Gastroenterol Hepatol. 2017;40(7):495-504

Gastroenterología y Hepatología

www.elsevier.es/gastroenterologia

SPECIAL ARTICLE

Nobel prizes and the pancreatic knowledge☆

Los premios Nobel y el conocimiento pancreático

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Received 19 August 2016; accepted 23 November 2016
Available online 14 July 2017

Introduction

On 27 November 1895, at the Swedish-Norwegian Club of Paris, Alfred Bernhard Nobel (Stockholm [Sweden], 1833-San Remo [Italy], 1896), chemist, engineer and inventor, signed his will, in which he established the prizes that bear his name. He contributed a large amount of money, thanks to the enormous fortune he had accumulated from his 355 inventions, among them, dynamite. These prizes were meant to be for people who would go on to distinguish themselves, throughout the practice of their profession, by means of their exceptional contributions to the fields of physiology or medicine, physics, chemistry, literature and peace. Then in 1968, the Nobel prize in economics, established by Sweden's central bank, was added to these. The awards are given each year on 10 December, the anniversary of Nobel's death. The peace prize is awarded by the Norwegian Nobel Committee and is given in Oslo, while the rest are given in Stockholm. The winners receive a medal, a diploma and a sum of money. The Nobel Assembly of the Karolinska Institute in Stockholm is in charge of awarding the physiology or medicine prize, and the Royal Swedish Academy of Sciences is responsible for awarding the chemistry prize.

As of 2015, 23 organisations and 870 people have been awarded prizes; 208 of these correspond to the physiology or medicine prize and 170 to the chemistry prize. The first prizes were awarded in 1901, with the prize in physiology or medicine given to the German bacteriologist Emil Adolf von Behring (Hansdorf [East Prussia], 1854-Marburg [Germany], 1917) for ''his work in serum therapy, especially in regard to its use to treat diphtheria'',[1] and the chemistry prize went to Jacobus Henricus van't Hoff (Rotterdam [Netherlands], 1852-Berlin [Germany], 1911) for ''establishing the principles of stereochemistry and chemical kinetics''.[2] No prizes in physiology or medicine were awarded from 1915 to 1918 or in 1921 and 1925; and the years 1916, 1917, 1919, 1924 and 1933 saw no prizes given in chemistry. Between 1940 and 1942 no prizes were awarded because of Nazi Germany's occupation of Norway.

This article refers to some important aspects in the lives of 11 people who received the Nobel prize in physiology or medicine and 3 that were honoured with the prize in chemistry, and at some point in their lives they all carried out some kind of research related to the pancreas and so were of great importance in contributing knowledge about this ''mysterious'' gland. The different protagonists are described in chronological order of when they received the prize.

Nobel prizes and the pancreas

Ivan Petrovich Pavlov

Ryazan [Russia], 1849-Leningrad (USSR), 1936
Nobel prize in physiology or medicine in 1904, ''in recognition of his work on the physiology of digestion, through which knowledge on vital aspects of the subject has been transformed and enlarged''.[3]

☆ Please cite this article as: Navarro Colás S. Los premios Nobel y el conocimiento pancreático. Gastroenterol Hepatol. 2017;40:495-504.

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2444-3824/

Regarding the pancreas, he described its innervation through the vagus nerve and studied pancreatic secretion and the activation in the intestine of some of its proenzymes, during which he identified enterokinase.

Pavlov was the son of an Orthodox priest in the city of Ryazan, where he began his studies. His religious vocation led him to the seminary, but he soon realised that his interest was in science. In 1870 he began studying physics and mathematics but quickly became passionate about physiology. As a first-year student of medicine and chemistry at the University of Saint Petersburg, he developed, together with another student named Afanasyev, a research project on the physiology of the pancreatic nerves that was awarded a gold medal. In 1875 he completed his training and went on to study at the Academy of Medical Surgery, where he finished in 1879 by winning another award and earning a scholarship to the academy that allowed him to work in the physiology laboratory, which was run by the famous doctor Sergey Petrovich Botkin (Moscow [Russia], 1832-Menton [France], 1889). In 1883 he presented his doctoral thesis entitled ''The Centrifugal Nerves of the Heart''. Between 1884 and 1886 he moved to Wrocław (Poland) and then Leipzig (Germany) to broaden his studies, and specialised in gastrointestinal physiology and the circulatory system. Then in 1890, he was invited to organise and direct the Physiology Department at the Institute of Experimental Medicine in Saint Petersburg, a position he held for 45 years, until the end of his life. That same year he was also named professor of pharmacology at the Military Medical Academy, and 5 years later, professor of physiology, which lasted until 1925.

In his laboratory he developed surgical techniques for the formation of digestive fistulas, especially in dogs, which allowed him to determine the functions of various glands under relatively physiological conditions. With this method he demonstrated the participation of the nervous system in regulating the digestive process. In 1897 he published a compendium of his findings under the title *Lektsii o Rabote glavnykh pishchevaritelnyteh zhelez* [The Work of the Digestive Glands], in which he described the ''conditioned reflex'' with regard to salivary, gastric and pancreatic secretion mediated by the vagus nerve, and different studies on pancreatic secretion. He also identified enterokinase, which allows the proenzyme trypsinogen to convert to its active form, trypsin.[3,4]

In 1901 he was chosen to be a member of the Russian Academy of Sciences. In 1903 he gave a detailed account of the results of his experiments at the 14th International Medical Congress in Madrid, where he presented a paper entitled ''*The Experimental Psychology and Psychopathology of Animals*''.

