Vignette Hyperparathyroidism: Glimpse Into Its History

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The parathyroid gland was first described by Sir Richard Owen. Ivor Sandstrom coined the term *glandulae parathyroidiae*. Vassale and Generali Francesco observed that tetany occurs following parathyroidectomy. Harald Salvesen firmly established the relationship of the parathyroid gland to calcium metabolism. A patient with skeletal disease and a tumor near the parathyroid gland was described by Max Askanazy in 1904. Schlagenhauser suggested in 1915 that in an attempt to cure bone disease, solitary parathyroid enlargement, if present, should be excised. The term *hyperparathyroidism* (HPT) was coined by Henry Dixon and colleagues. The parathyroid surgeries on Albert J. and Charles Martell were the first experience with successful parathyroidectomy. From a grossly symptomatic disease of bones, stones, abdominal groans, and psychic moans, HPT has evolved into asymptomatic HPT. Improvements in knowledge about the pathology of parathyroid diseases, including the genetic basis of HPT, and advances in the surgical techniques have brought about changes in the management of HPT over the decades.

Key words: Hyperparathyroidism – History – Parathyroid surgery – Parathyroid adenoma

In 1850 Sir Richard Owen, professor of anatomy at the Royal College of England (Fig. 1), identified the parathyroid gland in an Indian rhinoceros in a London zoo.¹ Ivor Sandstorm, a medical student at Uppsala University, dissected parathyroids in ani-

mals as well as in 50 human cadavers in 1887. He published his detailed work on the location and blood supply of “*glandulae parathyroidiae*” in the Swedish Medical Journal. Sandstorm, who suffered from hereditary mental disorder, later committed

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Fig. 1 Portrait of Sir Richard Owen, professor of anatomy at the Royal College of England, who identified the parathyroid gland in an Indian rhinoceros.

suicide.¹ In 1881, Cresswell Baber, from England, also independently described parathyroid glands; however, it was Gley's work in 1890 that led to the recognition of the function of the parathyroid gland.² Later Halsted and Evans,³ in 1907, detailed the human parathyroid blood supply. In 1938 John Gilmour,⁴ during autopsy in 400 cases, found 4 parathyroids in 87% of cases, 3 in 6%, and 2 in 0.2%. Five glands were found in 6%, and 6 glands were found in 0.5%.

Meanwhile, with the evolution of thyroid surgery and an increased understanding of thyroid gland-related physiology, some important observations were made. One of these was the occurrence of tetany after thyroidectomy. Victor Horsely, of London, had concluded that tetany was the immediate effect of thyroidectomy, and myxedema was the late effect; however, Vassale and Generali Francesco observed that tetany occurs following parathyroidectomy alone. They concluded that parathyroids removed toxins from the body.⁵ Other scientists opined that hypoglycemia and intoxication were the cause of tetany. It took another 8 years, but in 1909,

William MacCallum and Carl Voegtlin observed that parathyroidectomy was accompanied by hypocalcemia and that injections of parathyroid/calcium were effective to cure it.⁶ It was Harald Salvesen who firmly established the relation of parathyroid gland to calcium metabolism. Jacques Loeb, in 1901, found relief from neuromuscular irritability if calcium was injected. James Collip prepared the most potent form of parathyroid extract in 1925. Grenwald and Gross used this parathyroid extract to show that injection of this led to hypercalcemia in normal dogs.² Very soon it was discovered that parathyroid hormone (PTH) is a peptide hormone that is released in response to serum calcium levels.

Recognition of Primary Hyperparathyroidism as a Disease

Friedrich von Recklinghausen, in 1891 (Fig. 2A), reported on 3 patients with a condition called osteitis fibrosa cystica (OFC). For a long time, these bone tumors were thought to be sarcoma. A patient with skeletal disease and a tumor near the parathyroid gland was described by Max Askanazy in 1904. Similar cases were described by Schmorl in 1907, Molineus and Poltauf in 1913, and Harbitz in 1915.² Perhaps the earliest description of OFC was given by Denninger in the skeleton of a prehistoric American Indian excavated in Illinois. The findings in the bone leave no doubt that the person, who lived 1000 years ago, had hyperparathyroidism (HPT).² One of the earliest descriptions of a complete case of HPT was given by French surgeon Courtial in 1705. He provided the detailed medical history of patient Pierre Siga, who had progressive skeletal involvement and died at the age of 42 years.²

However, there was controversy over whether parathyroid was primary or secondary to skeletal disease.² The effects of intentional parathyroidectomy in rats was described by Jakob Erdheim of Vienna in 1906, and he believed that parathyroid enlargement was secondary to skeletal disease. Schlagenhauser suggested in 1915 that in an attempt to cure bone disease, solitary parathyroid enlargement, if present, should be excised. However, it took another 10 years before this relationship between parathyroid disease and bone involvement was accepted.² He also found that there was defective calcification of teeth after parathyroidectomy. Bauer *et al*, in 1929, injected rabbits with parathyroid extracts for 3 months and later studied the bone for gross changes, which revealed an increase in

