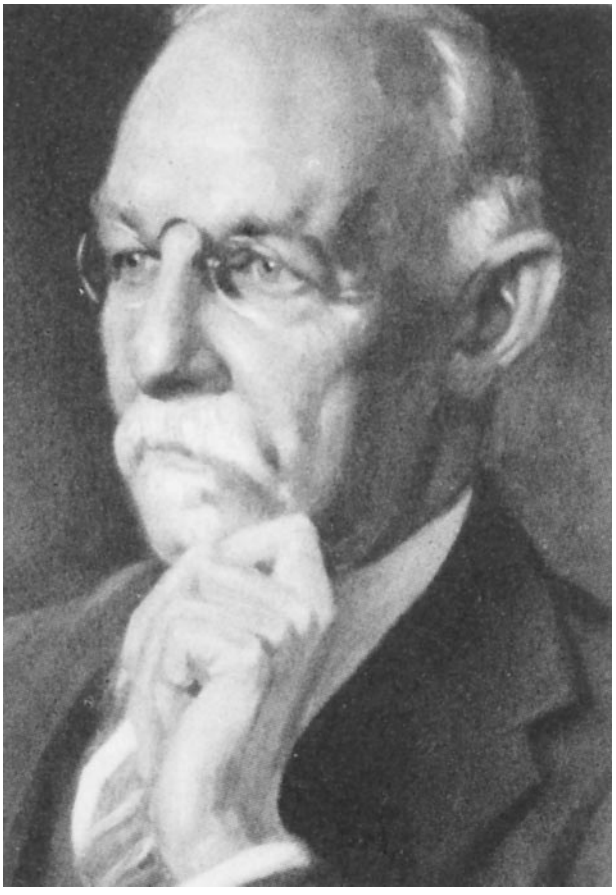

Figure 11. William Halsted, MD.

could be attributed to calcium deficiency and proved this when he discovered low calcium levels in the blood of patients with tetany. Although convinced that the glands regulated the level of blood calcium, it required availability of a potent and reliable parathyroid extract (not then available) to perform experiments that provide definitive proof.[23]

For the serious student of parathyroid surgery, one should read the classic 1926 manuscript of Felix Mandl (Fig. 12) of Vienna. Enter Patient #1: Mr Albert Gahne, a tram car conductor whose symptoms dated back to 1921. Bone x-rays in 1923 showed numerous cysts. In 1924, Mr Albert Gahne sustained a fracture of the femur for which he was admitted to the Hochenegg Clinic under the care of Felix Mandl. His blood and urinary calcium levels were found to be elevated, with an observed white urinary precipitate.

Mr Gahne was unsuccessfully treated with para-

Figure 12. Felix Mandl, MD (1892–1957).

thyroid extract. Mandl then grafted fresh parathyroid tissue from an accident victim into Mr Gahne. In presenting this to the Vienna Surgical Society, he was caustically criticized by his colleagues because the graft(s) had not been microscopically confirmed as parathyroid tissue. In July 1925, Mandl explored Gahne's neck and removed a parathyroid tumor with an initial successful result. His urine cleared within a week, calcium excretion decreased, and the bone pain lessened. A recurrence developed and Gahne was reexplored, only to die after the procedure.[30]

Mandl raised several issues that would confront surgeons for the next 50 years. He 1) placed the primary disease in the parathyroid gland and not bone; 2) used a parathyroid extract; 3) attempted unsuccessfully whole gland parathyroid transplantation; 4) successfully removed a parathyroid tumor; 5) described a tumor that was most surely parathyroid carcinoma; 6) noted a recurrence, a complication not generally appreciated at that time; and 7) suggested that this disease might be familial.

Figure 13. James P Collip, MD.