In recognition of all his works he received the Nobel prize in physiology or medicine in 1904. In 1912 he was given an honorary doctorate by the University of Cambridge, and in 1915, on the recommendation of the Paris Medical Academy, he was granted the National Order of the Legion of Honour.

After the October Revolution of 1917, the communist party and the Soviet government recognised Pavlov's brilliant scientific career and promoted the establishment of a centre for the study of physiology. He was appointed director of the Physiology Laboratory at the Institute of Experimental Medicine of the Academy of Sciences of the USSR (Fig. 1).

Pavlov died in Leningrad (USSR) on 27 February 1936.

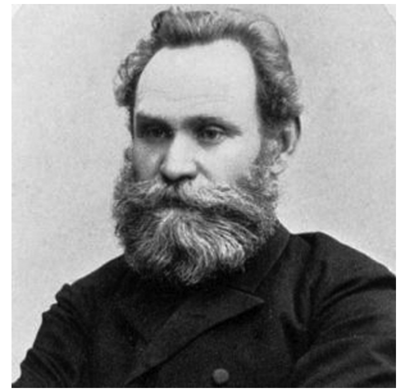

Figure 1 Ivan Petrovich Pavlov (1849–1936). Nobel prize in physiology or medicine, 1904.

In recognition of his work, a lunar crater and the asteroid Pawlowia, discovered by Vladimir Aleksandrovich Albitzky in 1923, were named after him.

Emil Theodor Kocher

Burgdorf [Bern, Switzerland], 1841-Bern, 1917
Nobel prize in physiology or medicine in 1909 for ''his work on the physiology, pathology and surgery of the thyroid gland''.[5]

In 1903 he described the surgical method that bears his name, also known as mobilisation of the duodenum, which is used to reach the pancreas during an operation on this organ.

Kocher was born in the Swiss canton of Bern in 1841. His father was an engineer. He received his doctorate from the University of Bern in 1865. He studied with Bernhard von Langenbeck in Berlin, with Theodor Billroth in Vienna and with Georg Lücke in Bern, whom he succeeded as chair and director of the university clinic there. Kocher help this position from 1872 to 1911 and established an influential school throughout the 39 years that he worked in this city. This school issued noted professionals such as César Roux and Harvey Cushing. From 1866 and onwards, he published several experimental works on haemostasis and described a new method that helped to reduce shoulder dislocation. He presented several works on the antiseptic treatment of wounds with chlorine solution, the preparation of antiseptic catgut and wound healing through the use of drainage tubes or Lister dressings. His interest in asepsis led him to publish, together with the bacteriologist E. Travel (1858–1912), two editions (1892 in Basel [Switzerland] and 1900 in Jena [Germany]) of a book entitled *Conferencias sobre enfermedades infecciosas en cirugía* [Lectures on Surgical Infections]. However, he was also interested in a number of surgical aspects, such as the treatment of rectal lesions (1874), radical treatment for strangulated hernia (1877), acute osteomyelitis (1878), treatment of wounds caused by bullets (1895) and radical resection in cases of gastric cancer (1909), among others. He performed his first goitre excision in 1878. Throughout his life he was able to perform more than 5,000 operations of this type. Interestingly, Bern is located in an area that has one of the highest rates of goitre in the world. He succeeded in reducing the postoperative death rate from this surgery from 18% to 0.5%.[6] He also published, with Hermann Matti (1879–1941), a work entitled ''One Hundred Operations on the Bile Ducts'', which simplified the technique of cholecystectomy that had been performed up to that point in time.[7] In his book *Enfermedades de la glándula tiroides* [Diseases of the Thyroid Gland], he described the aetiology, symptoms and treatment of goitre. He caused a great controversy with his innovative ideas about thyroid physiology and disease. He also conducted studies of Cretinism. For these studies he was awarded the Nobel prize in physiology or medicine in 1909, the first surgeon to be awarded this distinction. Three years later he donated 200,000 Swiss francs to his university to establish a biology research institute, which is now called the Theodor Kocher Institute.

In 1903, in the book entitled *Mobilisierung des Duodenum* [Mobilisation of the Duodenum], he described the surgical manoeuvre that bears his name, a technique which is widely known by surgeons and is relevant today.[8] This manoeuvre was considered a major advance in operations that affect the duodenum, and through the mobilisation involved, it allows for an excellent view of the pancreatic head, thus facilitating surgery on this gland.

Kocher also designed various surgical instruments, such as Kocher's forceps (haemostatic forceps), among others.

He was an honorary member of several medical societies in Germany, Sweden, Great Britain, Italy, the United States, Turkey and Austria.

He died of uraemic coma on 27 July 1907, in Bern, Switzerland.[9]

Frederick Grant Banting and John James Rickard Macleod

Alliston [Ontario, Canada] 1891-Newfoundland [Newfoundland, Canada], 1941; Clunie [Scotland], 1876-Aberdeen [Scotland], 1935

They shared the Nobel prize in physiology or medicine in 1923 for ''the discovery of insulin''.[10]

Banting was the youngest of five siblings. He attended public high school in Alliston and later studied medicine at the University of Toronto, where he graduated in 1916. He fought in World War I, where he was wounded; in 1919 he was decorated with the Military Cross.

