



ИСТОРИЯ ОТКРЫТИЯ ПОДЖЕЛУДОЧНОЙ ЖЕЛЕЗЫ

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PANCREAS: HISTORY IN A TIMELINE

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Summary

The article is devoted to the history of discovery and study of one of the most important organs of the digestive and endocrine system of the body — the pancreas. Chronologically, key discoveries in pancreatic anatomy, histology, physiology and biochemistry are presented. Brief data about life and activity of scientists, whose names immortalized in pancreatic eponyms (J.G. Wirsung, G.D. Santorini, P. Langerhans) are given. Circumstances of their discoveries are described.

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Резюме

Статья посвящена истории открытия и изучения одного из важнейших органов пищеварительной и эндокринной системы организма — поджелудочной железы. В хронологической последовательности представлены ключевые открытия в анатомии, гистологии, физиологии и биохимии органа. Приведены краткие сведения о жизни и деятельности ученых, чьи имена увековечены в эпонимах структур поджелудочной железы — И.Г. Вирсунга, Дж.Д. Санторини и П. Лангерганса. Описаны обстоятельства совершения их открытий.

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Figure 1.
Johann Georg Wirsung
(1589–1643).

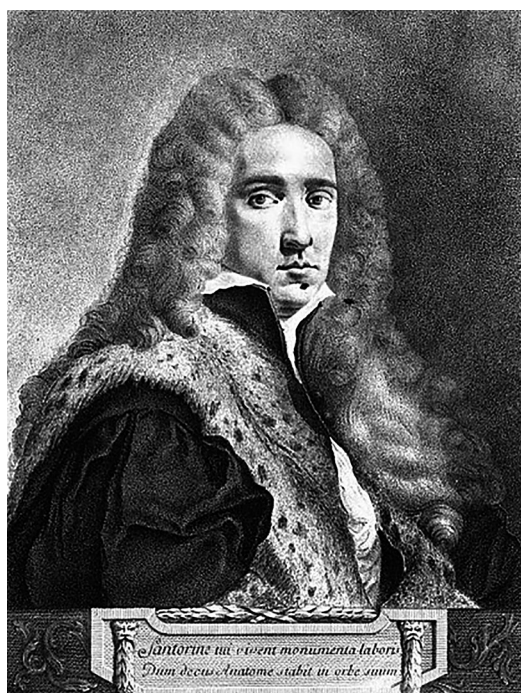


Figure 2.
Giovanni Domenico Santorini
(1681–1737).

It is well-known that the pancreas is one of the body's vital organs. At around 25 cm in length, the organ has dual roles; it is an organ of the digestive and endocrine system. The incidence of pancreatic pathology including diabetes is recently increasing. For example acute pancreatitis is one of the most common diseases of the digestive system, leading to tremendous emotional, physical, and financial human burden. The vast majority of modern educated people are well acquainted of the importance of pancreas in our body and it seems quite hard to believe that throughout many centuries the existence and functions of this organ were unrevealed.

In this article we will enlighten the history of pancreatic discovery and pay tribute to those prominent frontier scientists whose understandings and discoveries in the structure and function of pancreas made diagnosis and management of the pancreatic diseases possible.

Regretfully the name of scientist who officially discovered pancreas stays unknown. It was considered that it could be either Aristotle (384–322 BC) or Erasistratus (350–300 BC), or Herophilus of Chalcedon (335–280 BC) or even Rufus of Ephesus (53–117) [1]. For a long time function of this organ also remained unknown even until March 2, 1642, when Johann Georg Wirsung discovered the pancreatic duct while performing an autopsy of a recently executed criminal named Zuane Viaro della Badia. Unfortunately, neither he nor any of his contemporaries, to whom he sent the engraving of the detected anatomical structure, could explain its significance [1, 2].

Yet, Wirsung understood that the duct contains a fluid with strong corrosive properties, coming from the pancreas into the duodenum rather than in the opposite direction as other scientists believed according to that time popular theory of “sponge”. According to that theory pancreas absorbed duodenal chyle like a sponge for subsequent delivery to the liver and spleen.