Enter Medical Student #3, Adolf M Hanson: Working as a medical student in the pharmacology laboratory at the University of Minnesota, Hanson extracted from bovine parathyroid glands a stable substance that could be used to treat experimental tetany. He described his method in detail, reported experimental evidence that this extract would consistently raise serum calcium levels in thyroparathyroidectomized dogs, and observed that the parathyroid extract caused osteoporosis in these animals when administered for a long period of time.[31]

James P Collip (Fig. 13), a biochemist earlier at the University of Alberta, had been associated with Banting and Best in extracting insulin from the pancreas. Collip was convinced that the parathyroid glands contained a calcium-regulating hormone. His goal was to isolate this substance for use in patients with tetany or chronic hypoparathyroidism. Collip independently developed an extract technique essentially identical to that of Hanson. He continued to perform controlled experimental studies administering his preparation orally, subcutaneously, and intravenously to parathyroidectomized animals. Collip proved that tetany could be prevented when his extract was given early and could eliminate the symptoms when given later. He

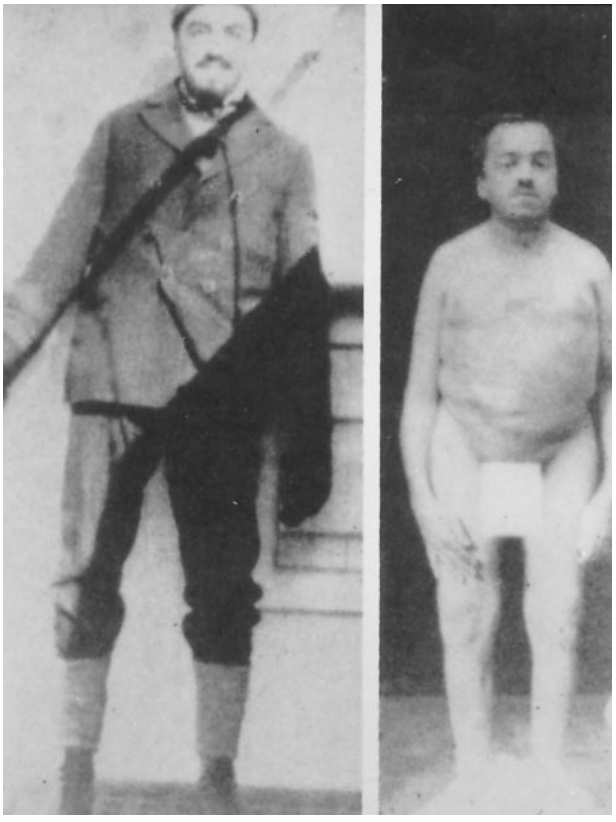

Figure 14. Captain Charles Martell.

Figure 15. Fuller Albright, MD.

further demonstrated a direct correlation between blood calcium levels and the quantity of the extract administered. Collip was the first to induce experimental hypercalcemia and to describe the effects of severe hypercalcemia.[32] His reports were widely read although he acknowledged that Hanson's extract was similar.

Enter Patient #2: Captain Charles Martell, of New York City (Fig. 14). The diagnosis of hyperparathyroidism in the United States was initially made in January 1926 by Eugene F Dubois at the Bellevue Hospital in New York City. The patient, 30-year-old Captain Charles Martell, was a vigorous marine sea captain until 3 years before admission, when generalized skeletal decalcification set in. Extensive calcium metabolism studies were performed on Captain Martell until April 1927, when he was transferred to Dr Aub, at the Massachusetts General Hospital (MGH), with calcium and phosphorus levels of 14.8 and 3.3 mg/dL, respectively.

After additional studies by Drs Aub, Albright (Fig. 15), and Bauer, the diagnosis of primary hyperparathyroidism was confirmed and in May 1927, Captain Martell underwent the first of two neck explorations by EP Richardson, chief of surgery at the MGH. During the first operation, through a collar incision, the right neck was explored without finding an adenoma. A single normal parathyroid gland was removed. The second operation was limited to the left side; only one normal parathyroid gland was found.[33]

In 1929, Captain Martell was rehospitalized in New York City, where he underwent a third neck exploration performed by Dr Russell Patterson. This, too, was a failed procedure. Because of decreasing renal function and increasing symptomatology, Captain Martell returned to MGH in May 1932; he was studied exclusively over 18 months in two metabolic wards by Albright and Castleman. During this period Oliver Cope (Fig. 16), at the direction of Churchill, carried out a series of parathyroid gland dissections in cadavers in preparation for Martell's procedure. With the assistance of Churchill, Cope performed several successful parathyroidectomies in early 1932. During the summer of 1932, Cope performed three negative cervical explorations. Martell, who had read extensively in

