Історія медицини

History of medicine

ISSN: 2411-6181(on-line); ISSN: 2311-9896 (print)
Current issues of social studies and history of medicine. Joint Ukrainian -Romanian scientific journal, 2020, N:4(28), P. 88-91
***UDK** 612. 014. 54*
***DOI** 10.24061/2411-6181.4.2020.227*

ПРИЩИТОПОДІБНІ ЗАЛОЗИ — ІСТОРИЧНИЙ НАРИС

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PARATHYROID GLANDS - HISTORICAL ESSAY

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Инга Тимофийчук, Светлана Семененко, Иванна Тимофийчук, Наталья Семененко, Василий Семененко. Околощитовидные железы — исторический очерк. Роль прищитовидных желез в регуляции функций организма известна и неоспорима. Но изучение функций околощитовидных желез и их роли в развитии патологических процессов происходило через множество ошибок, непониманий и даже сломанных судеб. **Цель** данной статьи – осветить наиболее значимые события в истории изучения прищитовидных желез, которые послужили стимулом в улучшении лечения патологических состояний, в том числе хирургических. **Актуальность** исследования обусловлена необходимостью создания обоснованного понимания изучения истории прищитовидной железы. **Методология** работы основана на анализе историографических публикаций. **Основная часть.** Изучение роли фосфорно-кальциевого обмена и роли околощитовидных желез в этом обмене происходило в период XIX начало XX в. Исследования проведенные Иваром Сандстремом, который по праву считается открывателем данной железы, около столетия пролежали незамеченными научным миром. Достижения в анатомии, физиологии, медицине, хирургии и биохимии внесли свой вклад в развитие эффективных методов диагностики и лечения, которые используются и сегодня. Усовершенствование гистологических методов исследования стали новой вехой в исследовании структуры околощитовидных желез. В настоящее время изучение спектра органных нарушений при поражениях околощитовидных желез и разработка диагностических и лечебных методик не ограничиваются участием только сообщества эндокринологов, но и притягивают все большее внимание смежных специалистов. **Выводы.** В обзоре статьи представлена история открытия околощитовидных желез, освещены основные этапы изучения их роли в кальций-фосфорном обмене, проанализированы работы, посвященные эволюции в представлениях об их анатомических, физиологических и патологических особенностях.

Ключевые слова*: околощитовидные железы, фосфорно-кальциевый обмен, Ивар Сандстрем, паратгормон.*

Introduction. Fundamental discoveries in medicine in the 19th century, new approaches to diagnostics and treatment increased interest in the study of endocrinology. In 1805 year Georges Cuvier described the structure of the adrenal gland[1]. In 1822 year, Jean-Louis Marc Alibert described acromegaly[2], in 1838 year, Martin Heinrich Rathke described the structure of what is now called Rathke's pocket cysts[3], and in 1860 year Hubert von Luschka the portal system of the pituitary gland. Research on reproductive endocrinology was developed. The idea of artificial insemination of humans was first proposed by John Hunter. In 1824 year Jean Louis Prévost and Jean Baptiste Dumas described the ovulation process, and in 1826 year Karl Ernst von Baer discovered the mammalian ovum.

Despite the fact that the parathyroid glands are among the last open important human organs, the history of the discovery of this structure calculated in centuries. Clinical manifestations of parathyroid insufficiency glands were known long before their discovery.

Thus, the parathyroid glands are the last of the open vital endocrine organs in humans, despite the fact that the clinical manifestations of their pathological conditions were described long before realizing the causal relationship of symptoms with their activity. J. DuBose and others researchers note the presence of such descriptions in the treatises of researchers from the times of antiquity, in particular, in ancient Egyptian manuscripts.

So, in the bones of the ancient Egyptians and North American Indians, dating back to the 11th and 7th centuries BC, which were discovered during archaeological excavations, they already found changes characteristic of such a widely known disease as fibrocystic osteitis, or Recklinghausen's disease[4].

Other pathological changes in bones, which can also be interpreted in the framework of complications of primary hyperparathyroidism, have been found since 1705, and since the 19th century. clinical observations are becoming more frequent[5].

