A HISTORY OF THE PARATHYROID GLANDS: FROM EARLY MISUNDERSTANDINGS TO MODERN CONCEPTS

Historia przytarczyc: od wczesnych nieporozumień do współczesnych koncepcji

Dorota Anna Brodowska-Kania[1], Natalia Osial[1], Piotr Zięcina[2], Grzegorz Kamiński[1]

1. *Military Institute of Medicine – National Research Institute, Department of Endocrinology and Radioisotope Therapy, Poland*
2. *Military Institute of Medicine – National Research Institute, Department of Interventional Radiology, Poland*

Natalia Osial – 0000-0003-2081-5592

Abstract

The parathyroid glands are small organs responsible for regulating calcium-phosphorus metabolism in the body. They were discovered in 1852 by Richard Owen. A comprehensive description of the parathyroid structure in humans was presented by Sandström in 1880. Several years later, Gley observed a connection between parathyroid damage and tetany. In 1908, MacCallum and Voegtlin suggested the impact of parathyroids on calcium metabolism, attributing tetany to hypocalcaemia following their removal. The link between parathyroid pathology and skeletal changes was noted by Erdheim in 1906. Another pivotal event was the isolation of parathyroid extract, independently accomplished by Hanson in 1923 and Collip in 1925. Mandl made history as the first surgeon to successfully perform parathyroidectomy due to a parathyroid adenoma in 1925. In the mid 20th century, Albright conducted extensive studies on hyperparathyroidism, distinguishing between primary, secondary, and tertiary hyperparathyroidism. The purification of the parathyroid hormone and the development of laboratory tests to assess its blood levels facilitated the diagnosis of parathyroid disorders, contributing to a significant increase in surgeries in the late 1980s. The turn of the 19th and 20th centuries marked a period of significant development in parathyroid imaging techniques and minimally invasive surgery. This article delineates key events in the history of parathyroids that have shaped contemporary knowledge and contributed to the development of effective methods for the diagnosis and treatment of parathyroid diseases.

Streszczenie

Przytarczyce są niewielkimi gruczołami, które odpowiadają za regulację gospodarki wapniowo-fosforanowej w organizmie. Zostały odkryte w 1852 roku przez Richarda Owena, natomiast pełnego ich opisu u ludzi dokonał Sandström w 1880 roku. Kilkanaście lat później Gley zauważył związek między uszkodzeniem przytarczyc a występowaniem tężyczki. W 1908 roku MacCallum i Voegtlin zasugerowali wpływ przytarczyc na metabolizm wapnia, a tężyczkę przypisali hipokalcemii spowodowanej ich usunięciem. Związek między patologią przytarczyc a zmianami kostnymi został stwierdzony w 1906 roku, dzięki badaniom Erdheima. Kolejnym przełomowym wydarzeniem była izolacja ekstraktu przytarczyc, przeprowadzona niezależnie przez Hansona w 1923 roku i Collipa w 1925 roku. Mandl przeszedł do historii jako pierwszy chirurg, który przeprowadził skuteczną paratyroidektomię z powodu guza przytarczyc, co miało miejsce w 1925 roku. Najobszerniejsze badania na temat nadczynności przytarczyc przeprowadził w połowie XX wieku Albright, który zróżnicował pierwotną, wtórną i trzeciorzędową nadczynność przytarczyc. Oczyszczenie hormonu przytarczyc i opracowanie testów laboratoryjnych do pomiaru jego stężenia we krwi ułatwiło diagnostykę chorób przytarczyc, co przyczyniło się do znacznego wzrostu liczby operacji pod koniec lat 80. XIX wieku. Przełom XIX i XX wieku był okresem istotnego rozwoju technik obrazowania przytarczyc i chirurgii małoinwazyjnej. W niniejszym artykule opisano najważniejsze wydarzenia w historii przytarczyc, które ukształtowały współczesną wiedzę oraz przyczyniły się do opracowania skutecznych metod diagnostyki i leczenia chorób przytarczyc.