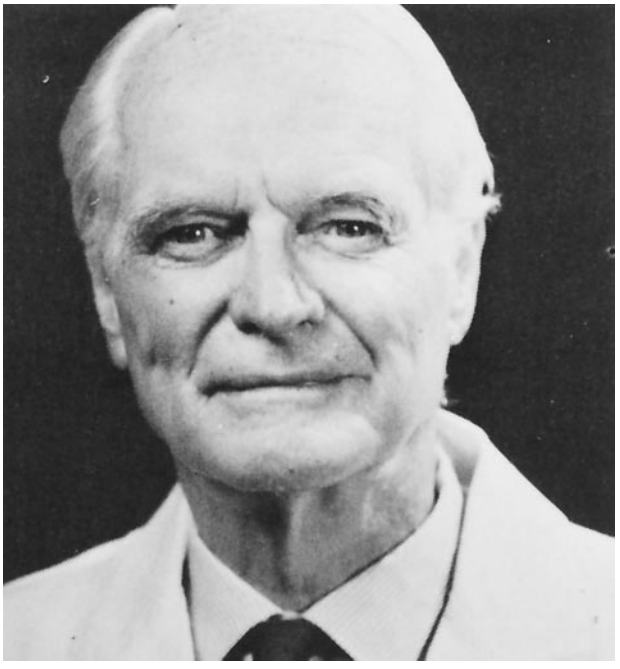

Figure 16. Oliver Cope, MD.

the Harvard Medical Library about the various locations of the parathyroid glands, insisted on an exploration of the mediastinum where he anticipated the tumor would be located.[34]

The seventh operation was performed by Churchill, with Cope's assistance, and a 3×3-cm mediastinal, encapsulated tumor was found. Churchill and Cope excised only 90% of the adenoma, attaching the remnant with its vascular pedicle to tissue in the region of the external notch. Despite these precautions, tetany developed on the third postoperative day. Six weeks after the operation a renal stone became impacted in the ureter and Captain Martell died from laryngospasm shortly after a surgical procedure to relieve his ureteral obstruction. Few patients in the annals of history have been studied as extensively as Captain Martell.

Enter Patient #3: Elva Dawkins, a 56-year-old farmer's wife with a 9-year history of urinary frequency, muscle weakness, spontaneous fractures, and bone tumors. Mrs Dawkins had been previously hospitalized at Barnes Hospital for a tumor involving the right index finger. The fourth finger was amputated and this turned out to be a giant cell sarcoma. There were irregular areas of skeletal rarefaction and bilateral renal stones. Enter Medical Student #4, Henry A Dixon, a fourth-year medical student at Washington University, who studied Elva Dawkins and was intrigued by her severe muscle weakness. Dixon found her serum calcium and phosphorus were 17 and 1.4 mg/dL, respectively. Mrs Dawkins was then transferred to Harold A Bulger's metabolic ward, where she was studied extensively. Issac Y Olch, an attending surgeon at Barnes Hospital (Washington University), performed the first successful parathyroidectomy in the United States on Mrs Dawkins on August 1, 1928.

At exploration Olch excised a 3×3-cm adenoma attached to the inferior pole of the left thyroid lobe confirmed by microscopic sectioning. Her serum calcium fell to 4.5 mg/dL and she was "saved only by heroic doses of Collip's parathyroid extract, intravenous calcium and calcium lactate by mouth."[35]

The earliest recorded excision of a parathyroid tumor in the United States was performed by EJ Lewis at Cook County Hospital in Chicago on January 6, 1926, on a 29-year-old woman, less than 6 months after Felix Mandl's operation and 4 months before Martell's first operation in Boston. This turned out to be a parathyroid carcinoma; multiple nodules were found in the neck. Subsequent recurrences required excision.[36]

The development of an immunoassay for the measurement of parathyroid hormone and other peptides by Berson and Yalow in 1963 was a seminal discovery that earned them the Nobel Prize.[37] The introduction of the serum chemical autoanalyzer, improved serum calcium determinations, and a better understanding of calcium diseases, dramatically increased the number of patients diagnosed with primary hyperparathyroidism. This era produced an impressive number of problems as metabolic experts and surgeons began to unravel the fascinating aspects of this gland and calcium metabolism.

