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The Contemporary Development of Parathyroid Surgery —an Exposé from an Uppsalian Perspective

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"Only the man who is familiar with the art and science of the past is competent to aid in its progress in the future"
Theodor Billroth

The endocrine organs have been the object of surgical therapy throughout the years. However, only during the past few decades this discipline has established its own profile, and within this time span, endocrine surgery has developed explosively with respect to both surgical technique and basic research. Within the area of endocrine surgery, parathyroid surgery has taken a central position. Throughout the world, surgeons are confronted with an increasing number of individuals presenting with primary and secondary hyperparathyroidism (HPT). There is a long tradition of parathyroid surgery in Uppsala. Therefore, I believe it would be of interest to present some of the history of Swedish parathyroid surgery, with special reference to contributions from Uppsala. Such an account is justified in that the history of any subject persists as the foundation of our current knowledge and practice, and is a prerequisite for future development.

Although the parathyroid gland was first demonstrated macroscopically by the English professor of comparative anatomy, Richard Owen, during the dissection of an Indian rhinoceros at the London Zoo in 1850, the credit for discovery of the parathyroid gland has rightly been given to the Uppsala anatomist Ivar Sandström. He was the first to demonstrate the parathyroid glands in man. His detailed studies of the anatomy and histology of the parathyroid glands were carried out from 1877 to 1880, and included

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both human and animal specimens. His human studies encompassed no fewer than 50 individuals. Sandström's discovery of the parathyroid glands - the last anatomical discovery - is now world renowned, and his name has without doubt given Uppsala and its endocrinological research a luminosity. A less well known fact is that Sandström's original manuscript, comprising 30 pages, was initially submitted to Rudolf Virchov for publication in his journal. Virchov, who was the biggest pathologist at the time, as well as the "pope" of medicine, refused the article due to its length. Instead, Sandström's work was published in "Uppsala Läkareförenings förhandlingar" (Proceedings of the Uppsala Physicians Society) in 1880. At the time of his epoch-making discovery, Ivar Sandström had no understanding of the gland's function. In 1891, however, the French physiologist Eugene Gley described a relationship between the parathyroid glands and tetany. In 1924, it became clear through the work of William MacCollum that this tetany was the direct result of calcium deficiency. Almost simultaneously, reports came that tetany could be treated with parathyroid extract, and continued research led to the isolation of the parathyroid hormone by James B. Collip in 1925.

Clinically, it was observed that a relationship seemed to exist between the parathyroid gland and bone disease, especially cystic bone changes (Recklinghausen's disease). At first, the enlargement of the parathyroid glands that accompanied the skeletal symptoms was interpreted as a compensatory phenomenon. In these circumstances it is understandable that the bone disease was treated with parathyroid extract. Freidrich Schlaugenhaufer therefore met with a great deal of surprise when he, in 1915, questioned the validity of this interpretation. He had observed that most often 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. The idea of surgical intervention was thus planted. In 1925, Felix Mandl in Vienna performed the first parathyroidectomy when he removed a tumour, an adenoma measuring 21 x 15 x 12 mm, from the trolley conductor Albert J., who suffered from a debilitating bone disease. The results of the operation were dramatic - a new surgical era was born.

During the decades following Mandl's parathyroidectomy, many surgeons entered the field. In our country, John Hellström, professor at the Karolinska hospital, Stockholm, was the great pioneer of parathyroid surgery. During his years as a surgeon, he presented no fewer than 138 patients whom he treated surgically for HPT. The first operation was performed in 1930, however, few patients were treated prior to 1950, after which there was a marked increase. In his studies, Hellström mainly developed new insights into the relationship between renal stones and HPT, a connection first observed and reported by Fuller Albright in 1934. Hellström's enthusiasm for

parathyroid surgery is evident in his publications, and he summarises his experiences in the article he wrote as professor emeritus, entitled "Reminiscence: Observations on hyperparathyroidism", published in Rev. Surg. 1965. The article recounts detailed case reports, such as the improvement that the removal of an adenoma can bring about in nephrolithiasis. This type of description of his patients illustrates Hellström's basic ideology in clinical research, namely that "scientific endeavour is built to a great extent on clinical observations and experience, in which a meticulous review of patient information is of importance."