Keywords: history; parathyroid glands; tetany; parathyroid surgery; osteitis fibrosa cystica

Słowa kluczowe: historia; przytarczyce; tężyczka; chirurgia przytarczyc; włóknisto-torbielowate zwyrodnienie kości

DOI 10.53301/lw/186294

Received: 04.03.2024

Accepted: 20.03.2024

Corresponding author:
Dorota Anna Brodowska-Kania
Military Institute of Medicine – National Research Institute, Department of Endocrinology and Radioisotope Therapy,
128 Szaserów St., 04-349 Warsaw
e-mail: dbrodowska-kania@wim.mil.pl

Introduction

The parathyroid glands are small endocrine organs producing parathyroid hormone (PTH), which plays a key function in regulating calcium and phosphate metabolism in the body. First reports on parathyroid glands appeared in the mid 19th century, making these organs the most recently discovered anatomical structures in humans. Currently, we have extensive knowledge about the parathyroid glands and advanced diagnostic and therapeutic approaches to manage their dysfunctions. Although relatively short, the history of these small glands is full of misunderstandings, speculations and intriguing anecdotes. This paper highlights key events and discoveries that have significantly contributed to the understanding of the role of the parathyroid glands in the human body.

Discovery of the parathyroid glands

The first description of the parathyroid glands dates back to the mid 19th century, when Richard Owen, a prominent British surgeon and anatomist, drew attention to independent anatomical structures located in the thyroid region during a necropsy of an Indian rhinoceros [1, 2]. In 1834, the Zoological Society of London purchased an Indian rhinoceros, which for 15 years was the main attraction at London Zoo. The animal died in November 1849 as a result of injuries inflicted by an elephant. During the winter months of late 1849 and early 1850, Richard Owen, who was a professor of Comparative Anatomy and a conservator of the Hunter's Museum at the Royal College of Surgeons in England at that time, conducted a detailed post-mortem examination of the 2-tonne animal, and then presented his findings to the Zoological Society of London on 12 February 1850 [1]. In the third part of his report, entitled 'Thoracic organs', Owen described the parathyroid gland for the first time as 'a small compact yellow glandular body attached to the thyroid at the point where the veins emerged' [1]. Although he did not perform a histological examination or speculate on the function of the newly identified structure, he fixed it along with the surrounding tissues, assuming that it might play an important role. The specimen was classified as RCSHM/L333.1 and is still available in the Hunter Museum in London. The entire post-mortem report on the rhinoceros was published in the fourth volume of Transactions of the Zoological Society of London. Unfortunately, the brief mention of a small anatomical structure was ignored among the extensive anatomical descriptions of the rhinoceros and Owen's discovery went unnoticed for the next 100 years. It was not until 1953 that British anatomist Alexander Cave, while analysing the Hunter Museum exhibits, discovered that Owen's paper, published on 2 March 1852, featured the first-ever description of the parathyroid glands, preceding all other reports on these organs [1].

Prior to this event, Ivar Viktor Sandström, a Swedish medical student who presented the first comprehensive description of the human parathyroid glands, was considered the discoverer of the these organs [1, 3]. In 1877, Sandström discovered 'a small organ, hardly as big as a hemp seed, which was enclosed in the same connective tissue capsule as the thyroid, but could be distinguished there from by a lighter colour' during a necropsy of a dog at the Department of Anatomy at Uppsala University. He then examined 50 human cadavers and found four glands in 43 of them, two on each side of the thyroid gland. Due to their location, he named the organs '*glandula parathyroideae*', i.e. parathyroid glands [4]. Hoping to make the discovery of the new organ more widely known, Sandström's findings were sent to a German journal, but the article was considered too long and rejected [3]. Finally, the paper was published in 1880 in a local Swedish journal [4]. In a 30-page paper, which contained many handwritten drawings and schematic images, Sandström thoroughly described the location, size, colour, variety of shapes and histological structure of the parathyroid glands. However, due to limited access to the scientific literature at the time, Sandström's work failed to gain international recognition for several more years, and his promising scientific career was interrupted by tragedy. Sandström, who struggled with chronic depression, committed suicide at the age of 37 years [3]. The importance of his research was only recognised a decade later, two years after his death, when Eugène Gley, a French physiologist and endocrinologist, linked the structures identified by the Swedish student to tetany, which was then a common complication of thyroidectomy [5].

The link between parathyroid glands and tetany and the 'detoxification theory'

The 19th century was a time of rapid development in thyroid surgery. The first attempts to operate on this organ were associated with severe complications and high intraoperative mortality. In the mid 19th century, two prominent surgeons, Theodor Billroth and Emil Theodor Kocher, independently developed techniques that revolutionised thyroid surgery, allowing for a significant improvement in treatment outcomes. However, their success in significantly increasing survival rates after thyroidectomy was associated with previously unknown postoperative complications. Symptoms of hypothyroidism were a common complication in patients operatively treated by Kocher, while many Billroth's patients developed tetany in the first few days post-surgery, usually with fatal outcome [6].