After the war he returned to Canada, studied orthopaedics and was resident surgeon at The Hospital for Sick Children in Toronto. He then went to the University of Western Ontario Hospital (Canada), became a professor of pharmacology at the University of Toronto and earned the Reeve Prize in 1922. Before this, he had been interested in the problem of diabetes, which, because of previous studies, was known to be caused by a lack of a protein secreted by the islets of Langerhans. In an article published by Moses Baron, he read that pancreatic duct ligation in experimental animals destroyed the cells of the exocrine pancreas but preserved islet cells intact.[11] This led him to speculate that if the cells that secreted trypsin could be destroyed, they might prevent the destruction of the islets and insulin may be extracted from them. Banting discussed his theory with several colleagues, including University of Toronto physiology professor John James Rickard Macleod, who suggested that his student Charles Herbert Best (West Pembroke [Maine, USA], 1899-Toronto [Canada], 1978) assist him in developing the hypothesis. In 1921 they began ligating pancreatic ducts in dogs, and in February of 1922 they isolated a hormone, initially called isletin, that came to be known as insulin. They also performed pancreatectomies on more dogs to induce diabetes in them, which they then resolved by administering the extract obtained from their pancreases. Finally they tested this in a patient named Leonard Thompson who had had diabetes type 1 since the age of 13 years and who, thanks to this treatment, survived for 14 years (he died of pneumonia, a complication that occurred after a motorcycle accident, when he was 27).[12]

For this reason, Banting received the Nobel prize in physiology or medicine in 1923, along with John James Rickard Macleod. Best, the student who had helped him, was overlooked. Banting felt uncomfortable at this, and so he shared with his young colleague the money that came with the prize.[12,13] Banting was an honorary member of several medical societies and received the title of Sir in 1934. He also participated in an expedition to the Arctic Circle that was sponsored by the Canadian government.

Banting died on 20 February 1941 in a plane crash on the island of Newfoundland at the beginning of World War II when he was travelling to London as a medical services liaison between North America and Great Britain.

A lunar crater and an asteroid discovered in 2000 by the astronomer John Broughton were named after him.

Macleod was the son of a reverend. He was born in Clunie, Scotland, but his family soon moved to Aberdeen, where he attended primary school and later entered Marischal College at the University of Aberdeen to study medicine; he graduated in 1898. He received a one-year scholarship to study at the Physiology Institute of the University of Leipzig. In 1899 he was an assistant to the physiologist Leonard Hill at the London Hospital Medical School, and 3 years later he became a professor at the same institution. In 1902 he obtained a scholarship from the *Royal Society* that allowed him to travel to the United States, where he was appointed professor of physiology at Case Western Reserve University in Cleveland, Ohio.

In 1918 he was elected professor and director of the physiology laboratory at the University of Toronto and associate dean of the Faculty of Medicine. In 1928 he was appointed *Regius Professor* of Physiology at the University of Aberdeen, a position he held almost until his death.

From 1905 and onwards, he was interested in carbohydrate metabolism, which was the subject of numerous publications. He had previously worked with von Mering and Minkowski, who observed that the removal of the pancreas in experimental animals caused diabetes, and sensed that the function lost could be restored by administering extracts from this gland.

In 1921, working from Banting's hypothesis about the possibility of obtaining a pancreatic extract capable of treating diabetes, he proposed that his student Best be an assistant to Banting. In December of that year, however, faced with the difficulties they had in isolating sufficiently purified pancreatic extract, Macleod freed James Bertram Collip (Belleville [Ontario, Canada], 1892–1965) from his other work obligations to focus on obtaining purer pancreatic extracts and to be able to conduct clinical trials.

Thanks to the research carried out by Banting, Best and Collip, together with Macleod, in February 1922 they announced the discovery of insulin.[14] The manufacture of pancreatic extracts was later patented so that they could be used to treat diabetic patients. The discoverers waived the *royalties* stemming from the patent.

In 1923 Macleod shared the Nobel prize in physiology or medicine with Frederick Grant Banting. Macleod donated half of the prize money (as Banting had done with Best) to Collip, who had been overlooked when the prize was awarded.

He was appointed an elected member of the *Royal Society* of Canada in 1919, the *Royal Society* of London in 1923, the Royal College of Physicians in London in 1930 and the *Royal Society* of Edinburgh in 1932. He also received an honorary doctorate from the Universities of Toronto, Cambridge, Aberdeen, Pennsylvania and Jefferson Medical College.

Macleod died on 16 March 1935.[10]

John Howard Northrop

Yonkers [New York, USA], 1891-Wickenburg [Arizona, USA], 1987

Nobel prize in chemistry in 1946 for ''the preparation of viral enzymes and proteins in pure form''.[15]

Regarding the pancreas, he crystallised trypsin, chymotrypsin and carboxypeptidase, in addition to pepsin and pepsinogen.

Northrop was a posthumous son of John I. Northrop, a Columbia University zoologist who died 2 months before his birth due to an explosion in his laboratory. His mother, Alice B. Rich Northrop, was a professor of botany at Hunter College—CUNY.

In 1908 he studied zoology and chemistry at Columbia University. One of his professors was Thomas H. Morgan, who would win the Nobel prize in physiology or medicine in 1933. He graduated in sciences 4 years later, and in 1915 he earned a doctorate in chemistry. The following year he began working at the Rockefeller Institute in Jacques Loeb's laboratory (German-born American physiologist and an expert in artificial parthenogenesis). During World War I, Northrop served as a captain in the Chemical Warfare Service (1917—1918). After his service he studied the kinetics of the enzymes associated with the process of life. In 1929 he isolated pure pepsin from gastric acid extracted from pigs,[16] and 2 years later he was able to crystallise trypsin, chymotrypsin, carboxypeptidase and pepsinogen, thus showing that these substances were proteins. He also worked on viral proteins and antibodies. He used the same methods that James B. Sumner had used in 1926 to crystallise urease (the first enzyme to be crystallised), which earned him the Nobel prize. From 1925 and for several years afterwards, following the death of Jacques Loeb, he replaced him as editor of the *Journal of General Physiology*, a publication of the Rockefeller Institute.