Johann Georg Wirsung (1589–1643) (fig. 1) studied firstly anatomy in Paris and Altdorf under the guidance

of Jean Riolan, Jr (1580–1657) and Caspar Hoffmann (1572–1648) respectively. In November 1629 Wirsung moved to Padua and next year he earned his degree in medicine. After graduation he was chosen by Johann Wesling (1598–1649), who was professor of anatomy at University of Padua that time, as a prosector. Wirsung occupied this position until his tragic death [1, 2, 4, 5].

On August 22, 1643, Wirsung was shot down by the student Jacques Cambier at the door of his house. This prominent anatomist was buried inside the wall of St. Anthony cathedral in Padua. And after 5 years of the Wirsung's death Moritz Hoffmann (1622–1698) who was also present at the pancreatic discovery and became later a professor of anatomy and surgery in Altdorf, claimed his rights for the discovery of this anatomical structure. According to his version, in September 1641 (when he was 19-years-old) he found pancreatic duct inside the turkey-cock [3]. However, we have no documentary evidence of this, as Hoffmann did not publish his observations. And whether this is true fact, it still remains unknown. Ultimately, main pancreatic duct is now referred to as «Wirsung's duct».

In 1659 Dutch anatomist Franciscus Sylvius (1614–1672) first suggested an important role of pancreatic juice in the digestion [6].

In 1662 22-year-old student of Leiden University Regnier de Graaf (1641–1673) conducted one of the first experiments in the history of medicine, for the first time he received a clean pancreatic juice drained from dog's pancreatic duct by the tube made from goose feather. However, the young experimenter made no attempt to investigate its properties and functions [3, 7].

In 1724 Italian anatomist Giovanni Domenico Santorini (1681–1737) had discovered an accessory pancreatic duct in humans currently known as «duct of Santorini». However, in anatomical literature there are present at least eight description of this formation made before (by Johann Georg Wirsung, Thomas Wharton (1614–1673), Johann Rhode (1587–1656),

Figure 3.
Title page of Santorini's
"Observationes anatomicae".

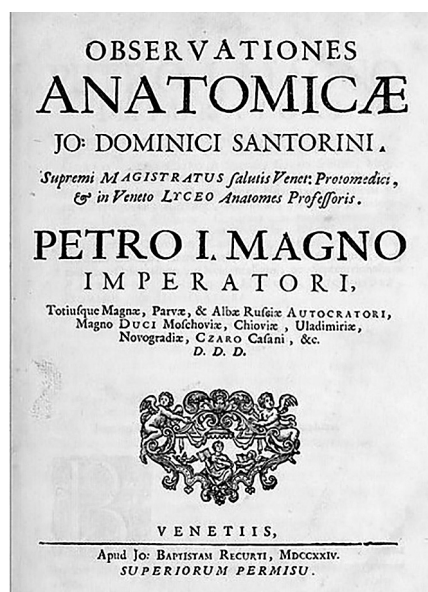
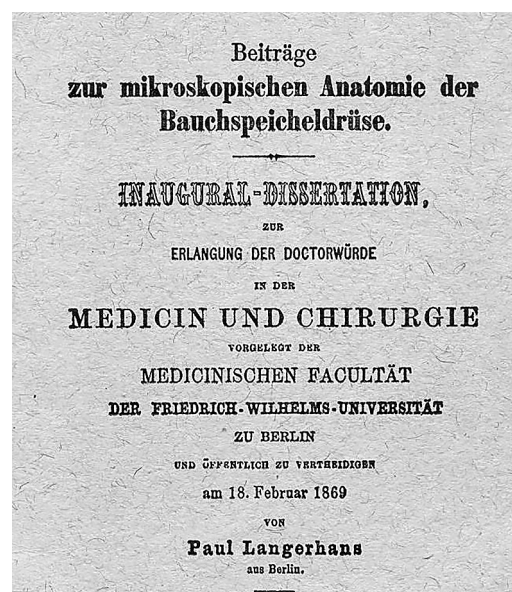


Figure 4.
Title page of Langerhans' thesis.



Niels Stensen (1638–1686), Regnier de Graaf, Franciscus Sylvius, Frederick Ruysch (1638–1731), Samuel Collins (1618–1710)). Santorini treated it as an independent anatomical structure while other anatomists considered it to be a variant of development [1].