In 1891, Eugène Gley discovered that intraoperative damage to the parathyroid glands led to tetany. He showed in animal experiments that tetany attacks after thyroid surgery occurred only if the excised material included the parathyroid glands, previously described by Sandström. Sparing the parathyroid glands during thyroidectomy prevented tetany. Gley believed that there was a functional relationship between parathyroid glands and the thyroid gland, and only their simultaneous removal induced tetany symptoms. He additionally believed that the parathyroid glands were responsible for the elimination of toxins from the body and proposed a theory that postoperative tetany was caused by toxin accumulation due to detoxification dysfunction of the glands [5]. Although his theory was proven wrong, Gley was the first person to attribute

a vital role to the parathyroid glands, previously considered to be non-functional.

During the same period, Italian surgeons Giulio Vassale and Francesco Generali also conducted research on parathyroid glands. By conducting experiments on cats and dogs, they identified four parathyroid glands in each individual and showed in 1896 that tetany also develops after selective removal of all the parathyroid glands while preserving the thyroid [7]. On this basis, they proved that the parathyroid glands are not part of the thyroid gland, but play a separate role in the body. Despite the lack of scientific evidence, Vassale and Generali supported the 'detoxification' theory proposed by Gley, which was believed for the next 10 years.

Relationship between tetany and hypocalcaemia

In 1909, American pathologists William MacCallum and Carl Voegtlin from the Johns Hopkins Hospital demonstrated that tetany is not caused by poisoning, but results from impaired calcium metabolism. They observed that parathyroidectomy in animals caused a decrease in tissue calcium levels and excessive urinary and faecal excretion of this ion, which correlated with the severity of tetany. They then conducted a study in which they administered calcium, sodium and potassium salts to dogs with parathyroidectomy-induced tetany. Of the substances tested, only calcium salts caused symptom alleviation and prevented death in the animals. It was shown based on these observations that the parathyroid glands play a key role in maintaining proper blood calcium levels and that tetany arises from hypocalcaemia caused by insufficient secretory function of these glands [8]. Thus, after 10 years, they resolved the misconception about the detoxifying function of the parathyroid glands.

The role of the parathyroid glands in bone disease and the 'compensatory hypertrophy theory'

Brown tumours, which are osseous lesions caused by parathyroid pathology, had been described already before identifying the function of these glands and their role in regulating calcium-phosphate metabolism. In 1891, German pathologist Friedrich Daniel von Recklinghausen published a series of clinical cases of patients with unknown bone disorders. One of these patients presented with typical clinical and pathological features of hyperparathyroidism. The man suffered from multiple painful bone deformities, had a history of multiple pathological poorly healing fractures, and died as a result of complications following femoral shaft fracture. At post-mortem examination, Recklinghausen observed typical signs of bone disease that accompanies hyperparathyroidism, such as generalised fibrosis, bone cysts and brown tumours composed of multinucleated giant cells. He used the term 'osteitis fibrosa cystica' (OFC) [9], today also known as osteitis fibrosa, osteodystrophia fibrosa, and von Recklinghausen's bone disease, due to the morphology of these lesions. Although the disorder is still named after Recklinghausen, he did not see a link between the bone lesions described and parathyroid dysfunction at that time.

It was only a dozen or so years later, when MacCallum and Voegtlin were investigating the relationship between parathyroid glands and tetany, that the Viennese pathologist Jacob Erdheim focused his interest on the correlation between parathyroids and bone disease. In 1906, he noted that rats after parathyroidectomy developed decalcified incisors, which was reversed after reimplantation of the glands [10]. He then conducted post-mortem examinations of deaths due to bone disease, paying particular attention to the parathyroid glands. The glands were found to be significantly enlarged in many patients [11]. Erdheim wrongly concluded that parathyroid hypertrophy was a compensatory phenomenon secondary to primary bone disease, whose role was to increase calcium levels in the affected bone tissue. On this basis, he suggested that gland transplantation and parathyroid extract could be potential therapeutic options for bone disease [11]. Since Erdheim was highly respected in the medical community at the time, his theory was widely accepted and patients with bone disease were inappropriately treated with parathyroid extract for years to come despite the fact that he never provided any scientific evidence to support his theory [12].

Isolation of parathyroid extract

The first attempts to treat tetany with a crude extract derived directly from animal parathyroids were made in the first decade of the 20th century; however, not always successfully [13]. The breakthrough is owed to Adolph Hanson and James Collip, who, around the same time, independently developed purified, stable extracts showing efficacy in treating tetany [14].