In 1939 he won the Daniel Giraud Elliot Medal of the US National Academy of Sciences for his research published in the book Crystalline Enzymes: The Chemistry of Pepsin, Trypsin, and Bacteriophage.[17]

During World War II, he was a consultant for the *National Defense Research Committee*, studying the effect of gases used in war and methods to detect them. In 1946, he received the Nobel prize in chemistry, together with James B. Sumner and Wendell M. Stanley.

In 1949 he was appointed professor of bacteriology at Columbia University and later, professor of biophysics.

During his life he received numerous distinctions, besides being awarded honorary doctorates from several Universities (Harvard, Columbia, Yale, Princeton and Rutgers).[15]

He died on 27 May 1987 in Wickenburg (Arizona), where he had retired.

Frederick Sanger

Rendcomb [Great Britain], 1918-Cambridge [Great Britain], 2013

Nobel prize in chemistry in 1958 for ''his work on the structure of proteins, especially insulin''.[18] In 1980 he received a second prize, shared with biochemist Walter Gilbert, for ''his contribution concerning the sequencing of nucleic acids''.[19]

Sanger earned a bachelor's degree in natural sciences at St. John's College and another in biochemistry from the University of Cambridge, and was awarded his doctorate in 1943 for his work on lysine, under the supervision of Albert Neuberger (an eminent German-born British chemist).

In 1948 he worked in Uppsala with the Swedish biochemist who won the Nobel prize in chemistry that year, Arne Wilhelm Kaurin Tiselius, an expert in electrophoresis and serum protein absorption.

In 1951 he worked in the Molecular Biology Laboratory at Cambridge, where he became director of the Proteins Division. That same year he received the Corday—Morgan Prize, which was established in 1949 by chemist Gilbert Thomas Morgan to award the most deserving contributions in experimental chemistry. This award is presented by the *Royal Society of Chemistry*. In 1954 he was appointed a member of the *Royal Society* and of King's College and, in later years, a foreign honorary member of the *American Academy of Arts and Sciences*, the *American Society of Biological Chemist*, the Argentine Chemistry Association and the Japanese Society for Biochemistry.

In 1958 he received the Nobel prize in chemistry for discovering (in 1955) the structure of insulin, specifically bovine insulin, by developing the entire amino acid sequence. For this research he worked with the Australian E.O.P. Thompson[20,21] and the esteemed Viennese biochemist Hans Tuppy, who were working in Sanger's laboratory.

In 1960 he became interested in nucleic acids, and 15 years later he developed the ''dideoxy'' method of DNA sequencing, for which he received his second Nobel prize in 1980. This method was later modernised and automated, thus allowing the human genome to be identified by a faster analysis.[22]

Sanger is one of four people to have won the Noble prize twice: Marie Curie (physics in 1903 and chemistry in 1911), Linus Carl Pauling (chemistry in 1954 and peace in 1962) and John Bardeen (physics in 1956 and 1972).

Sanger retired in 1983 and died in Cambridge on 19 November 2013.

Dorothy Crowfoot Hodgkin

Cairo [Egypt], 1910–Shipston-on-Stour [Great Britain], 1994

Nobel prize in chemistry in 1964 for ''her determinations of structures of important biochemical substances by X-ray crystallography''.[23]

She determined the three-dimensional structure of insulin, penicillin and vitamin B_{12}, among others.

Hodgkin was born in Cairo, where her parents, English archaeologists, were working. Later they moved to Sudan, where they lived for 3 years, until 1926, when they moved to Palestine. Living with two experts in archaeology, she decided to dedicate herself to the chemistry used in this science. In 1928 she went to study at Oxford in Somerville College, where she remained until 1932. She studied crystallography and, on the advice of her tutor F.M. Bewer, investigated the use of X-rays in this science. This technique, developed by the English physicists William and Lawrence Bragg (father and son, respectively), who had been awarded the Nobel prize for physics in 1915,[24] is used to determine the three-dimensional structures of biomolecules. Hodgkin did a traineeship in Cambridge, where she investigated sterols on the recommendation of John Desmond Bernal, an Irish scientist who was an expert in crystallography. In 1934 she returned to Oxford, where she taught chemistry for the women's colleges. Among her students in 1940 was Margaret Thatcher, who would later become prime minister. That same year, with the help of Sir Robert Robinson (a professor at the University of Oxford and winner of a Nobel prize in chemistry in 1947 for his studies of alkaloids), she began to seek funding to acquire a state-of-the-art X-ray machine. In the end she received significant help from the *Rockefeller and Nuffield Foundations*, which allowed her to continue her studies of sterols at Cambridge, and she began to work in the field of other substances, such as insulin (1934), penicillin (1942, during World War II)[25] and vitamin B_{12} (1948).[26]

In 1964 she became the third woman to receive the Nobel prize in chemistry (Marie Curie won it in 1911 for discovering radium and polonium and her daughter Irène Joliot-Curie won it in 1935 for synthesising radioactive elements) after working intensively on the structures of various biochemical substances. Israeli crystallographer Ada Yonath is the only other woman to have won one, in 2009, for her studies on the structure and function of the ribosome. The amino acid sequence of insulin (the first protein to be sequenced) was known since 1955 via the works of Frederick Sanger, but in 1969 Dorothy Hodgkin published the rhomboidal structure of insulin at a resolution of 2.8 Å.[27] She deciphered its complex three-dimensional structure formed by 777 atoms, studies that began in 1934.