Fig. 2 Portraits of (A) Friedrich von Recklinghausen and (B) Felix Mandl.

trabeculae of the spongiosa. Turnbull published the classical features of OFC later.² The term *hyperparathyroidism* was coined by Henry Dixon and colleagues.³

Parathyroidectomy: The Early Operative Scenario

One of the earliest attempts at parathyroidectomy was made by Oscar Hirsch in April 1925. It was a failed attempt because the patient was having only fibrous dysplasia.⁷

The life history of Albert J. is to be remembered by all parathyroid surgeons. He developed fatigue and leg pains in 1921 at the age of 34. Earlier he was expelled from the Austrian army due to tuberculosis. At the age of 36, his X-rays showed osteopenia and cysts. For this he was treated with cod liver oil. He subsequently developed a fracture after 1 year. He was examined by Felix Mandl (Fig. 2B), who found that he had high serum calcium and urinary calcium excretion. Albert was treated with “thyroid extract” and later with “parathyroid extracts” based on the prevailing concepts at that time. Mandl then used fresh parathyroid tissue from a street accident victim and transplanted it but without success. In July 1925, he explored Albert’s neck and removed a parathyroid tumour 21 × 15 × 12 mm. This had a dramatic effect, and Albert started walking with support. His bone pains decreased and his urine became clear. Albert was not so lucky, because his disease recurred after 7 years, in 1932. Though reexploration was done, he died of renal failure. His autopsy failed to reveal any parathyroid disease.⁷

Charles Martell was a sea captain who had severe bone disease. He would have 7 operations in New York and Boston before his tumor was removed.⁷ In May 1926, Edward Richardson at the Massachusetts General Hospital (MGH) operated on Martell twice without success. Oliver Cope studied parathyroid glands in autopsies before starting an operation for parathyroid in 1932. Edward Churchill and Cope together explored Martell’s neck and made sure that there were no parathyroids in the neck. They then opened the chest, which was at the request of Martell, only to find the gland there. Postoperatively, Martell developed renal failure and tetany and expired.⁷

At this time, more surgeons noted that hypocalcemia after surgery was so severe that it resulted in mortality.⁸ Churchill and Cope together went on to perform about 30 cases within one year after Martell’s operation; they described parathyroid surgery in detail.⁹ They employed frozen sections in selected cases and routinely performed biopsy from one normal thyroid to rule out hyperplasia. To overcome the tetany, they even advocated partial adenomectomy. This was later abandoned because the treatment of hypocalcemia had improved. Hypocalcemia was effectively treated by surgeons at this time with a high-calcium, low-phosphate diet as well as intravenous calcium. Some tried parathyroid extracts, which had no beneficial effect and resulted in severe antigenic reactions. Vitamin D was not in use. James Walton stressed the need for wide exposure of the neck and also a search of the retrotracheal and retroesophageal regions.¹⁰ They advised that sternal split is rarely required.

Spread of Parathyroid Surgery

Considerable experience in parathyroidectomy was gained by surgeons worldwide by the year 1950. From the Mayo Clinic, Marden Black reported 140 cases; John Hellstrom reported 17 cases from Stockholm. The mortality in these series was attributed to renal disease.¹¹ The MGH series had increased to 230 and Hellstroms to 138 by 1960.¹² Experience with 95 cases was reported from Northern Ireland by Ernest Morrison in 1963.¹³ As more and more experiences were reported, it was realized that HPT may not be due to parathyroid adenoma involving a single gland. In his series of 200 patients, Cope described adenoma in 79%, double adenoma in 5%, and hyperplasia in 7% of cases.¹⁴ Soon multiple endocrine neoplasia (MEN) was also recognized, with HPT as its most common component. Chiu-an

Fig. 3 Portrait of Berson and Yalow.

Wang reported the follow-up of Cope's original cases of double adenoma wherein a majority had recurrences, which led to the belief that all double adenomas are in fact hyperplasia.¹⁵ Most surgeons performed subtotal parathyroidectomy for multiglandular disease, leaving 60 mg of one gland.⁷ Wells practiced auto-transplantation to the forearm, and freezing of parathyroid tissue with late transplantation also began.^{16,17} Thompson advocated total parathyroidectomy and cervical thymectomy in MEN 1 cases. In MEN 2A, it was realized that HPT is mild and only involves glands that can be removed.^{4,7} Parathyroid carcinoma was described by Russell Wilder in 1929. By the year 1953, 120 cases of parathyroid carcinoma had been reported.¹⁸ The histopathologic criteria to diagnose parathyroid cancer were reported in detail by Schantz and Castleman¹⁹ as late as 1973. Historically, all initial operations were bilateral explorations of the neck because of the lack of proper localization; it later became unilateral exploration, and finally focused parathyroidectomy.