Adolph Hanson was an American neurosurgeon who, after returning to his hometown after the First World War, set up a private medical practice and built his own laboratory. In 1923, after a series of experiments using bovine parathyroid glands, he independently developed a stable parathyroid extract containing a previously unknown active organic compound, which he named '*hydrochloric X*'. Since further investigations of the isolated substance were impossible under home conditions, Hanson teamed up with the University of North Dakota. He conducted a study in an academic laboratory on dogs treated with *hydrochloric X* within 24 hours of parathyroidectomy. Tetany resolved in all dogs within six hours of administration, and the effect was sustained with subsequent smaller doses of the substance [15]. Following this discovery, Hanson contacted the Eli Lilly pharmaceutical company in 1924 to collaborate on the manufacture of a new tetany drug. However, as an independent researcher working in a home laboratory, he faced rejection. As it later turned out, Eli Lilly was already working with another scientist, James Collip, at that time [14].

James Collip was a professor of biochemistry at the University of Alberta, where he managed a thriving academic laboratory. In 1925, he isolated and purified proteins contained in parathyroid tissue, obtaining an extract he called '*parathyrin*'. Subsequently, like Hanson, he performed a series of successful experiments using parathyrin for parathyroidectomy-induced tetany in

dogs [16]. The extraction methods used by Hanson and Collip were relatively similar. Both researchers treated bovine parathyroid glands with dilute hydrochloric acid, then concentrated the solution by evaporation and titrated until reaching a neutral pH [14]. Since Collip had far greater financial resources and better technical equipment at his disposal, his experiments were more detailed, systematised and involved a significantly larger sample of animals. Although he has gained wider recognition in the scientific community, Adolph Hanson, who through his passion and commitment was the first to independently isolate parathyroid extract, should not be forgotten. Achievements of these two scientists allowed for the production of a stable parathyroid extract on a large scale, resulting in a significant improvement in the treatment of patients with tetany [14]. Following Erdheim's theory of compensatory parathyroid hypertrophy in response to bone disease, parathyroid extract was also used in patients with bone disorders [12].

Two breakthrough clinical cases of primary hyperparathyroidism

Following Erdheim's reports on the relationship between the parathyroid glands and bone disease, OFC was considered a primary bone disease. It was not until 20 years later that the actual relationship between these conditions was shown to be quite the opposite, with parathyroid pathology being the primary lesion giving rise to secondary bone damage [12].

Albert Gahne, who was admitted to hospital in Vienna in 1924 and put under the care of surgical resident Felix Mandel due to femoral fracture, was the first patient with documented primary hyperparathyroidism (PHPT). He was diagnosed with OFC during his hospital stay. Following Erdheim's earlier postulates, treatment with parathyroid extract was initiated, and four parathyroids were transplanted from a deceased donor. As the treatment failed, Mandl decided to resect the hypertrophied gland. On 30 July 1925, he removed the left inferior parathyroid gland, measuring 25 × 15 × 12 mm, which he described as yellowish-brown, enlarged, closely adherent to the recurrent laryngeal nerve. The other three parathyroid glands were unremarkable. Postoperatively, the patient's condition improved significantly, with resolution of bone pain and normalisation of serum calcium [17, 18]. Unfortunately, a few years later, the patient experienced a recurrence with symptoms of severe kidney stones. During reoperation, no tumour was found in the neck or the mediastinal region and the man passed in 1936, probably as a result of metastatic parathyroid carcinoma. In addition to bone lesions, postmortem findings included severe bilateral nephrocalcinosis [17, 18]. Mandl was the first to prove that OFC is a disorder secondary to primary parathyroid pathology, and he went down in history as the first surgeon to perform parathyroidectomy for parathyroid tumours.

Over a similar period, PHPT was also diagnosed in an American naval officer, Charles Martell, who also presented with OFC. In 1926, Martell was admitted to Massachusetts General Hospital and put under the care of endocrinologist Joseph Charles Aub, who specialised in calcium metabolism. After many laboratory investigations and consultations, Aub, in cooperation with his colleagues Fuller Albright and Walter Bauer, ultimately diagnosed PHPT and decided to remove the affected glands. Between 1926 and 1931, Captain Martell underwent six neck surgeries, during which two healthy glands were excised. Unfortunately, the affected parathyroid gland was not identified. It was not until 1932 that Edward Churchill, chief of surgery at Johns Hopkins Hospital, in cooperation with resident Oliver Cop, performed a sternotomy in the hope of identifying the affected mediastinal parathyroid gland. During Martell's seventh surgery for hyperparathyroidism and first mediastinal exploration, the surgeons performed a subtotal resection of a 3 × 3 cm mediastinal parathyroid adenoma, which led to an improved patient health status. Unfortunately, six weeks after this successful intervention, Captain Martell developed ureteral obstruction and died due to complications after a urological procedure. The man already had a past history of severe urinary symptoms. Several acute attacks of renal colic and urinary stasis were documented in the course of the disease, with X-ray findings of advanced kidney stones and nephrocalcinosis, as confirmed at post-mortem examination [19, 20].

