MEDICINA NEI SECOLI ARTE E SCIENZA, 21/1 (2009) 387-401
Journal of History of Medicine

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PARATHYROID HISTORY AND THE UPPSALA ANATOMIST IVAR SANDSTRÖM

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SUMMARY

The parathyroid gland was first recognized in 1850 by Richard Owen during a dissection of an Indian rhinoceros at the London Zoo. The credit for the discovery of the parathyroid has, however, been given to the Uppsala anatomist Ivar Sandström, who was the first to demonstrate the gland in man. His dissection studies were undertaken between 1877 and 1880, when he still was a medical student in Uppsala. Sandström's detailed anatomical and histological studies of the parathyroid gland were published in a Swedish journal, "Upsala Läkareförenings förhandlingar", in 1880.
Ivar Sandström, the man behind the discovery of the parathyroid gland, often called the last anatomical discovery, was a disharmonious person with psychiatric problems and he committed suicide in 1889 at the age of 37 years.

Decades later Sandström's findings turned out to be of considerable physiological and clinical importance, when the glands were realized to be crucially involved in calcium regulation and calcium regulatory disorders. The association between a hyperfunctioning parathyroid gland and the bone disease "osteitis fibrosa cystica", Rechlinghausen's disease, was suggested in 1915. By that the idea of surgical intervention was planted and in 1925 the first parathyroidectomy was performed when Felix Mandl in Vienna removed a parathyroid tumor in a 38-year-old trolley conducter suffering from

Key words: Parathyroid history

a severe, crippling bone disease. In 1925 the parathyroid hormone was isolated by James Collip. During the years the clinical manifestations of hyperfunctioning glands, hyperparathyroidism, have changed and to-day parathyroidectomy has become a common operation in the treatment of this parathyroid disorder.

Introduction

The endocrine organs have been the object of surgical treatment throughout the years. Our knowledge about the parathyroid gland now covers slightly more than 150 years but the history of parathyroid surgery is younger. It started in Vienna in 1925 when the Austrian surgeon Felix Mandl undertook the first parathyroidectomy by removing a parathyroid tumor in a crippled man suffering from von Recklinghausen's disease[1]. Less than a decade after Mandl's report more than hundred cases of hyperparathyroidism – overproduction of hormone from the parathyroid gland - had been mentioned in the literature[2]. Since then parathyroid surgery has developed enormously and it nowadays has a central position in endocrine surgery. Throughout the world surgeons are dealing with an increasing number of individuals presenting with hyperparathyroidism.

The discovery of the parathyroid gland

The parathyroid gland was first recognized in 1850 by the English professor of comparative anatomy, Sir Richard Owen.
He made his discovery during a dissection of an Indian rhinoceros at the London Zoo. His observation was reported to the Zoological Society of London, but the paper was not published until 1862, when it appeared in the Transactions of the Society[3]. In his article Owen describes the parathyroid gland as

> *a small compact yellow glandular body attached to the thyroid gland at the point where the veins emerge.*

Owen had probably no prior knowledge of the presence of this organ and no microscopic examination was performed and he never mentioned such glands in other animals. Owen's anatomical finding passed unknown until 1905, when it was mentioned in a paper in the British Medical Journal.

The credit for the discovery of the parathyroid gland has generally been given to *the Uppsala anatomist Ivar Sandström*, who was the first to demonstrate the parathyroid in man. His dissection studies were undertaken between 1877 and 1880, when he still was a medical student, and included not less than 50 human autopsy cases. Sandström named the new structures "glandulae parathyroideae". His detailed anatomical and histological studies of the parathyroid gland, including both human and animal specimens, were published in a paper entitled "On a New Gland in Man and Several Animals". His original manuscript, comprising 30 pages, was first submitted to Rudolf Virshow, the greatest pathologist at the time, for publication in his journal, but he refused the article due to its length. Therefore Sandström's discovery, often called the last anatomical discovery, was published in a Swedish journal "*Upsala Läkareförenings förhandlingar*" in 1880[4].