[1] Medvei VC. *A history of endocrinology*, London, 1982, 820 p. [in English].
[2] Cook M, Molto E, Anderson C. "Possible case of hyperparathyroidism in a Roman period skeleton from the Dakhleh Oasis, Egypt, diagnosed using bone histomorphometry", *Am J Phys Anthropol*, 1988, N 1, P. 23–30 [in English].
[3] Kalra S, Baruah MP, Sahay R, Sawhney K. "The history of parathyroid endocrinology", *Indian J Endocrinol Metab,* 2013, N 2, P. 320–322 [in English].
[4] Mokryshev N.G., Krupinova Yu.A. "Istoriya otkrytiya okoloshchitovidnyh zhelez, i ih rol' v organizme" [The history of the discovery of the parathyroid glands, and their role in the body], Vestnik RAMN [AMS Bulletin], 2019, N 1, P. 35–43 [in Russian].
[5] Kalra S., Manash P., Sahey R. "The history of parathyroid endocrinology", *Indian J. Endocrinol*, 2013, N 17, P. 320–322 [in English].

Formulation of the problem. Despite the accumulated clinical experience, the role of the parathyroid glands in the body was unclear until the end of the 19th century. Looking back at the theories of scientists of that time, it is safe to say that many of them significantly slowed down the discovery of the physiology of calcium metabolism.

The purpose of this article is to highlight the most significant events in the history of the study of the thyroid gland, which were a powerful impetus in improving the treatment of pathological conditions, including surgery.

The relevance of the study is due to the need to create a sound understanding of the study of the history of knowledge about the protection of similar glands. The **methodology of work** is based on the analysis of historiographical publications.

Presenting main material. The existence of the parathyroid glands in the human body was first noted in 1855 year in the works of R. Remak and in 1863 year by P. Virkhov. The description of the parathyroid glands of R. Owen (1852), who, upon dissection of the Indian rhinoceros, found a yellow, compact glandular organ attached to the thyroid gland in the region of the lateral surface of the superior pole. Despite the description of R. Owen, the discovery and name of the parathyroid glands is attributed to the Swedish scientist I. Sandström. In 1880 year, he discovered small masses in the area of the thyroid gland in a dog, rabbit, cat, bull and horse. The scientist made a detailed anatomical description of the structures found, and from that moment this organ was called the "parathyroid gland". The first attempt to detect the parathyroid glands in humans was crowned with success, and in the last 50 corpses, the size, typical location and its variants, as well as the blood supply of the glands, were described in detail[6].

From other sources, the primacy of the discovery of the thyroid glands began with the work of the aristocrat Richard Owen, one of the foremost scientists in England at the time. At 23, while serving as curator of the Natural History Museum of the Royal College of Surgeons of England, Owen accepted an offer from the London Zoo to examine the body of an Indian rhinoceros that had died in November 1849 year. So, after sectional studies of the body, which continued throughout the winter of 1849–1850 years, Richard Owen discovered a gland weighing 8 g and described it as "a small compact yellow glandular body in the neck of a rhinoceros, adjacent to the thyroid gland."

The first discovered parathyroid gland is still kept in the collection of the Royal College of Surgeons in London, along with a picture of a rhinoceros in whose body it was found. It is no coincidence that the symbolic rhino is now the sign of the Association of Endocrine Surgeons of France, which holds the scalpel and parathyroid adenoma.

Despite the accumulated knowledge, clinicians did not attach much importance to the data obtained.

In 1852 year, the year of Owen's presentation of the glands, Ivar Viktor Sandström was born in Sweden (Stockholm), who made a great contribution to the history of the study of this organ.

The young man early showed good research abilities in histology, a penchant for teaching. The histological preparations he made were of very high quality and were widely used for teaching students. The opening of the thyroid glands was made by Sandstrom when he was a 25-year-old student in the summer of 1877 year Faculty of Medicine passed practice as an assistant to Professor E. Klason. While dissecting a dog's neck, he first discovered "new glands." Three years later, in the spring of 1880 year, in his work "On new glands in humans and some animals", which has become a classic, he described how it was. "About three years ago, I accidentally discovered on the thyroid gland of a dog a small, the size of a hemp seed, which was in the same capsule with the gland, but had a brighter color[7]."