Over the next few years, more than a dozen other cases of PHPT were correctly diagnosed at Massachusetts General Hospital, marking the beginning of a novel, correct approach to parathyroid physiology and pathophysiology [21, 22].

The beginning of a novel, correct approach

Fuller Albright, a prominent endocrinologist who was part of the team of specialists in charge of Captain Charles Martell, devoted almost his entire career to the study of the parathyroid glands, as well as calcium and phosphorus metabolism disorders. His groundbreaking research provided the basis for the development of modern concepts on calcium-phosphate metabolism and parathyroid disease. As a young practitioner, he trained alongside Joseph Charles Aub. It was during this period that Albright was involved in the extensive diagnosis of Captain Martell, who was at that time admitted to Massachusetts General Hospital for the first time. He then did an internship at Johns Hopkins Hospital and spent a year in Vienna, working with Erdheim. In 1929, he returned to Massachusetts General Hospital, where he began his own research. In the years that followed, Albright and his team published extensive papers on calcium and phosphorus metabolism and PHPT, including its pathophysiology, biochemistry, diagnosis, treatment and prognosis [23]. Albright showed that, in addition to its effects on calcium levels, PTH reduces blood phosphorus and increases its excretion in the urine [24]. Furthermore, he was the first to link hyperparathyroidism with kidney stones and nephrocalcinosis. Based on this, he implemented screening for hyperparathyroidism in a group of patients with kidney stones but without bone disease, which contributed to an increase in the number of diagnosed cases [21]. At that time, all parathyroid pathologies presenting with overactive glands were

considered the same clinical entity, i.e. PHPT, which was identified as an isolated adenoma and treated operatively [22, 23]. Albright noted that diffuse hyperplasia of all parathyroid glands rather than just an adenoma of a single gland may underlie hyperparathyroidism [25]. This led him to a conclusion that hyperparathyroidism could have a diverse aetiology. He was the first to accurately describe primary, secondary and tertiary hyperparathyroidism. His findings were summarised in a comprehensive study published in 1948 in the book 'The parathyroid glands and metabolic bone disease' [26].

Albright's research paved the way for further studies at Massachusetts General Hospital, which became a leading centre for the treatment of parathyroid disease and calcium metabolism disorders, with 343 diagnosed cases of hyperparathyroidism between 1930 and 1965. In addition to bone and kidney disease, patients presented with comorbidities such as gastric ulcers, pancreatitis, muscle weakness and hypertension [22].

Isolation of pure PTH and development of assays for measuring its blood levels

The importance of a stable form of parathyroid extract became apparent after the first findings of Hanson and Collip were presented [14–16]. Nevertheless, it took another 40 years before a hormone of sufficient purity was developed and its chemical composition determined.

Pure PTH was isolated in 1959 by Howard Rasmussen and Lyman Craig from the Rockefeller Institute in New York. A few years later, in 1962, they described the peptide structure of the hormone [27], for which Craig received the Albert Lasker Prize in 1963 and 29 nominations for the Nobel Prize in Chemistry.

In 1963, Solomon A. Berson and Rosalyn Yalow discovered the antigenic properties of protein hormones and developed an effective radioimmunoassay method for assessing their blood levels, which revolutionised endocrine diagnosis [28]. In 1977, Yalow was awarded the Nobel Prize for this groundbreaking achievement.

Advances in parathyroid surgery and diagnostic imaging

Since the first targeted parathyroid tumour resection by Felix Mandel in 1925, parathyroid surgery has evolved towards increasingly less invasive procedures. Initially, wide neck exposure was recommended to visually identify all four parathyroid glands and remove only the involved ones [22].