She received several honorary titles, including Honorary Foreign Member of the *American Academy of Arts and Sciences* (1958), *Order of Merit* (1965), *Copley Medal* of the *Royal Society* of London, Lenin Peace Prize, Chancellor of the University of Bristol and the Austrian Decoration for Science and Art (1983), among others. She was one of 5 women selected to appear on a postage stamp in a collection published in August 1996.

Hodgkin suffered from rheumatoid arthritis for many years and died on 29 July 1994 in a domestic accident.

Christian René de Duve; George E. Palade; Albert Claude

Thames Ditton [Great Britain], 1917-Nethen [Belgium], 2013; Jassy [Iaşi, Romania], 1912-Del Mar [California, USA], 2008; Longlier [Belgium], 1899-Brussels [Belgium], 1983

They received the Nobel prize in physiology or medicine in 1974 for ''their discoveries regarding the structural and functional organisation of the cell''.[28]

De Duve not only discovered insulin's mechanism of action, but he also helped to rediscover glucagon. George E. Palade and Albert Claude described the fundamentally different intracellular structures of the pancreatic acinar cells.

De Duve was the son of Belgian parents who during World War I had to take refuge in Great Britain, where he was born. In 1920 they returned to Belgium, and he began his studies in a school run by Jesuits. In 1934 he joined the Catholic University of Leuven, where he studied medicine. Soon he had the chance to work in Professor J.P. Bouckaert's physiology laboratory, where he researched the effect of insulin on glucose intake. This influenced him very positively in terms of his career; after graduating in 1941, his goal was to investigate insulin's mechanism of action. This project was slowed during World War II, but in 1945 he presented his doctoral thesis entitled ''Glucose, Insulin and Diabetes'', in which he elaborated insulin's mechanism of action.

In 1946 and 1947 he worked in Axel Hugo Theodor Theorell's laboratory at the *Nobel Medical Institute* in Stockholm. (Theorell himself won the Nobel prize in physiology or medicine in 1955.) Later, de Duve went to the *Rockefeller Foundation* at Washington University [St. Louis, MO] under the tutelage of Carl and Gerty Cori (winners of the Nobel prize in physiology or medicine in 1947) and then to St. Louis University where he collaborated with Earl W. Sutherland (who would receive the Nobel prize in physiology or medicine in 1971 for his discoveries on the mechanisms of action of hormones).

With all this scientific experience he returned to Leuven, where he taught physiology at the Faculty of Medicine, and in 1951 he was named professor. He continued his research, which led to the discovery, not only of a new part of the cell that in 1955 would come to be known as the lysosome, but also of another organelle, the peroxisome.

He continued to be interested in the endocrine secretion of the pancreas, insulin's mechanisms of action, and as a result, he was also interested in glucagon, which he helped to rediscover. This hormone, secreted by the cells α of the pancreas, exerts a hyperglycaemic and glycogenolytic effect and acts as a defence mechanism against hypoglycaemia. It had been identified in the duodenal and pancreatic mucosa of dogs in 1923 by John Raymond Murlin (1874–1960), professor of physiology at the University of Rochester between 1919 and 1945, and his collaborator Charles P. Kimball.[29] In 1966, M.H. McGravan observed that an exaggerated secretion of glucagon due to a tumoural lesion in pancreatic α cells was responsible for glucagonoma syndrome.[30,31]

In the early 1970s, de Duve founded the International Institute of Cellular and Molecular Pathology in Leuven. Starting in 1980, he investigated the biological origin of life, contributing to the progressive consensus of endosymbiotic theory.

In 1985 he was appointed professor emeritus at the University of Leuven, and in 1988 at the Rockefeller University, where he had been a professor since 1962. He ran the *International Institute of Cellular and Molecular Pathology* until 1991, which was renamed in his honour in 1997 as the de Duve Institute of Cellular Pathology.

On 4 May 2013, de Duve ended his life by legal euthanasia, after noting a significant deterioration in his health in the months before.[31]

Palade was born in Iași, which is in the historical region of Moldavia. His father was a professor of philosophy and his mother a teacher. In 1930 he began his studies in medicine at the University of Bucharest. His doctoral thesis was entitled ''Microscopic Anatomy of *Delphinus delphis*'' (1940). During World War II, he served in the Romanian army's medical corps. After the war in 1946, he moved to the United States and worked at the Marine Biological Laboratory run by Robert Chambers, where he met Albert Claude, who gave a seminar on electron microscopy. He invited him to work with him at the Rockefeller Institute for Medical Research. There he worked on cell fractionation to develop, together with Hogeboom and Schneider, who were collaborating with James Murphy (head of the Pathology Department), the ''sucrose method'' for the homogenisation and fragmentation of liver tissue. He soon began to work with electron microscopy, making improvements in microtomy and tissue fixation. In 1955 he joined Philip Siekevitz's laboratory, and together they showed that Albert Claude's ''microsomes'', known as such since 1948, were fragments of the endoplasmic reticulum and that the ribosomes were ribonucleoprotein particles. There they began to integrate the morphological and biochemical analysis of the secretory process in guinea pig pancreases.[32,33]

In 1960 his research led him to characterise zymogen granules and to discover the way products are secreted in the internal space of the endoplasmic reticulum. During this time, they worked with Lucien Caro and James Jamieson, obtaining important results on the synthesis and exocytosis of proteins of pancreatic exocrine cells.[34,35] Palade presented a critical review of all these processes at the speech he delivered at the Nobel prize ceremony.

In 1973 he left the Rockefeller Institute and moved to Yale to analyse interactions between pathology and clinical medicine and the new field of cell biology. He continued to investigate the mechanisms of cellular secretion, the endoplasmic reticulum, the Golgi complex and cell membranes.