At a meeting of the American Surgical Association in 1977, the following statements were made during a discussion of the surgical management of primary hyperparathyroidism (HPT): "double adenomas, if they exist, are rare;" "the number of recurrences among patients having less than three glands removed at the primary operation is distressingly high;" and "a probable recurrence rate of 1% and no

instances of permanent hypoparathyroidism appear to support our conservative approach to treatment when a single enlarged gland is found." Obviously these three statements are not compatible.[38]

The confusing microscopic interpretation of the pathology of this gland led to overly aggressive procedures in the mid-1970s and early 1980s. Krementz, in 1978, reported 100 cases of primary hyperparathyroidism; 96% were adenomas and 3% were hyperplasia. Paloyan, in 1973, reported 84 cases of HPT; 33% were adenomas and 66% were hyperplasia. But in 1981 the same author reported 87 additional cases of which 86% were adenomas and 11% were hyperplasia—clearly a wide variation in the interpretation of the glandular pathology. Esselstyn, in 1974, reported 100 cases of which 51% were adenomas and 49% were hyperplasia; in 1981 he would report 162 additional cases of which 83% were adenomas and 17% were hyperplasia. Wang, in 1976, reported on 431 cases of which 82% were adenomas and 14% hyperplasia, and Beahrs, from the Mayo Clinic, in 1977 reported on 207 cases of hyperparathyroidism of which 90% were adenomas and 8% were hyperplasia. These data represent the confusion that existed in the interpretation of parathyroid (PT) gland pathology.[38]

The presenting symptoms and signs since the mid-1960s have undergone significant change. HPT patients from 1948 through 1968 presented with bone and stone disease. With the introduction of the serum channel autoanalyzer, a precipitous increase in the number of cases that were asymptomatic, asignomatic, or both occurred with a parallel reduction in the number of cases with stone and bone disease. This issued in a new era of parathyroid surgery and placed additional responsibility on surgeons.

In reviewing asymptomatic hyperparathyroidism, the NIH consensus group concluded that medical monitoring was permissible in moderately hypercalcemic patients if there were no life-threatening hypercalcemic states and no renal or bone disease. No consensus could be reached regarding specific tests during the monitoring period or their sequence. No predictive factors were identified to alert clinicians as to when the disease is activated.[39]

A sparsity of information exists regarding surgical management of the patient with asymptomatic-asignomatic primary hyperparathyroidism. Two classic papers have reviewed this subset in detail: the Scholz-Purnell report from the Mayo Clinic;[40] and the Kaiser report by Rubinoff.[41] In a 10-year followup of 143 cases of asymptomatic asignomatic hyperparathyroidism at the Mayo Clinic, they concluded that: 1) there was a significant lack of followup compliance by both physician and patient; 2) there was no consensus on specific tests that should be routinely performed and at what intervals; 3) no predictive factors were discovered regarding the activation of this disease; and 4) "our recommendation for patients whose clinical and laboratory studies support the diagnosis of primary hyperparathyroidism has been and continues to be surgical exploration by an experienced parathyroid surgeon." There is general agreement that an experienced parathyroid surgeon should perform a minimum of 9 to 10 explorations annually.[40]

Rubinoff and colleagues[41] compared 160 patients with primary hyperparathyroidism with matched controls and found no difference in their symptoms or renal function. Rubinoff questioned the high incidence of hypercalcemia and the therapeutic benefit of parathyroidectomy.

Is bilateral exploration always necessary or is unilateral exploration adequate when the adenoma is found and one normal gland is identified? The surgical community continues to be divided on this issue, and it is unlikely that a resolution will be reached in the 20th century. A survey of endocrine surgeons further highlights the diversity of opinions regarding universal bilateral exploration: 1) Seventeen percent advocate unilateral exploration stating that an adenoma and a normal gland are the minimal requirements, particularly if found on the same side; 2) it reduces the operating time and costs; 3) there is less morbidity; and 4) the contralateral side remains untouched. Eighty-three percent preferred bilateral exploration because: 1) there is a better assessment of the pathologic process; 2) double adenomas or hyperplasia are better detected; 3) uniglandular or multiglandular disease (MGD) is better assessed (5%); 4) when the wrong side is entered initially; and 5) a second gland is identified.[39]