In Sandström's paper a detailed macro- and microscopical description is presented. The various positions and forms of the glands are described and he mentions that the glands have a variable distribution between the two tissue components, the parenchymal and fat cells. Many of Sandström's epoch-making anatomical and histological observations are still of interest for modern pathology and surgery.

Ivar Sandström (1852-1889) - the discoverer

Ivar Sandström was born in Stockholm in 1852, that is in the very year that Richard Owen first announced his discovery. In 1872 he began medical studies at the University of Uppsala, where he became

medicine candidate in 1878. He worked as an assistant at the department of anatomy and during 1879-80 he was appointed " prosector" at the department. In 1881 he became extra teacher in histology and remained on this position until 1886, while he continued his medical studies. In 1886 he became licensed physician at Uppsala University.

He married in 1885 and had two children. The family was poor and Sandström had to split his time between his own medical studies, his research and the necessity of earning money for living. His wife was distressed by his hard work and the family's poor economy. After a few years she left him together with their two children.

Sandström suffered from a hereditary mental disease and he became early a disharmonious person with psychiatric and alcoholic problems. Sandström was disappointed with the reception of his scientific contribution and his own impression of the Scandinavian meeting of Natural Sciences in Stockholm in 1880 when he presented his discovery that is was regarded as "a big Scandinavian humbug"[4]. His disillusionment is reflected in a letter to his sister, dated August 8th 1880, where he writes:

> *... I accepted an invitation from Stockholm to attend an international meeting of the Natural Scientists in order that I might do my part so that we Swedes should not succumb to our guests - which later on proved not to be the case at all..... One should, of course, at a personal meeting of so many men who devote themselves to science, be inclined to expect less of a hurried reading of, more or less unimportant products of genius whose creators in any case would not forget to publish them if they are of any value, than rather a friendly exchange of thoughts and of trustful communication of personal experiences and impressions. Nothing of the kind was seen .... everyone seemed to be there with the intention of showing what "discoveries" he had made and at the same time give the astonished world the opportunity to have a look at the fortunate discoverer. But for the discovery itself, for the revealed truth, the interest was little or none.*

In time Sandström became more and more depressed and in 1886 he was treated for an acute psychosis at Ulleråker's Hospital in Uppsala. In 1889 he committed suicide at the age of 37 years. The day before his suicide he was sitting together with his brother's family saying "*it would have been nice to become a professor and get a name*"[5]. Sandström never became a professor but his discovery as a medical student of the parathyroid gland has given him a name to be remembered in the medical history and his scientific work has often been praised for its accuracy.

The parathyroid gland and calcium

At the time for his discovery Sandström had no idea of parathyroid function and about a possible physiological role of the parathyroids he says

> *from reasons that are quite apparent I am not able to allow myself even to make a guess.*

He, however, expressed some speculations on their chemical relevance by saying

> *for the purpose of diagnosing a tumor of the parathyroid gland, I want to point out the proximity of the glands to the esophagus and the recurrent nerve…*

In 1891 the French physiologist Eugéne Gley published the first report on a relationship between the parathyroid glands and tetany. Experimentally on dogs he found that thyroidectomy was followed by tetany and death only if the parathyroids also were removed[6]. Shortly thereafter two Italians, Giorlio Vassala and Francesco Generali, observed that tetany could be caused by parathyroidectomy alone. They suggested that tetany was caused by intoxication and that the parathyroids were the organs that removed the toxins

from the body. However, the parathyroid glands were now considered as vital organs to be managed with great care in thyroid surgery. The theory that tetany was caused by an intoxication persisted for many years. However, in 1924 it became clear through the work of William MacCollum, pathologist at Johns Hopkins Hospital, that this tetany was directly the result of calcium deficiency. About the same time it was proved that the hypocalcemic tetany could be treated with injections of crude parathyroid extract. Further research led to the isolation of the parathyroid hormone by the Canadian professor James Collip in 1925 and it became clear that the hormone was calcium-regulating[7].