The scientist returned to similar studies in late 1879 year- early 1880 year By that time he had already taken (since 1878) a more serious position of dissector at the Department of Anatomy. Studies have been carried out on bulls, horses. And in all cases, the previously described parathyroid glands were located on the posterior surface of the thyroid gland. Encouraged by the result, the scientist suggested the presence of similar structures in humans, although he conducted research with a certain degree of skepticism. However, studies performed on 50 human corpses confirmed the hypothesis. Histological studies, which by that time had improved somewhat, showed that the gland has its own histological structure. The histological examination showed that this organ is completely different from the thyroid tissue." Despite the lack of great interest of the scientific community in its discovery, in 1880 year Sandstrom was invited to Stockholm for a meeting of the Scandinavian Society of Natural Sciences. During in his speeches, he described the size, shape, color, blood supply and histology of the normal parathyroid gland, but was disappointed with the reaction to his discovery, calling the meeting "a great Scandinavian hoax." Over time, Sandstrom became more and more depressed and suffering from frequent bouts of depression and other psychiatric problems, on June 2, 1889 year, at the age of 37, he committed suicide. Now it is rightfully believed that it was he who discovered the last of the known human organs, giving the gland the first detailed description, as well as the term "parathyroid glands"[8]. Finally, he suggested that the parathyroid glands can be a source of tumor growth[9].

In 1880 year, his work was still published, but in the less prestigious Swedish magazine "Upsala Läkareförenings Förhandlingar", and for several years went unreported. In the article, Sandstrom writes: “Nearly three years ago, I discovered a small organ on a dog's thyroid gland, barely larger than a hemp seed. He was enclosed in the same connecting tissue as the thyroid gland, but differed from it in a lighter color. The histological examination showed that this organ is completely different from the thyroid tissue "

But here fate turned out to be unkind to the young author. R. Virkhov observed the parathyroid glands as early as 1863 year and did not attach importance to his discovery.

He obviously did not really want to give the palm in

[6] Barbier J. , Henry J-F. *Primary hyperparathyroidism,* Paris: Springer-Verlag, 1992, 156 p. [in English].

[7] Rybkov S.I. “Viktor Sandström — velikoe otkrytie i tragicheskaya sud'ba” [Viktor Sandström – great discovery and tragic fate], *Endokrinologiya* [Endocrinology], 2016, N 2I, P. 177–182 [in Russian].

[8] VanHeerden J., Grant C. “Surgical treatment of primary hyperparathyroidism: an institutional perspective”, *World. J. Surg*., 1991, N 15, P. 688–692 [in English].

[9] Bilezikian J., Potts J., Fuleihan G-H. “Summery statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for 21-st century”, *J.Clin. Endocr. Metab*., 2002, N 87, P. 5353–5361 [in English].

the discovery of a new organ to an unknown young Swedish researcher. Thus, "the last great discovery in anatomy", as contemporaries defined, was threatened with oblivion even before his birth[10].

Another 10 years passed before scientists became interested in the epoch-making discovery of a humble Swedish student. The outstanding French physiologist E. Gley, in a series of brilliantly performed experiments, proved the vital role of the parathyroid glands in the body. In the meantime, the attitude towards this outstanding achievement remained more than restrained.

A year after the message of I. Sandström, in 1881 year, the English histologist E. Beiber also identified the parathyroid glands and described their microscopic structure. Like I. Sandström, whose work he was not aware of, he believed that the discovered formations represent "An undeveloped part of the thyroid gland, but subsequently they do not differentiate into thyroid tissue." Although he reported on his find at a meeting of the Royal Society, the results of the research remained unknown until 1966 year[11].

In 1855 year R. Remak, while studying the thymus in kittens, reported that he had found "... in the area of its upper pole, a small yellow gland, which in its the structure did not correspond to either the thymus, or the lymph node, or the thyroid gland. " R. Virkhov in 1863 year in the area of the upper edge of the isthmus and the posterior surface of the lobes of the thyroid gland in one case observed small, pea-sized rounded formations, which, according to his opinion, they were neither additional thyroid tissue, nor a lymph node or other known formations. Both researchers did not address this question anymore.

There is every reason to consider Ivar Viktor Sandstrom the author a great discovery in medicine - the discovery and description of the parathyroid glands. His name can rightfully be put on a par with the great researchers (Hippocrates, A. Vesalius, L. da Vinci, T. Warton), who discovered and described the thyroid gland, and B. Eustachius, who first discovered the adrenal glands Neither during his lifetime, nor for a certain time after his death, Sandstrom received due recognition. Many years passed before society realized the importance of the discovery of the parathyroid glands, their general biological role in the body, participation in physiological and pathological processes. 87 years later in Uppsala, on the building of the Faculty of Medicine of the University was a memorial plaque was installed. The literal inscription on it reads: "In memory of Ivar Sandstrom, 1852–1889 years, the discoverer of the parathyroid glands, 1887 year, the Faculty of Medicine installed this plaque, 1967 year". By the way, the marble slab was taken from an anatomical table, on which I. Sandström, possibly performed his dissections.