In his articles, Hellström underscores his belief that the only rational treatment for HPT is the removal of all hyperfunctioning parathyroid tissue. If there is a single adenoma in its normal position on the neck, surgical intervention is usually a simple matter. On the other hand, as Hellström points out, considerable difficulties may appear, and the causes of unsuccessful or inadequate exploration are many. Thus, almost 20% of his patients had been operated on in other hospitals, and came to him for reoperation. Multiple adenomas were overlooked in some cases, inadequate resection of primary hyperplasia in other cases. However, in most cases the neck dissection was incomplete and Hellström emphasised that parathyroid surgery should be carried out "in hospitals where the services of surgeons and pathologists experienced in this branch are available."

In Uppsala, the first neck exploration for the parathyroid glands was performed in 1941 on a woman carrying the diagnosis "Rachitis tarda". Only a normal-sized parathyroid gland was demonstrated, and the patient was discharged unimproved. The first extirpation of an adenoma, i.e. the first time a pathological finding was demonstrated, was performed in 1946. The operation was done on a 37 year old woman with multiple spontaneous fractures. This woman had already undergone neck exploration the previous year. One parathyroid gland was then removed, but her condition remained unchanged. However, a marked improvement was observed following oestrogen (stilbol) treatment. At reoperation (which was performed by the same surgeon, Olle Hultén, professor in Uppsala 1942-64) a kidney bean-sized adenoma was found in the mediastinum, following sternotomy. The outcome was dramatic, and, as is recounted in the patient record, the patient died of tetany despite intravenous infusion of calcium and parathormone. At autopsy, no additional parathyroid gland was found. The first compilation of HPT data from Uppsala was done by Lars Thorén and Ivar Werner, and was published in Acta Chir Scand 1969. Altogether 85 patients were included in the study, all of whom had undergone surgery between 1958 and 1967. Only three years later, a new compilation was done by Johansson, Thorén, and Werner. This study was published in "Upsala Journal of Medical Sciences", and was based on no fewer than

208 patients (including the 85 from the previous publication). At that time point, this was a sizeable body of information, and also bears witness to the rapid development of parathyroid surgery that took place in Uppsala, especially from the mid 1960s onward. Nephrolithiasis dominated the symptomatology, but particularly interesting was the prominent role that non-specific symptoms such as tiredness, muscle weakness, and mental disturbances played. This may be interpreted as an expression of the active, even enthusiastic, investigation that was pursued. This active examination was also reflected by the serum calcium levels, which were to a great extent only moderately increased, indicating that HPT was caught at an early stage. Another expression of the early diagnosis is that, comparing data from 1958-67 and 1968-71, the number of hyperplasias increased dramatically, from 7% to 26%, in that hyperplasia is assumed to represent the primary lesion, while adenoma represents a later stage of development in the pathological process. The results of surgery vis-à-vis serum calcium were good, but there was a post-operative mortality rate of 2%. However, the mortality was only related to patients in crisis, and to the period of 1958-67. Subsequently, the grave and complicated state of hypercalcemic crisis, or pernicious HPT - a name which better describes the development of the disease - could be more adequately controlled.

In the early 1970s, pernicious HPT and its clinical management were described from Uppsala. The material included 14 individuals, an unusually large group at the time, since the literature only presented series of solitary patients. In contrast to earlier cases described, the Uppsala series was made up solely of elderly persons, all over 60 years of age. This may be seen as an indicator that the clinical picture developed by these patients as a result of hypercalcemia is easily misunderstood among older individuals, if serum calcium measurements are not routinely performed - which was rare at that time. The mortality (8/14) was high, in accordance with contemporary reports, despite the precise correction of electrolyte imbalances, e.g. hypokalemia and hypomagnesemia, which accompanied the disease. Of particular interest in this series, approximately half of the patients had previously been considered asymptomatic. Therefore, the article questions the term "asymptomatic HPT" which was expressed as follows: "We would like to suggest that the diagnosis 'asymptomatic HPT' be used with greatest restriction." Additionally, in the early 1970s, a couple of reports on so-called normo-calcemic HPT emerged. Simultaneously, in Uppsala, it was observed that persons with a history of massive nephrolithiasis not uncommonly showed borderline serum calcium levels. Since additional biochemical data inferred an underlying disturbance of parathyroid function, such individuals were explored, and in 1973, these experiences of normocalcemic HPT were reported. The study included 32 patients with predominantly positive results. Two years later (1975), a publication was released from Uppsala that described a unique group of 84 patients with normocalcemic HPT. The histological

investigation demonstrated that there were pathological changes in 70% of the parathyroid glands: adenoma in nearly 25% and hyperplasia in 45%. In essence, the postoperative results showed that serum calcium decreased in a similar manner in all groups - one patient developed a mild hypocalcemia. The incidence of renal stones was reduced in the adenoma group by 100%, and in the hyperplasia group by 75% (average follow up time of 5 and 3 years, respectively). It must, however, be noted that most of the patients with a favourable outcome had solitary, marginally increased, serum calcium levels (peak values), but some were strictly normocalcemic. To what extent the hyperplasia was secondary to an idiopathic hypercalciuria was difficult to determine.