Multisystem Involvement in HPT

As the understanding of HPT improved, it was realized that HPT has an effect on multiple systems in the body, such as renal effects, pancreatitis, and acid peptic disease, apart from the bony lesions. Renal calculi were reported by John Davies-Colley and also by Albright.⁷ X-rays of the urinary tracts and renal functions were routine tests performed in all cases.⁹ Albright observed the incidence of renal

stones was 80% among his patients. He was one of the earliest surgeons who screened patients with renal stones for primary HPT (PHPT). It was estimated that 20% of the patients attending renal stone clinics would have PHPT.²⁰ Cope reported 67 patients; Walton at the Mayo Clinic reported 14 cases. Subsequently, the early effects on the bone were described, such as the subperiosteal erosions and loss of lamina dura.⁷

By 1940, peptic ulcer and dyspepsia were recognized in patients with HPT. In 1946, Milton Rofers and Raymond Keating described an association between parathyroid disease and peptic ulcer.²¹ The incidence was reported as 8% to 30% in patients with PHPT.¹³ Later, Walter St. Goar described it as the disease of "Bones, stones and abdominal groans."²² The association of pancreatitis and HPT was described by Cope *et al*²⁴ in 1957. They reported this in 2 cases, 1 of which was parathyroid carcinoma.²³

Diagnostic Tests for HPT in the Past

A cortisone suppression test was used to differentiate hypercalcemia of HPT from that of other conditions.⁷ High plasma chloride, low serum bicarbonate, and high urinary hydroxyproline excretion were considered to be suggestive of HPT. To diagnose bone demineralization, bone biopsy and radiology were used. Slit-lamp ophthalmoscopy was used to diagnose corneal calcification.⁷ Serum calcium was measured only in symptomatic patients. In the 1960s, routine biochemical screening was introduced. Bioassay of PTH was used in 1925 but was found to be not useful. Nobel Prize winners Solomon Berson and Rosalyn Yalow (Fig. 3) developed the immunoassay measurement that made the hormone assay easy.²⁴ Those early assays used monoclonal antibodies directed against epitopes predominantly within the mid- or carboxyl terminal portions of the PTH molecule. The carboxyl terminal fragments have been found to be high in patients with renal failure. Though the radioimmunoassay with specificity for the amino terminal portion of PTH was developed, it had inadequate sensitivity.^{25,26} The currently available immunoradiometric assays are highly sensitive to PTH.²⁶

Localization of the parathyroids was attempted from 1950 onward because the occasional parathyroid surgeons found it difficult to complete successful parathyroidectomy. Cine-esophagography and arteriography were started in the 1950s. Preoperative selenomethionine scanning and selective ve-

nous sampling came into use.⁷ Preoperative injections of toluidine blue and methylene blue injections were started subsequently. Thyroid ultrasound and computerized tomography were started in the 1970s for parathyroid localization. In the 1980s, subtraction isotopic scanning was also started. Thallium 201 Tc 99 pertechnetate was used in combination. Coakley and colleagues introduced Tc 99 sestamibi (MIBI) scanning to parathyroid imaging, which led to many changes in the surgical approach to the disease.²⁷ However, most of the experienced surgeons who had a success rate of >95% for parathyroidectomy without localization used localization studies only for recurrent/persistent HPT.⁷

Era of Asymptomatic HPT

The prevalence of HPT was estimated in 1965 at 1 in 1000 after screening with serum calcium was instituted in asymptomatic patients. In 1977, Robert Coffey, from Washington DC, reported that the incidence of asymptomatic HPT was 5% before 1970 (n = 100) and 40% after 1970 (n = 100). Similarly, the Mayo Clinic reported that 64% of their cases of HPT during the period 1974 to 1980 were asymptomatic.¹⁷ Overall, the incidence of parathyroidectomy increased from 36 cases in the period between 1935 and 1962 to 1000 cases between 1970 and 1983.³

In the 1970s, all patients with asymptomatic HPT were subjected to parathyroidectomy. This was based on the observation from the Mayo Clinic. Around 147 patients who received follow-up for 10 years by the Mayo Clinic were found to have a higher incidence of cardiovascular system-related mortality. Another 25% developed complications related to HPT.²⁸ These observations led to parathyroidectomy in all cases. Now it has been recognized that not all cases of asymptomatic HPT need parathyroidectomy. Guidelines for parathyroidectomy in asymptomatic HPT were established, and the latest modification was done in 2008.²⁹

To conclude, management of HPT has evolved over the centuries. With advances in the hormonal assays and localization studies like the MIBI scan, diagnosis of HPT has become more accurate. Improvements in knowledge about the pathology of parathyroid diseases, including the genetic basis of HPT, and advances in the surgical technique have brought about changes in the management of HPT. Now, more and more, asymptomatic HPT is being recognized and treated, especially because of the

inclusion of calcium estimation in routine health screening.

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