He received several awards, such as the *Lasker Award* (1966), the *Gairdner Special Award* (1967) and the *Hurwitz Prize* (1970), among others. In 1974 he received the Nobel prize in physiology or medicine for his discoveries regarding the structure of pancreatic acinar cells and the description of the synthesis, transport, storage and secretion of the cell proteins of the exocrine pancreas in guinea pigs. In 1990 he was named *Dean* of the School of Medicine at the University of California, San Diego. He retired in 2001 and died on 7 October 2008 from complications of Parkinson's disease, from which he had suffered for years.

Claude was born in Longlier, situated in a valley at the foot of the Alps in the Belgian Ardennes. He was the youngest of 4 siblings. He studied medicine at the University of Liège and graduated in 1928. During 1928 and 1929, he was in Berlin, at the Kaiser Wilhelm Institute, working in Professor Albert Fischer's tissue cultures laboratory. In 1929 he moved to the United States, to the Rockefeller Institute for Medical Research in New York, where he dedicated himself to the study of cell structures by means of electron microscopy. He also developed the method of differential centrifugation that separates the different cell components according to their density. He worked on research with the microbiologist Francesc Duran i Reynals (1899–1958), who was from Barcelona and who had worked at this institution since 1928.[36,37] At one of his lectures he met George E. Palade, who joined him at the Rockefeller Institute to work with a team studying the structures and functions of cells. In 1941 he obtained US citizenship and in 1949 he returned to Belgium. He kept his position at the Rockefeller Institute and was professor emeritus of the Faculty of Medicine of the Free University of Brussels and the Catholic University of Leuven, and director of the University of Leuven's Cell Biology and Oncology Laboratory and the Jules Bordet Institute. In 1974 he was awarded the Nobel prize in physiology or medicine for his contribution to the knowledge of cell structures.[38]

He died on 22 May 1983.

Rosalyn Sussman Yalow, Roger Guillemin and Andrew Viktor Schally

New York [USA], 1921–2011, Dijon [France], 1924, Vilno [Poland] (now Vilnius [Lithuania]), 1926

They shared the Nobel prize in physiology or medicine in 1977; Yalow for ''the development of radioimmunoassay of peptide hormones''[39] and Guillemin and Schally for ''their discoveries regarding the production of the peptide hormone in the brain.''[40,41] Yalow used this technique to measure, among other hormones, circulating insulin. Guillemin and Schally discovered, separately, somatostatin, the sites of synthesis (brain, stomach, intestine and pancreas) and its mechanisms of action.

Yalow was born into a humble family. She soon became interested in reading, mathematics and physics. She was fascinated by a biography of Marie Curie published by her daughter Eve (concert pianist, journalist and writer) and a lecture given in 1939 by the Italian physicist Enrico Fermi (Nobel prize in physics in 1938) at Columbia University who aroused her interest in physics. She studied at Hunter College for girls in New York, and later, in 1941, she moved to the University of Illinois, where was the only woman among 400 students, the first since 1917. In 1945 she returned to New York and started working immediately at ITT (Federal Telecommunications Laboratory), being the company's only woman engineer. She received her doctorate in nuclear physics in 1947 and was hired by the Radiotherapy Service at the Bronx Veterans Administration Hospital, where she worked throughout her working life, dedicating herself in particular to the study of radioisotopes. In 1949 she started her own laboratory, as she was especially interested at that time in thyroid function. A year later she met Salomon Aaron Berson, with whom she worked in close collaboration for 22 years, until his death in 1972. Soon both were interested in the technique of radioimmunoassay, which was applied to the study of insulin metabolism in patients with type 2 diabetes treated by the administration of cow or pig insulin. They saw that these patients developed antibodies against the insulin administered over time, showing that a small protein could elicit an immune response. The paper in which she intended to publish her finding was initially rejected until the word ''antibody'' was removed from the title.[42,43]

When studying the reaction of insulin with antibodies, they realised that they had developed a tool with the potential to measure circulating insulin. Based on the development of this method, they could gradually determine the plasma concentration of different hormones and other substances that circulate in the blood in very small quantities.

Neither Yalow nor Berson ever wanted to patent their analytical method despite its potential economic impact. Thanks to their findings, it is considered that the era of radioimmunoassay began in 1959. Their method has been used to measure hundreds of substances of biological interest in thousands of laboratories around the world.

This technique is based on the principle of competitive inhibition following the law of mass action proposed by Cato Maximilian Guldberg (Oslo, Norway, 1836—1902) and his brother-in-law Peter Petersen Waage (Hydra [Norway], 1833—1900), which states that the rate of a chemical reaction is directly proportional to the concentration of the reactants.

For her discoveries, Yalow was awarded the Nobel prize in physiology or medicine in 1977. She was also named a member of the *National Academy of Sciences* and in 1976 received the Albert Lasker Medical Research award. She received honorary doctorates from the Universities of Hartford and Connecticut.

She died in New York on 11 May 2011.