Two studies present opposing points of view. With regard to bilateral neck exploration, Proye, from France, in a review of 918 bilateral neck ex-

plorations reported that before 1989, 624 procedures were performed in which multiglandular disease was found (21%); after 1989 an additional 294 patients were explored and multiglandular disease was encountered in 17.3%. The total MGD experience for Proye and his group was 19.7%. They strongly recommended bilateral exploration.[42]

In contrast, Worsey and colleagues, from the University of Pittsburgh, in reporting on 350 cases of unilateral and bilateral exploration, demonstrated that in the unilateral group of 120 patients their success rate was 96%; in a comparative group of 220 patients undergoing bilateral neck exploration, the success rate was 92%. They concluded that MGD was missed in only 1.5% of patients, which justified their recommendation of unilateral exploration.[43]

To further confuse matters, Bongér and colleagues[44] reported on 582 patients with primary HPT single gland enlargement observed in 74% of the cases, double tumors in 18%, and triple tumors in 7% (MGD in 25%).

The experience of surgeons has led to several interesting quotations: 1) "the ectopic position of the gland is when you can't find it; the normal position is when you can"; 2) "the best localizing test is a good parathyroid surgeon"; 3) "preserve all parathyroid tissue for cryopreservation and subsequent implantation if needed"; and 4) "a little bit of calcium is better than a little bit of tetany."

Three anatomic dissections of the parathyroid gland were reported from 1938 through 1975 and provided clarification of supernumerary glands. Gilmour in 1938,[45] Alveryd in 1966,[46] and Wang in 1971[47] demonstrated that four glands existed in 87% to 97% of the patients, five glands in 1.9% to 6%, and six glands in 0.5%, respectively. Additional studies by other authors between 1977 and 1991 in both primary and secondary hyperparathyroidism, reported an incidence of supernumerary glands to vary between 2.4% and 38%.

Wang, from the MGH, states that the inferior parathyroid gland (previously called the parathymus gland by embryologists) is not in a juxtathyroidal position in 43% of patients. This is useful information for surgeons in search of the inferior parathyroid or migratory gland.[47] Several anatomic reports further established that the superior gland is stationary and in a juxtathyroidal position in 99% of the dissections.

The 1991 NIH Consensus Statement noted that data from parathyroid localizing studies do not support its use at the initial diagnosis and treatment. These studies were: 1) not found to be cost effective; 2) did not improve surgical cure rates; 3) were not indicated for the initial explorations; and 4) did not help decrease the operating time. In addition, these studies were often misleading; the false-positive rate was 15%, the true-positive rate 80%, and we are presently at a successful surgical exploration rate of over 90%.[39]

During Phase III aggressive surgical approaches stimulated continued investigation of parathyroid autotransplantation, site(s) of implantation, and assessment of graft function. Common sites used were the platysma, the flexor muscles of the forearm, and the medial surface of the thigh. Neovascularization does not imply functionality. Graft function could be determined by: 1) parathyroid hormone (PTH) determinations proximal and distal to the graft with a gradient of 2 to 1; 2) following the patient with urinary cyclic AMP levels; 3) withholding calcium and vitamin D to determine if they are needed; and 4) a differential thallium technetium 99 scan. Between 25% and 30% of these grafts are unsuccessful. Investigators pursued parathyroid autotransplantation simultaneously with neck exploration and delayed transplantation led by the preeminent work of Wells and coworkers, from the NIH and Duke University. Their carefully performed experiments as to the use, rejection, and cryopreservation of these glands was a definitive contribution to the advancement of parathyroid surgery during this era of aggressive surgery.[48]

The approach since 1975 of localizing studies for the parathyroid glands has been no less rigorous. Numerous modalities have been introduced including ultrasonography, CT, MRI, thallium technetium subtraction scans, sestamibi, etc. Innovations of these scans have produced varying degrees of success. Despite our current success rate of identifying hyperfunctioning parathyroid tissue at the initial operation, these localizing studies are expensive and appear unnecessary. There is a continuing effort among modern parathyroid surgeons to make these localizing studies cost effective in an ambulatory setting.