In 1980, 100 years after Sandström's discovery of the parathyroid gland, Åkerström and his colleagues presented their unique work on the anatomy and histology of the parathyroid glands. Through studies of autopsy material encompassing 450 cases, a detailed description was given of the normal variation of position, weight, shape, and composition with respect to fat and parenchymal mass, as well as of the fact that deviant shape constitutes a risk factor for extranumerous glands. These studies form the foundation for the surgical strategy applied in parathyroid surgery, particularly at reoperation. Åkerström made the unexpected observation that parathyroid adenoma was present in 2.8% of the subjects, and hyperplasia in 7%. In other words, nearly 10% demonstrated parathyroid pathology (mean age 64 years). Later, screening studies performed by Uppsala researchers showed that an estimated 1% of the population has HPT. Prevalence was higher with increasing age, and among women over 70 years was as high as 3%. In a study performed in the early 80's involving a gerio-psychiatric patient group, Ljunghall et al demonstrated hypercalcemia among 10%, and at least 6% were found to have underlying HPT. These studies from Uppsala convinced us that primary HPT represented a new national disease. During the mid 1980s, a lively debate was waged as to whether it was justified to surgically treat individuals with asymptomatic HPT. At the Mayo Clinic, Rochester, USA, a prospective study involving 150 patients was started in the late 1960s, in order to elucidate the natural course of untreated HPT. The intention was to evaluate the need for surgery after 10 years, but the study was inconclusive due to a high drop out rate. Several research groups in Uppsala have, however, through various investigations, made substantial contributions to our knowledge of the natural course of this disease. From the starting point of a health examination carried out in Gävle 1969-71, 170 patients were identified as having mild-moderate hypercalcemia from HPT. These persons were followed up for 14 years, and compared with age- and gender-matched controls derived from the same population. The study revealed that the hypercalcemic group had an increased mortality rate, due to a subgroup of patients under 70 years. The mortality was due to cardiovascular disease in most cases. Subsequent studies from Uppsala demonstrated

that the increased mortality associated with hypercalcemia could be reduced by successful surgery. Similar results have been demonstrated in excellent studies from Gothenburg and Helsinki.

An important question to answer is to what degree so-called asymptomatic HPT patients were truly without symptoms. This issue was elucidated in Charlotte Joborn's dissertation from 1988. With the use of a special psychological test model, she showed that 65-80% had psychiatric disorders of various types, although at the time of diagnosis many of the individuals considered themselves completely fit. The most common symptoms were fatigue, lack of initiative, lack of concentration, and memory disturbances. The symptomatology was thereby depressive in character. According to the test system, the HPT patients had a mean score of 17 before surgery, while post-operative scores averaged 4. The patients treated surgically demonstrated scores comparable to those of age-matched controls, who had a mean score of 4 and individual values all under 10.

Altogether, the studies from Uppsala have provided results which support a liberal attitude towards surgical treatment of HPT. This attitude has even been applied to elderly individuals with HPT, since experience has shown that they often improve dramatically. The same point of view should also be valid for reoperation - it should be performed on broad indications, given that the gain expected can be balanced against the risk of complications at an acceptable level.

Recently, new perspectives on primary HPT have been put forward. The patho-anatomical diagnosis has been based traditionally on two main alternatives, adenoma or hyperplasia. However, the extent to which this delineation can be made is questionable. In primary HPT, several glands are often involved, even if the disease appears to be caused by a single adenoma. This was demonstrated in Hans Johansson's doctoral thesis from 1988; using a microfluorometric technique, he showed that, in "adenomatous" HPT, even the associated glands presented a defect in intracellular calcium regulation. Modern studies also indicate that the pathogenesis of HPT lies in factors that exert a general attack on the parathyroid glands. It was already known - through the work of Lars Erik Tisell, among others - that ionising radiation is a risk factor for HPT. Investigations performed recently in Uppsala point to the possible involvement of immunological derangements or viral attack in the development of HPT. How these factors may affect the calcium-dependent regulation of the secretion of parathyroid hormone, which is now the subject of efforts by investigators in Uppsala, remains to be seen. It will be exciting to follow this area of research, although I suspect that it will lead to a greater role for medical rather than surgical treatment of HPT.