Although the anatomy of the thyroid glands was already good enough described, their physiology remained unclear for a long time. At the same time, descriptions of the clinical manifestations of hypoparathyroidism were already encountered quite often. So, by John Clark in 1815 year tetany was described in children, by George Kelly tetany in 1816 year- spasm of the glottis. The symptoms of Trousseau and Chvostek, which are well known to modern medical students, are described Armand Trousseau in 1861 year and Frantisek Chvostek in 1876 year[12].

The death of patients after thyroidectomy was explained by a mystical manifestation. Anton Wolfer in 1880 was the first to describe a patient with a tetanus attack in a patient after thyroidectomy performed by Theodore Billroth thyroid gland. This assumption was the impetus for the birth of the theory of detoxification, which implied that the cause of seizures is an excess of toxins that cannot be removed from the bloodstream if the thyroid gland is removed. The first to suggest the development of seizures with the absence of the thyroid glands, became Eugene Gley, professor of physiology at the University of Paris. Gley learned about Sandstrom's discovery from the anatomy textbook Die Anatomie des Kaninchens, published in 1884 year Gley published the results of his work in 15 articles (from 1881 to 1897 years) and was one of the first to appreciate the importance of glands, recommending that surgeons avoid their damage during thyroidectomy[13].

In 1901 year, Julio Vassale and Francesco Generali made a discovery in Italy that demonstrated the value of the organ. It was experimentally shown that with an intact thyroid gland, the removal of the upper and lower thyroid glands leads to the death of animals due to the development of paralytic and convulsive symptoms, while scientists, like Gley, did not associate this with a lack of calcium. At the beginning of the XX century it became clear that the removal of the thyroid glands, as well as damage to their blood supply, leads to the development of tetany.

In 1901 year, the American professor of biology at the University of California, Jacob Loeb, carried out experiments with an isolated frog muscle placed in a saline solution. He observed her rhythmic contractions, which stopped after adding calcium to the solution. So it was concluded that this trace element prevents persistent spastic muscle contractions[14].

A close connection between the thyroid glands and calcium was noticed by the Viennese pathologist Jacob Erdheim in 1906 year. Since 1909 year, with the advent of the ability to determine the level of calcium in the blood, pathologist William McCallum and chemist Karl Vogtlin were able to establish a connection between the removal of the thyroid glands, calcium and the development of seizures. Experiments on dogs with removal of glands demonstrated the development of tetany in dogs, which was stopped by the administration of calcium[15]. Despite the compelling clinical data of McCallum and Vogtlin about the role of calcium in the development of tetany, many researchers continued to adhere to the theory of the detoxification function of the glands until the early 1920s. In 1912, an article by William Frederick Koch, "On the occurrence of methyl guanidine in the urine of parathyroidectomized animals," was published, in which an increased concentration of methylguanidine was considered the cause of tetany in animals due to parathyroidectomy. In

[10] Johnson H. "Parathyroid history and the Uppsala anatomist Ivar Sandström", *J. History Medicine,* 2009, N 21, P. 387–401 [in English].
[11] Johnson H. "The Uppsala anatomist Ivar Sandström and the parathyroid glands" *Ups. J. Med. Sci.,* 2015, N 2, P. 72–77 [in English].
[12] Ruda J., Hollenbeak C., Stack B. "A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003", *Otolaryngol. Head Neck Surg.,* 2005, N 132, P. 359–372 [in English].
[13] Romanchishen A.F. *Chirurgia shitovidnoy I parashitovidnoy gelez* [Surgery of thyroid and parathyroid glands], SPb, 2009, 647 p. [in Russian].
[14] Kafezis I. D., Diamantopoulos A. , Christakis I. "The history of the parathyroid glands", *Hormones*, 2011, N 10, P. 80–84 [in English].
[15] Mokrysheva N.G., Krupinova J.A., Voronkova I.A. "Okoloshchitovidnye zhelezy: normal'noe razvitie, anatomicheskoe i gistologicheskoe stroenie" [Parathyroid glands: the normal development, anatomy and histological structure], *Endokrinnaya hirurgiya* [Endocrine Surgery], 2018, N 4, P. 178–187 [in Russian].