Advances in laboratory diagnosis resulting from the development of radioimmunoassays to measure PTH have contributed to a significant increase in the number of diagnosed cases of hyperparathyroidism. A population-based study conducted in Rochester (Minnesota) documented a significant increase in the incidence of hyperparathyroidism between 1965 and 1975. The incidence rate increased from 15 to 112 cases per 100,000 population during this period [29]. For this reason, many patients, including those asymptomatic, underwent surgical resection of the glands in the late 1980s [22]. Eventually, uncertainties about the specific indications for surgical treatment arose. Surgery is currently recommended in all symptomatic PHPT cases. It is also advised in asymptomatic patients with serum calcium greater than 1 mg/dL higher than the upper limit of normal, urinary calcium excretion >400 mg/24 h, reduced glomerular filtration rate, kidney stones, osteoporosis and age < 50 years. Secondary and tertiary hyperparathyroidism, on the other hand, is treated conservatively, with parathyroidectomy recommended only in cases of refractory hypercalcaemia, hyperphosphatemia, and severe clinical symptoms [30].

In the 1990s, ^{99m}Tc-MIBI single-photon emission computed tomography associated with computed tomography scintigraphy (SPECT/CT) was shown to be an effective and precise tool for localising hyperactive parathyroid glands [30, 31]. The use of this preoperative imaging approach in combination with intraoperative measurement of PTH has allowed for gradual reduction of surgical extent [32]. Currently, minimally invasive surgical techniques, endoscopic and videoscopic approaches are preferred. The advantages of minimally invasive surgery include a shorter hospital stay, lower costs, faster recovery and a better postoperative aesthetic outcome [33]. Accurate preoperative imaging is essential for choosing the optimal surgical strategy. Recent years have witnessed significant advances in diagnostic imaging, with increasingly precise and sensitive techniques for preoperative assessment of the parathyroid glands. Ultrasound combined with ^{99m}Tc-MIBI SPECT/CT scintigraphy is currently a preferred approach for localising pathological parathyroid tissue. These techniques are highly sensitive in cases when hyperparathyroidism arises from a single adenoma. However, their sensitivity decreases in the case of multiple or ectopic parathyroid pathologies. Positron emission tomography/computed tomography (PET/CT), four-dimensional computed tomography (4D-CT), and magnetic resonance imaging (MRI) are imaging techniques offering better localisation in some situations. [^{18}F]-fluorocholine PET/CT ([^{11}F]-FCH PET/CT) showed nearly 100% efficiency in imaging hyperfunctioning parathyroid glands [34]. In turn, a large study in 19 patients with tertiary hyperparathyroidism treated with renal replacement therapy showed high efficiency of [^{11}C]-methionine PET/CT ([^{11}C]-MET PET/CT)[35]. Due to their low invasiveness and high efficiency in imaging hyperactive parathyroid glands, PET/CT are leading diagnostic localisation tools. Selective venous sampling (SVS) to assess blood PTH levels is indicated in patients with persistent or neoplastic hyperparathyroidism, in whom imaging methods failed to locate the lesions. There is ongoing research investigating novel approaches, such as robotic surgery or intraoperative imaging techniques, which in the future may contribute to even greater improvement in the management of patients with parathyroid disease.

Our home centre also holds a place in the history of parathyroid glands, where several innovative procedures of selective embolization of parathyroid arter-