Son of an apothecary Giovanni Domenico Santorini (fig. 2) studied medicine at Bologna (under noted anatomist Marcello Malpighi), Padua and Pisa, where he earned his medical degree in 1701. In 1703 began public anatomical dissections, and was a demonstrator in anatomy at Venice from 1706 to 1728. After that he worked as a physician at the Spedaletto (hospital) in Venice, where he also taught obstetrics [1, 5, 8]. Santorini was one of the best known anatomists of his time. His greatest contribution came in 1724 with the publication of "Observationes anatomicae" (dedicated to the Peter the Great of Russia) (fig. 3), in which he presented his numerous discoveries. Today he is best remembered for his description of the muscles of facial expression, prostatic venous plexus, accessory pancreatic duct, emissary veins, supreme nasal concha, some laryngeal cartilages, etc [8]. More than 10 anatomical entities were named in his honor.

In 1812 German anatomist Johann Friedrich Meckel, Jr. (1781–1833) found that the pancreas develops from two primordia, a ventral and dorsal [9].

In 1838 Czech scientist Jan Evangelista Purkinje (1787–1869) and his assistant Samuel Moritz Pappenheim (1811–1882) revealed that the substance in pancreatic secretions breaks down proteins [6, 9].

In 1844 German-Swiss physiologist Gabriel Gustav Valentin (1810–1883) discovered the ability of pancreatic juice to break down the starch, thereby opening the "sugaring" effect of pancreatic secretion [6, 9].

In 1849 French physiologist Claude Bernard (1813–1878) began to publish the results of his studies on the secretory function of the pancreas. He admitted the ability of pancreatic secret to work on three food components (proteins, fats, carbohydrates), and in particular, to break down and emulsify the neutral fats and the impossibility of fat absorption to the exclusion of pancreatic secretion of digestive process [1, 6, 10].

In 1852^{4th}-year student from Paris D. Moyse first described the histological structure of the pancreas. In his dissertation for a degree of doctor of medicine he portrayed the structure of pancreatic acini [1, 3]. Unfortunately, this is all that is known about this man. Neither his name nor the years of his life could not be found in the literature.

In 1861 practitioner from Kharkov Alexander Yakovlevich Danilevsky (1838–1923) by studying the composition of the pancreatic secretion concluded that the ability of pancreatic juice to hydrolyze a fundamentally different substances (proteins, fats and carbohydrates) is associated with the presence in it of not only one but three different enzymes [11].

In 1869 German physician Paul Langerhans (1847–1888) defended his thesis «Beiträge zur mikroskopischen Anatomie der Bauchspeicheldrüse» («Contributions to the microscopical anatomy of the pancreas») (fig. 4), which contained first description of the structure of pancreatic islets now known as the "islets of Langerhans" [1, 3, 12, 13]. With the new staining technique he identified nine types of cells, including small, irregularly shaped cells lacking granules. They had a number of features: arranged in groups and were not connected to the excretory ductules. He believed that these structures were related to the lymphatic system. Other scientists have believed that they were the remnants of embryonic structures.

Paul Langerhans (1847–1888) (fig. 5) studied medicine at University of Jena and Berlin. Among his teachers were eminent naturalist Ernst Haeckel (1834–1919), famous physiologist Emil Du Bois-Reymond (1818–1896), "the father of modern pathology" Rudolf Virchow (1821–1902) and one of Germany's leading pathologists Julius Cohnheim (1839–1884). After graduation, he spent some time working in Virchow's laboratory. In 1870 he travelled with young cartographer Richard Kiepert to the Middle East. During this scientific journey, he made several anthropological observations and studied leprosy. Returning to Europe, Langerhans served as medical officer in Franco-Prussian war (1870–1871). In 1871, he became prosecutor in Freiburg, and then full professor at the same University. In 1874,



Figure 5.
Paul Langerhans (1847–1888).

he interrupted his academic career due to tuberculosis. He settled in Madeira to seek cure for his illness. He died of renal infection 5 days before his 41st birthday. Besides his description of the exocrine pancreatic cells Langerhans is also remembered for his discovery of the dendritic cells in the skin which are named after him “Langerhans cells” [12, 13]. On Madeira he studied marine fauna, especially worms, discovering a new genus which he termed “Virchowia” in honor of his teacher. He also had an interest in meteorology, especially the effects of climate on tuberculosis, and wrote “Handbook of Madeira” dealing with the climatic and curative properties of that island [14].