The parathyroid gland and bone disease

In 1891 the German pathologist Friedrich van Rechlinghausen, in a Festschrift for Rudolf Virshow, described the typical parathyroid cystic bone disease, which was named "osteitis fibrosa cystica"[8]. However, the association between this bone disorder and the parathyroid disease was established first in 1904, when Max Askanazy of Tubingen, Germany described a patient with bone changes and a parathyroid tumor[9]. The next important contribution in this field was given by the Viennese pathologist Jakob Erdheim. In 1907 he reported that patients dying of severe skeletal disease frequently exhibited hyperplastic parathyroid glands[10]. At first, the enlargement of the parathyroids that accompanied the bone changes was interpreted as a compensatory phenomenon and consequently the skeletal disease was treated with parathyroid extract. In 1915 Friedrich Schlaugenhaufer questioned the validity of this interpretation. He had observed that mostly only one of the four glands was enlarged, and proposed therefore that the changes in the parathyroid glands were the primary event leading to the skeletal disease[11]. The idea of surgical intervention was thus planted.

The first parathyroidectomy

The first parathyroidectomy was performed by Felix Mandl in Vienna in 1925. Mandl's patient Albert Jahne was a 38-year-old trolley conductor suffering from a severe, crippling bone disease. The year before he had fractured his femur and his blood calcium level was very high. His disorder was recognized as a generalized osteitis fibrosa. Mandl thought that the disease was due to a parathyroid deficiency. Therefore the patient was first treated by parathyroid extract and grafted fresh parathyroid tissue but this made his condition worse. As the patient seemed likely to die Mandl decided to explore Albert Jahne's neck. On July 30 in 1925 the operation was carried out under local anesthesia. A parathyroid tumor, measuring 21x12x12 mm, was removed. The three remaining glands were considered normal. The result of this operation was dramatic and Mandl had for the first time shown that Schlagenhaufer's hypothesis was correct, namely that the bone disease was secondary to the parathyroid disease.

Another well-known patient in the "parathyroid history" is Captain Charles Martel, who was treated at the Mayo Clinic[12]. Like Jahne he had a severe bone disease in association with high blood calcium. Without any knowledge of Mandl's work one postulated that Martel's disorder was due to a primary overproduction of the parathyroid glands. In May 1926 the patients neck was explored by Edward Richardson but he failed to find a tumor. After a total of six operations the surgeons Edward Churchill and Oliver Cope found at the seventh exploration a mediastinal parathyroid tumor (30x30 mm) which was successfully removed in 1932[13]. As the normal glands had been extirpated at the previous explorations, a remnant of the adenoma was transplanted in muscular tissue. In spite of this the patient developed tetany on the third day postoperatively. Administration of calcium and parathyroid hormone cured him from the postoperative hypocalcemia but he died six weeks after operation in renal complications.

News of Mandl's operation soon spread and in 1931 about twenty more operations had been undertaken in Europe and USA. Around 1950 several surgeons had gained experience of parathyroid surgery and in 1960:s the series of operated patients for hyperparathyroidism had increased. Already in 1960:s also routine biochemical screening, including serum calcium determination, began to be introduced and since than hyperparathyroidism has been more frequently diagnosed.

Clinical manifestations of hyperparathyreoidism during the years

During the decades after the first parathyroidectomies primary hyperparathyroidism was searched for only on patients suffering from severe bone deseases. Around 1950 particularly the American endocrinologist Fuller Albright suggested that hypercalcemic patients could be presenting symptoms only in form of renal stones. More knowledges on the relationship between renal stones and hyperparathyroidism was also developed by the Swedish surgeon John Hellström, professor at the Karolinska Hospital in Stockholm.