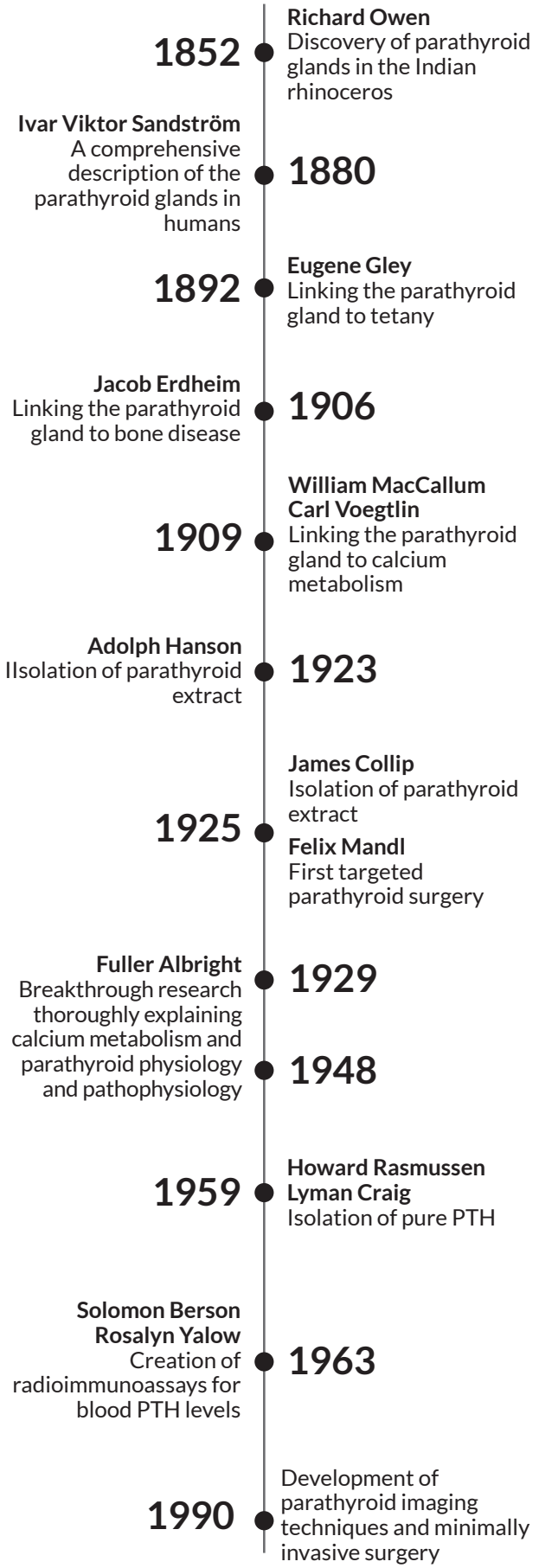

Figure 1. Timeline showing key events in the history of parathyroid research development

ies supplying parathyroid adenoma have recently been performed, with good clinical outcomes. Long-term outcomes and an assessment of the efficacy of this minimally invasive method are still awaited.

Conclusions

The endocrinology of the parathyroid glands developed slowly throughout the 19th and 20th centuries, creating a fascinating history that involved many prominent scientists (fig. 1). Owen, Sandström, Gley, MacCallum, Voegtlin, Erdheim, Hanson, Collip, Mandl, Albright, Craig, and Yalow are just a few of those who contributed to advances in the knowledge of the anatomy, physiology, biochemistry, and surgery of the parathyroid glands. Their groundbreaking discoveries shaped our modern understanding of these glands and contributed to the development of effective diagnostic and therapeutic approaches for the management of disorders arising from their dysfunction.

References

1. Cave AJE. Richard Owen and the discovery of the parathyroid glands. In: Underwood EA, ed. Science, medicine and history, essays of the evolution of scientific thought and medical practice, written in honour of Charles Singer. London, Oxford University Press, 1953: 217–222
2. Owen R. On the anatomy of the Indian Rhinoceros (*Rh. unicornis*, L.). Trans Zool Soc Lond, 1852; 4: 31–58
3. Breimer L, Sourander P. The discovery of the parathyroid glands in 1880: triumph and tragedy for Ivar Sandström. Bull Hist Med, 1981; 5: 558–563
4. Sandström IV. Om en ny körtel hos menniskan och åtskilliga däggdjur. Ups Läk Förh, 1880; 15: 441–471
5. Gley E. Sur les fonctions du corps thyroide. CR Soc Biol (Paris), 1891; 43: 841–847
6. Halsted WS. The operative story of goiter. The author's observations. The Johns Hopkins Hospital Report, 1920; 19: 71–257
7. Vassale G, Generali F. Sugli effetti delle stirpazione delle ghiandole paratirodee. Riv Patol Nerv Ment, 1896; 1: 249–252
8. Maccallum WG, Voegtlin C. On the relation of tetany to the parathyroid glands and to calcium metabolism. J Exp Med, 1909; 11: 118–151
9. von Recklinghausen FD. Die fibrose oder deformative ostitis, die osteomalacie und die osteoplastische karzinose in ihren ge-genseitigen beziehungen. In: Festschrift für Rudolph Virchow. Berlin, Riemer, 1891: 1–89
10. Erdheim J. Tetania parathyreopriva. Mitt Grenzgeb Med Chir, 1906; 16: 632–744
11. Erdheim J. Über Epithelkörperbefunde bei Osteomalacie. Sitzungsber d kais Akad d Wissensch in Wien, math naturw. Klasse Abt. III, 1907; 116: 311–370
12. Vermeulen AHM. The birth of endocrine pathology. How Erdheim misunderstood parathyroids. Virchows Arch, 2010; 457: 283–290. doi: 10.1007/s00428-010-0953-1
13. Halsted WS. Hypoparathyreosis, status parathyreoprivus, and transplantation of the parathyroid glands. Am J Med Sci, 1907; 134: 1–12
14. Li A. J. B. Collip, A. M. Hanson and the isolation of the parathyroid hormone, or endocrines and enterprise. J Hist Med Allied Sci, 1992; 47: 405–438. doi: 10.1093/jhmas/47.4.405