Guillemin was born in the small town of Dijon. He began his medical studies in 1943 in Nazi-occupied France until 1944. He graduated in 1949 from the Faculty of Medicine at the University of Lyon. He had an eminently clinical education and a special interest in endocrinology, essentially after listening to Hans Selye's lecture on general adaptation syndrome in Paris. Due to this enthusiasm he spoke with Selye, who offered to work with him at the recently created Institute of Medicine and Experimental Surgery at the University of Montreal. At this centre he did experimental work on rats that were given nephrectomies and kept alive with peritoneal dialysis; he presented his doctoral thesis on this in Lyon. Returning to the Selye Institute in Montreal, in 1953 he received his doctorate in physiology and worked with the Department of Physiology at Baylor College of Medicine in Houston, Texas, where he served as assistant professor until 1970. This same year he moved to the Salk Institute at La Jolla (California), where he established the Neuroendocrinology Laboratory. He isolated and characterised thyrotropin-releasing hormone, isolated luteinising hormone-releasing hormone, and in 1972, purified, isolated and characterised somatostatin. Regarding somatostatin, he observed that its action inhibits growth hormone, thyrotropin, glucagon secretion, insulin, gastrin, secretin and acetylcholine. He observed that somatostatin was not only located in the brain, but also widely distributed in the stomach, intestine and pancreas.[40] In the pancreas it is produced by the cells δ. In 1977 (the same year he was given the Nobel prize) the American endocrinologist of Hindu origin Om P. Ganda,[44] of the Joslin Diabetes Centre in Boston, described the first case of a pancreatic tumour producing somatostatin that inhibits pancreatic and gastrointestinal hormones, which is manifested by diabetes (insulin inhibition), achlorhydria (gastrin), vesicular lithiasis (cholecystokinin) and steatorrhoea (secretin and cholecystokinin). Receptors of this hormone are expressed in 80% of pancreatic neuroendocrine tumours, except in insulinoma, which expresses it in only 50% of cases, which helps the localisation of this type of neoplasm.

Guillemin received numerous awards, including the Order of the Legion of Honour of the French Government (1973); was elected a member of the *National Academy of Sciences* of the United States (1974), the *American Academy of Arts and Sciences* (1976); and received honorary doctorates from the Universities of Rochester and Chicago (1976 and 1977). In 1977 he received the Nobel prize in physiology or medicine, which he shared with Andrew Viktor Schally.

Since his retirement in 1989, Guillemin has become an expert in abstract art. Using his Macintosh computer, he produces images that are transferred to fabrics or paper via printing processes or lithography. His works have been exhibited in famous art galleries in Europe and America.

Schally is an American endocrinologist of Polish origin who survived the Nazi occupation. In 1945 he emigrated to Great Britain and studied chemistry in London. His interest in medical research was awakened in 1949 while working at the National Institute for Medical Research at Mill Hill in London under the supervision of several scientists, some of whom would win Nobel prizes in chemistry (Archer J.P. Martin in 1952 and John W. Cornforth in 1975) and in physiology or medicine (Rodney R. Porter in 1972). In 1952 he moved to Montreal, Canada, where he studied at McGill University, and became interested in endocrinology. He began research on the relationship between hypothalamic function and endocrine activity, working with M. Saffran at the Allan Memorial Institute of Psychiatry run by Professor R.A. Cleghorn. He obtained his doctorate in 1957 at McGill, and then moved to Baylor College of Medicine in Houston, Texas, where he met Roger Guillemin, with whom he would share the Nobel prize.

In 1961 he moved to the Uppsala Biochemistry Institute to gain experience in electrophoresis and then to Stockholm to experiment with gastrointestinal hormones. In 1962 he obtained US citizenship and was appointed head of the Endocrinology and Polypeptides Laboratory of the Veterans Administration Hospital of New Orleans and an associate professor at Tulane University. In 1969 he established the amino acid sequence of the porcine thyroid-stimulating hormone and synthesised it. He shared this honour with Roger Guillemin's team, which had done the same with this hormone, but of ovine origin. He also did research with gonadotropins, purifying them and determining their structure. He also synthesised somatostatin from the porcine hypothalamus in 1973. In collaboration with the laboratories of Professors R. Hall, Royal Victoria Infirmary of Newcastle, and G.M. Besser, St. Bartholomew's Hospital in London, he demonstrated that somatostatin inhibits growth hormone, thyrotropin, glucagon, insulin, gastrin, secretin and cholecystokinin. The immunological study of his collaborator A. Arimura showed the presence of somatostatin in the pancreas, the stomach and the intestine, which suggested that this substance influences not only the regulation of pituitary gland but also that of the pancreas, stomach and duodenum. His colleagues D.H. Coy and C. Meyers successfully synthesised long-acting somatostatin analogues with significant clinical effects. He worked with R. Hall and G.M. Besser on the first clinical evaluations of the effect of this hormone on neuroendocrine tumours, which, although no true oncological effect was shown, seems to slow tumour growth. However, labelled analogues are widely used today to identify the location of neuroendocrine tumours and their metastases, including those of pancreatic origin. His team has also synthesised several antitumour peptides (gonadotrophin, bombesin and growth hormone antagonists) that have shown some efficacy in the treatment of prostate, neuroendocrine, breast and ovarian cancers, among others.

In 1973 he was named *Senior Medical Investigator* of the Veterans Administration, a rare honour. In addition, he has been awarded with numerous scientific distinctions from several countries.[41]

Günter Blobel

Waltersdorf [Germany], 1936

He was awarded the Nobel prize in physiology or medicine in 1999 for ''discovering that proteins have intrinsic signals that govern their transport and status in cells''. For his discoveries he used pancreatic acinar cells. He is known for proposing the ''signal hypothesis''.[45]

Blobel was born in Waltersdorf in the Prussian province of Lower Silesia (now the Niegosławice municipality in Poland). His father was a veterinarian. In January 1945 he and his family fled west, to a town near Dresden, before the advance of the Soviet troops. In 1954 they escaped to Frankfurt, where he began medical studies that he completed in Tübingen in 1960. In 1962 he received a scholarship to work at the University of Wisconsin (Madison) beside Har Gobind Khorana (Nobel prize in physiology or medicine in 1968) and Van R. Potter. In 1967 he joined George Palade's Cell Biology Laboratory at the Rockefeller University in New York (Fig. 2) and joined the ''Molecular Analysis of Cell Functions'' project. In the 1970s he began to study the process by which proteins are transported through the membranes of different organelles in the canine pancreas. His works reveal the existence of a cellular coding system whereby each synthesised protein has established an organelle-specific direction that is recognised by receptors on the surface of the organelle.[46] In 1975 he called this theory the ''signal hypothesis''.[47,48] These findings are related to various diseases, including cystic fibrosis, Alzheimer's disease and AIDS.