In 1875 German physiologist and histologist Rudolf Peter Heidenhain (1834–1897) found out that the pancreatic cells do not contain active enzymes, but only their precursors, which he proposed to call «zymogen» [1, 6].

In 1875–1876 German physiologist Friedrich Wilhelm Kühne (1837–1900) coined term «enzyme» to refer to particular chemical substances, and determined the pancreatic enzyme that breaks down proteins and named it «trypsin» [15].

In 1892 Emmanuel Hedon (1863–1933) proved the existence of endocrine function in the pancreas. By grafting fragment of the gland under the skin or on the spleen to the pancreatectomized dogs, he found a normalization of blood sugar level. On the other hand he pointed out the development of severe diabetes while removing the graft [1].

In 1893 French histologist Gustave-Edouard Laguesse (1861–1927) discovered that the endocrine function of the gland is associated with groups of cells described by Langerhans and proposed to name these structures in his honor “islets of Langerhans” [16].

In 1901 Russian pathologist Leonid Sobolev (1876–1919) in his thesis “On the morphology of the pancreatic duct with its ligation, diabetes and other conditions,” found out that ligation of excretory pancreatic duct leads to atrophy of the acini without affecting the Langerhans islets. He suggested the idea of separation

of islets for organ therapy. Based on these results he has developed the instructional techniques which allowed to come close to a method for producing an anti-diabetic hormone, which unfortunately was prevented by his early death during the Civil War in Russia [11, 17, 18].

In 1902 British physiologists William Maddock Bayliss (1860–1924) and Ernest Henry Starling (1866–1927) discovered secretin, a substance produced by the epithelium of duodenum which stimulates the production of pancreatic juice. Starling offered to name such chemical messengers «hormones» [19].

In 1909 Belgian physiologist Jean de Meyer (1878–1934) proposed to name the hormone of the islets of Langerhans as «insulin» [1].

In 1921 Canadian orthopedic surgeon Frederick Grant Banting (1891–1941) and medical student Charles Herbert Best (1899–1978) by using the methods of L. Sobolev identified insulin and offered technology of its extraction from the animal (pig) pancreas. In 1923 “for the discovery of insulin” Banting was awarded the Nobel Prize [20]. Having learned that the Nobel Committee ignored Best, Banting wanted to refuse the award, but eventually split with him half the money amount and always publicly spoke about the contribution of the young colleague to the discovery.

In 1923 American physiologist John Murlin (1874–1960) discovered the pancreatic hormone which had hyperglycemic effect and named it «glucagon» [21].

In 1943 two physiologists from University of Manchester Alfred Alexander Harper and Henry Stanley Raper (1882–1951) isolated peptide from the small intestine mucosa and named for its ability to stimulate pancreatic secretion “pancreozymin”. In 1964 properties of this peptide were proved to be closely linked to cholecystokinin, discovered in 1928. Now this substance is known as cholecystokinin / pancreozymin [22, 23].

In 1958 English biochemist Frederick Sanger (1918–2013) was awarded the Nobel Prize in chemistry for determining the molecular structure of insulin [24].

In 1974 Nobel Prize in Physiology or Medicine was awarded to the American biologist George Emil Palade (1912–2008) together with Albert Claude and Christian de Duve “for their discoveries concerning the structural and functional organization of the cell”. In experiments on the exocrine cells of the pancreas in guinea pigs Palade explored the ways of protein synthesis and secretion of enzymes and determined the organelles to be responsible for each stage of the secretory process [25].

In 2002 Korotko G.F. in the monograph “The secretion of the pancreas” brought information about the presence of valves in the ducts of the gland, which provide orthograde flow of pancreatic juice and prevent bilio- and duodenopancreatic reflux [26].

In 2008 Professor Joseph Kennedy presented his invention — an «artificial pancreas» at the Congress of the American Chemical Society in New Orleans. The device is shown to be effective in animals with experimental diabetes.

We believe the history of pancreas will be continued.

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