15. Hanson AM. The standardization of parathyroid activity. JAMA, 1928; 90: 747–748
16. Collip JB. The extraction of a parathyroid hormone which will prevent or control parathyroid tetany and which regulates the level of blood calcium. J Biol Chem, 1925; 63: 395–438
17. Mandl F. Therapeutischer versuch bein einem falls von otitis fibrosa generalisata mittles. Exstirpation eines epithelkorperchentumors. Wien Klin Wochenschr Zentral, 1926; 53: 260–264
18. Niederle BE, Schmidt G, Organ CH, et al. Albert J and his surgeon: a historical reevaluation of the first parathyroidectomy. J Am Coll Surg, 2006; 202: 181–190. doi: 10.1016/j.jamcollsurg.2005.03.036
19. Bauer W, Albright F, Aub JC. A case of osteitis fibrosa cystica (osteomalacia?) with evidence of hyperactivity of the para-thyroid bodies. Metabolic Study II. J Clin Invest, 1930; 8: 229–248. doi: 10.1172/JCI100262
20. Spence HM. The life and death of captain Charles Martell and kidney stone disease. J Urol, 1984; 132: 1204–1207. doi: 10.1016/s0022-5347(17)50098-1
21. Albright F, Aub JC, Bauer W. Hyperparathyroidism – a common and polymorphic condition, as illustrated by seventeen proved cases from one clinic. J Am Med Assoc, 1934; 102: 1276–1287
22. Cope O. The story of hyperparathyroidism at the Massachusetts General Hospital. N Engl J Med, 1966; 274: 1174–1182. doi: 10.1056/NEJM196605262742105
23. Albright F. A page out of the history of hyperparathyroidism. J Clin Endocrinol Metab, 1948; 8: 637–657. doi: 10.1210/jcem-8-8-637
24. Albright F, Ellsworth R. Studies on the physiology of the parathyroid glands: I. Calcium and phosphorus studies on a case of idiopathic hypoparathyroidism. J Clin Invest, 1929; 7: 183–201. doi: 10.1172/JCI100224
25. Albright F, Bloomberg E, Castleman B, et al. Hyperparathyroidism due to diffuse hyperplasia of all parathyroid glands rather than adenoma of one. Arch Intern Med, 1934; 54: 314–329
26. Albright F, Reifenstein EC. The parathyroid glands and metabolic bone disease. Baltimore, Williams & Wilkins, 1948
27. Rasmussen H, Craig LC. The parathyroid polypeptides. Recent Progr Hormone Res, 1962; 18, 269–295
28. Berson SA, Yalow RS, Aurbach GD, Potts JT. Immunoassay of bovine and human parathyroid hormone. Proc Natl Acad Sci U S A, 1963; 49: 613–617. doi: 10.1073/pnas.49.5.613
29. Wermers RA, Khosla S, Atkinson EJ, et al. The rise and fall of primary hyperparathyroidism, a population-based study in Rochester, Minnesota, 1965–1992. Ann Intern Med, 1997; 126: 433–440. doi: 10.7326/0003-4819-126-6-199703150-00003
30. Wang Y, Ladie DE. Parathyroidectomy. In: StatPearls. Treasure Island (FL), StatPearls Publishing, 2024
31. Coakley AJ, Kettle AG, Wells CP, et al. 99Tcm sestamibi – a new agent for parathyroid imaging. Nucl Med Commun, 1989; 10: 791–794. doi: 10.1097/00006231-198911000-00003
32. Chen H, Sokoll LJ, Udelsman R. Outpatient minimally invasive parathyroidectomy: a combination of sestamibi-SPECT localization, cervical block anesthesia, and intraoperative parathyroid hormone assay. Surgery, 1999; 126: 1016–1022. doi: 10.1067/msy.2099.101433
33. Udelsman R, Lin Z, Donovan P. The superiority of minimally invasive parathyroidectomy based on 1650 consecutive patients with primary hyperparathyroidism. Ann Surg, 2011; 253: 585–591. doi: 10.1097/SLA.0b013e318208fed9
34. Mazurek A, Dziuk M, Witkowska-Patena E, et al. The utility of 18F-fluorocholine PET/CT in the imaging of parathyroid adenomas. Endokrynol Pol, 2022; 73: 43–48. doi: 10.5603/EP.a2021.0107
35. Kołodziej M, Saracyn M, Lubas A, et al. Usefulness of PET/CT with carbon-11-labeled methionine in the diagnosis of tertiary hyperparathyroidism. Nutrients, 2022; 15: 188. doi: 10.3390/nu15010188