1924 year, Edward Albert Sharpay-Schafer was of the opinion that the thyroid glands secrete a biologically active substance that is involved in protein metabolism, in particular in the metabolic processes of guanidine. McCallum argued "that the parathyroid glands control calcium in such a way that their removal leads to its sharp excretion from the body and deprives the tissue of this element. Thus, McCallum was the first to suggest that low calcium levels are the cause of postoperative tetany in the blood, and came closer to understanding the physiology and role of the thyroid glands, as well as the relationship with calcium-phosphorus metabolism.

In 1953 year L. Anderdal described 8 patients with a combination of pituitary adenoma, thyroid gland and islet cells of the pancreas. An important contribution to the study of parathyroid pathology was made by Professor of Columbia University P. Vermer, who in 1954 year described a patient with a combination of tumors of the thyroid glands, pituitary gland, pancreas and adrenal cortex and substantiated the dominant type of inheritance this symptom complex. These discoveries contributed to a deeper understanding of the pathogenesis of hereditary forms of hyperparathyroidism, which later influenced the tactics of surgical treatment[16].

The development of laboratory diagnostics has made it possible to achieve success in improving the diagnosis of pathology of the thyroid glands. Early 1970s breakthroughs in molecular biology culminated in the development of recombinant DNA technology, which made it possible to deduce a polypeptide sequence, which made it possible to decipher the sequence amino acids in the parathyroid hormone molecule and all its isoforms, clone his gene and the gene for his receptor, which served impetus for further research of calcium-phosphorus metabolism[17].

Conclusions. The study of the role of phosphorus-calcium metabolism and the role of the thyroid glands in this exchange proceeded very slowly, in the period of the 19th and early 20th centuries. The studies carried out by Ivar Sandstrom, who is rightfully considered the discoverer of this gland, have lain unnoticed by the scientific world for about a century. Advances in anatomy, physiology, medicine, surgery, and biochemistry have contributed to the development of effective diagnostic and therapeutic methods that are still used today. The improvement of histological research methods has become a new milestone in the study of the structure of the thyroid glands. Currently, the study of the spectrum of organ disorders in lesions of the thyroid glands and the development of diagnostic and therapeutic techniques are not limited to the participation of only the endocrinological community, but also attract more and more attention of related specialists.

Інга Тимофійчук, Світлана Семененко, Іванна Тимофійчук, Наталія Семененко, Василь Семененко. Прищитоподібні залози - історичний нарис. Роль прищитовидних залоз в регуляції функцій організму відома і незаперечна. Але вивчення функцій прищитовидних залоз і їх ролі в розвитку патологічних процесів відбувалося через безліч помилок, непорозумінь і навіть зламаних доль. **Мета** даної статті - висвітлити найбільш значущі події в історії вивчення прищитовидних залоз, які послужили стимулом у поліпшенні лікування патологічних станів, в тому числі хірургічних. **Актуальність** дослідження зумовлена необхідністю створення обгрунтованого розуміння вивчення історії прищитовидних железі. **Методологія** роботи заснована на аналізі історіографічних публікацій. **Основна частина**. Вивчення ролі фосфорно-кальцієвого обміну і ролі прищитовидних залоз в цьому обміні відбувалося в період XIX початок XX в. Дослідження проведені Іваром Сандстремом, який по праву вважається відкривачем цієї залози, близько століття пролежали непоміченими науковим світом. Досягнення в анатомії, фізіології, медицині, хірургії та біохімії внесли свій вклад в розвиток ефективних методів діагностики і лікування, які використовуються і сьогодні. Удосконалення гістологічних методів дослідження стали новою віхою в дослідженні структури прищитовидних залоз. В даний час вивчення спектру органних порушень при ураженнях прищитовидних залоз і розробка діагностичних і лікувальних методик не обмежуються участю всього суспільства ендокринологів, а й притягують все більшу увагу суміжних фахівців. **Висновки.** В огляді статті представлена історія відкриття прищитовидних залоз, висвітлено основні етапи вивчення їх ролі в кальцій-фосфорному обміні, проаналізовані роботи, присвячені еволюції в уявленнях про їх анатомічних, фізіологічних і патологічних особливостей.

Ключові слова. *прищитоподібні залози, фосфорно-кальцієвий обмін, Івар Сандстрем, паратгормон.*

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Received: *15.11.2020*
Advance Access Published: *December, 2020*

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