The clinical manifestations of hyperparathyroidism have changed during the years. Since two-three decades a majority of patients are found to have psychiatric or neuromuscular symptoms. Many patients are diagnosed *en passant* and the proportion of the so-called asymptomatic group was reported already in 1980 to be 50-60%[14,15]. However, an important question has been to what degree these "asymptomatic" patients really are without symptoms. This issue was studied in an Uppsala-dissertation from 1988[16]. In this study it was found that among the so-called asymptomatic individuals 65-80% had psychiatric symptoms. These results - and similar from other authors - support a liberal attitude towards surgery.

Anatomy, histology and pathology

In Sandströms article from 1880 there is a detailed description on the number, anatomical location, gross appearance and microscopic

features of the parathyroid glands. In humans he found four glands, two on each side. About 10% had fewer than four glands - this may be due to that Sandström's dissection was incomplete in some of his 50 cases. Sandström mentions that the parathyroids were always found close to the thyroid, at the posterior surface of the lateral lobes or close to their inferior border. Frequently they were located along the thyroid inferior artery. The glands varied in size and form, which is expressed as follows:

> *Sometimes the glands are only 3 mm in their largest dimension, in other cases they reach a length of up to 15 mm. The most usual size is apparently about 6 mm. Their form is generally more or less compressed and plate-like, sometimes so much so that the thickness is hardly 2 mm, while the width and length are of the usual dimensions or even larger. The superior gland has not infrequently a rather elongated form.*

Of interest is that Sandström noted a variable distribution between parenchymal and fat cells.

Somewhat more than fifty years after Sandström's publication John Gilmour, both alone and together with W. Martin, described the embryology, number, weight and histology of the parathyroid gland[17,18,19]. In a study of 527 individuals Gilmour found that 86% had four or more glands. The mean weight for an individual normal gland in men and women was 29.4 and 32.8 mg, respectively. The ratio of parenchymal tissue to interstitial tissue in a gland with an "average" structure was 70:30.

Gilmour found that there were two main types of parenchymal cells, namely chief and oxyphil cells, the former of two subtypes: transitional cells and water-clear cells.

In 1980, hundred years after Sandström's discovery of the parathyroid gland, another unique work was presented from Uppsala by Åkerström and his colleagues on the anatomy and histology of the parathyroids[20]. Through studies of autopsy material of 368 "normo-

calcemic" cases they found four glands in 96%. The mean individual weight of a "normal" gland was 31 mg; the maximum weight (upper 95% limit) was 59 mg. The parenchymal cell mass was calculated to be 22 mg (74%); the maximum weight (upper 95% limit) was 39 mg (88%).

From a surgical point of view Åkerström and his group found that a deviant shape constitutes a risk for extra numerous glands. The authors also made the observation that adenomas were present in 2.8% and hyperplasia in 7%; in other words parathyroid pathology was found in almost 10% (mean age 64 years) in this autopsy material.

During the early years of parathyroid surgery a *single* adenoma was the predominant pathological entity. This was the case in the first 100 patients of hyperparathyrioodism reported after Mandl's operation in 1925. In 1934 Albright and associates[21] reported three cases of a *multiple* glandular disease, in these cases in form of water clear cell hyperplasia. Primary chief cell hyperplasia was described first in 1958 by Cope et al. This form of pathology occurred in 10% of their first 200 cases of primary hyperparathyroidism[22].

Parathyroid cancer is an extremely rare cause of hyperparathyroidism. This is reflected in the limited number of cancer cases in the literature; up to now only slightly more than 200 cases seem to be reported. The first "malignant adenoma" was reported from the Mayo Clinic in 1929[23]; whether the parathyroid tumor removed by Felix Mandl in 1925 was a malignant one remains unresolved.