Other concerns registered at the consensus conference were: 1) women were twice as often affected by this disease than men; 2) 100,000 new cases are being reported each year; 3) is mild primary hyperparathyroidism benign? 4) there is an absence of predictive factors when this disease is activated from an asymptomatic stage; and 5) surgery is very successful at the present time.

PHASE IV: FAILURES AND NEW VISTAS

The geometric increase in the number of cases of primary hyperparathyroidism identified after 1965 made it almost inevitable that we would encounter cases of failed surgical operations for this disease. We have been victimized by our own successes. Our success rate of 95% in converting the hypercalcemic patient to normocalcemia by surgical exploration is impressive. A significant burden is placed on the shoulder of surgeons by the apparently asymptomatic or asignomatic patients with biochemical confirmation of primary hyperparathyroidism. This large volume of procedures has raised pertinent issues that require continued clinical and biomolecular investigation, ie, parathyroid hyperplasia, the development of a profile for secondary and tertiary hyperparathyroidism, tumor hypercalcemia, familial hypocalcuric hypercalcemia, the relationship of primary hyperparathyroidism to the MEN-I and MEN-II syndromes, intraoperative monitoring, intraoperative use of dyes (methylene blue and toluidine blue), parathyroid gland cryopreservation, and a clear definition of indications for parathyroid transplantation. Extensive surgical experience has identified parathyroid adenomas from the tracheoesophageal groove to the aorticpulmonary window. This phase of parathyroid surgery continues to unfold at a rapid pace.

A better understanding of biomolecular events, and genetic testing has initiated studies involving the parathyroid gland. Estrogen receptor gene polymorphism has been reviewed in postmenopausal primary hyperparathyroid patients. Their findings suggest that estrogen receptor gene polymorphism interacts with the extent of biochemical derangements of primary hyperparathyroidism, which could influence both the peripheral action of PTH and the altered calcium regulation of the secretion.[49]

The Duke University group has concluded that there is no apparent relationship between steady state levels of mRNA or calcium-sensing receptor (Ca R) in parathyroid adenomas compared with normal parathyroid tissues. This highly sensitive assay should prove useful in further examining the role of Ca R mRNA and calcium-sensing normal and abnormal parathyroid tissues.[50]

By using a biochemical assay instead of estimated size to predict which parathyroid glands are hypersecreting, the incidence of multiple glandular disease in primary hyperparathyroidism was found to be 5%.[51]

Intraoperative PTH monitoring reproducibly demonstrates the clinically relevant decrease in PTH levels after parathyroidectomy for secondary hyperparathyroidism similar to those previously documented in patients with primary hyperparathyroidism. Longterm followup and increasing numbers of patients are crucial in defining the role of quick parathyroid hormone (qPTH) monitoring during parathyroidectomy for secondary hyperparathyroidism.[52]

The Mayo Clinic Group has further defined the current role of parathyroid cryopreservation and autotransplantation in aggressive parathyroid surgery. Cryopreservation and autotransplantation are mechanisms to correct postexploration hypocalcemia. The indications for cryopreservation are rare and should be refined. The principal indication for cryopreservation is uncertainty and vascularity of the remaining parathyroid tissue. So cryopreservation plays a small but integral role in parathyroid surgery.[53]

There is an increasing body of opinion that primary hyperparathyroidism is not an asymptomatic condition. Measurement of outcomes after parathyroidectomy for asymptomatic-asignomatic primary hyperparathyroidism have demonstrated improvement in all aspects of health status 6 months after the operation. Most dramatic improvements were reported in the reduction of body pain, improved energy levels, and improved emotional and physical function. Their conclusion was that the correction of non-symptomatic hyperparathyroidism (NSHPT) improves patient health status.[54]

Since 1980, contributions to clinical and biomolecular information concerning the parathyroid glands have increased at a rapid pace. These events

parallel new information, improved technology, and clearly defined outcomes measures. The 21st century will certainly bring added developments to better define and treat abnormalities of these glands. Sandström, MacCallum, Dixon, Mandl, Hanson, Martell, Churchill, Cope, Wells, Yalow, Halsted, Evans, and Albright are a few who have contributed to this cavalcade of progress.

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