Fig. 1 - Ivar Sandström, 1852-1889, portrait

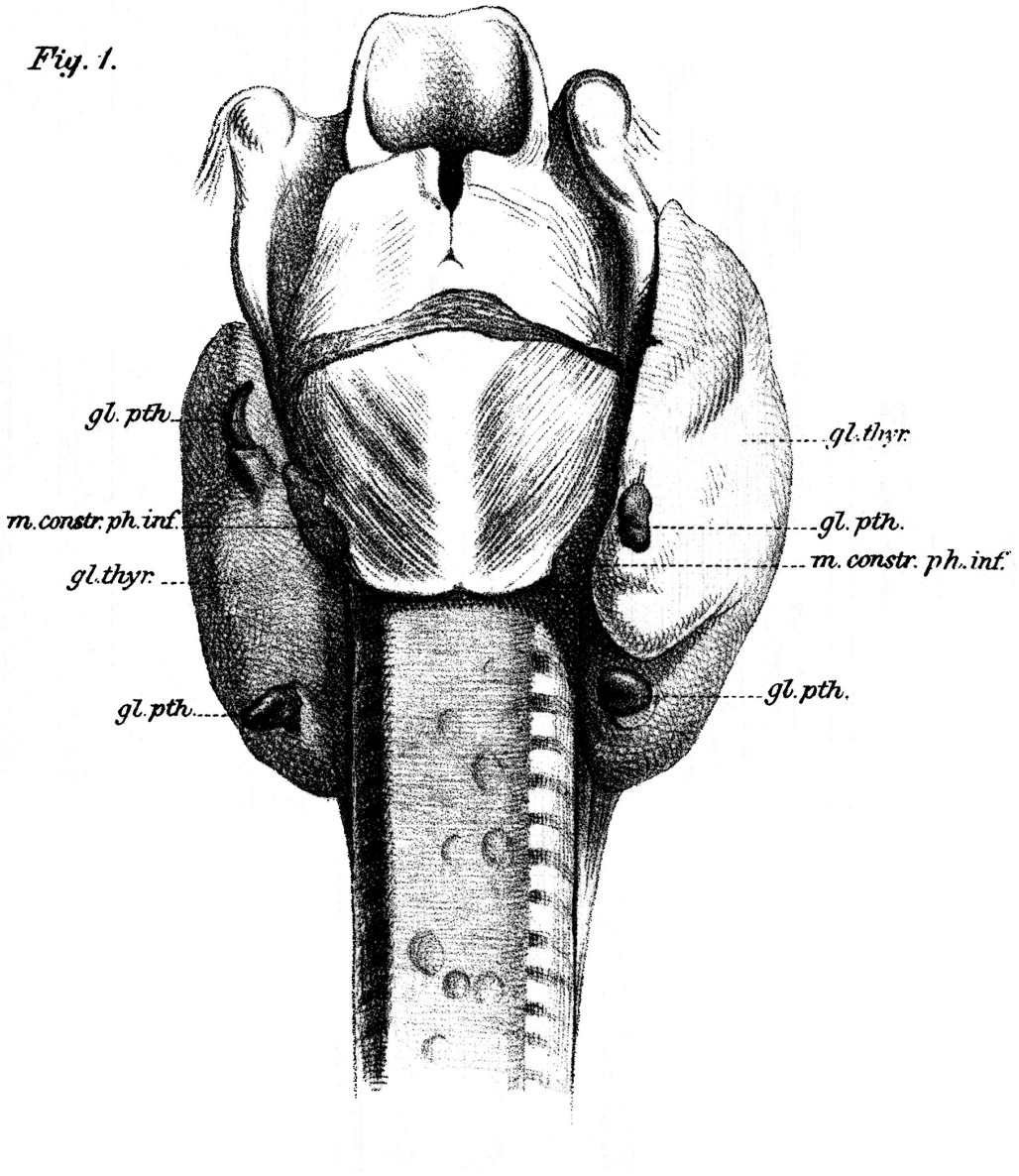

Fig. 2 - Drawing by Sandström of human parathyroid glandular anatomy

Fig. 3 - The building where Sandström discovered the parathyroid gland

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