In 1994 he established the Friends of Dresden Foundation to rebuild the cathedral and various monuments that had been destroyed during his stay near this city during World War II. As a result, on receiving the Nobel prize in physiology or medicine in 1999, he donated the entire amount for the restoration of the city. He has also received other awards such as the Canada Gairdner International Award (1982), the Louisa Gross Horwitz Award (1989), the *Albert Lasker Award* for Basic Medical Research (1993) and the *King Faisal Award* (1996). He is a member of the *National Academy of Sciences*, the *American Philosophical Society* and the Pontifical Academy of Sciences. He also received the *Otto Warburg Medal*, the highest distinction of the German Society for Biochemistry.

Figure 2 Buildings of the Rockefeller University in New York, founded in 1901, where 24 Nobel-prize winners, among them J. Northrop, G. Palade, Ch. de Duve, A. Claude and G. Blobel, did research.

Epilogue

This article reviewed the biographies of 14 scientists who shared 9 Nobel prizes and have at least one thing in common: they carried out research that improved our knowledge of the pancreas. Some received this award for contributing innovations directly related to this gland, such as the discovery of insulin (Banting and Macleod), its sequencing (Sanger), its structure (Hodgkin), circulating insulin (Yalow) and its mechanism of action (de Duve). Others investigated the physiology of the gastrointestinal tract, including the physiology of the pancreas (Pavlov); showed the protein-related nature of trypsin, chymotrypsin and carboxypeptidase (Northrop); discovered the synthesis, transport, storage and exocytosis of the cell proteins of pancreatic acinar cells (Palade); described the structure of various intracellular organelles (Claude); developed the ''signal hypothesis'' (Blobel); identified glucagon (de Duve); discovered somatostatin, the sites where it is secreted and its mechanism of action (Guillemin and Schally); and established a series of hormone analogues with therapeutic capacity (Schally). In contrast to these scientists, Kocher received the award for his work regarding the thyroid but also devised a way to mobilise the duodenum, also called the Kocher manoeuvre, which is essential for operating on the pancreas.

This article aims at paying homage to all these researchers who dedicated their lives to advance scientific knowledge related to the pancreas.

Conflicts of interest

The author declares that he has no conflicts of interest.

References

1. The Nobel Prize in Physiology or Medicine 1901. Nobelprize.org. Nobel Media AB 2014. Available from: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1901/index.html [accessed 20.08.15].
2. The Nobel Prize in Chemistry 1901. Nonelprize.org. Nobel Media AB 2014. Available from: http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1901/index.html [accessed 27.02.16].
3. The Nobel Prize in Physiology or Medicine 1904. Nobelprize.org. Nobel Media AB 2014. Available from: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1904/index.html [accessed 15.08.15].
4. Busnardo AC, DiDio LJA, Tidrick RT, Thomford NR. History of the pancreas. Am J Surg. 1983;146:539–50.
5. The Nobel Prize in Physiology or Medicine 1909. Nobelprize.org. Nobel Media AB 2014. Available from: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1909/index.html [accessed 15.08.15].
6. Choong C, Kaye AH. Emil Theodor Kocher (1841–1917). J Clin Neurosci. 2009;16:1552–4.
7. Parquet RA. Reseñas históricas. Emil Theodor Kocher. Acta Gastroenterol Latinoam. 2011;41:95.
8. Androulakis J, Colborn GL, Skandalakis PN, Skandalakis LJ, Skamdalakis JE. Embryologic and anatomic basis of duodenal surgery. Surg Clin North Am. 2000;80:171–99.
9. Martinez G, Toledo-Pereyra LH. Emil Theodore Kocher. Cirujano, maestro y Nobel. Cir Cirug. 1999;67:226–32.
10. The Nobel Prize in Physiology or Medicine 1923. Nobelprize.org. Nobel Media AB 2014. Available from: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1923/index.html [accessed 15.08.15].
11. Navarro S. Breve historia de la anatomía y fisiología de una recóndita y enigmática glándula llamada páncreas. Gastroenterol Hepatol. 2014;37:527–34.
12. Howard JM. History of the pancreas. Available from: http://www.pancreasclub.com/history.html [accessed 10.03.14].
13. Martinez-Mier G, Toledo-Pereyra LH. Frederick Grant Banting. Cirujano, caballero y premio Nobel. Cir Cirug. 2000;68:124–31.
14. Banting FG, Best CH, Collip JB, Campbell WR, Fletcher AA. Pancreatic extract in treatment of diabetes mellitus. Can Med Assoc J. 1922;12:141–6.
15. John H. Northrop — Biographical. Nobelprize.org. Nobel Media AB 2014. Available from: http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1946/northrop-bio.html [accessed 11.05.16].
16. Northrop JH. Crystalline pepsin. Science. 1929;69:580.
17. Northrop JH. Crystalline enzymes. The chemistry of pepsin, trypsin and bacteriophage. New York: Columbia University Press; 1939.
18. The Nobel Prize in Chemistry 1958. Nobelprize.org. Nobel Media AB 2014. Available from: http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1958/index.html [accessed 31.08.15].
19. The Nobel Prize in Chemistry 1980. Nobelprize.org. Nobel Media AB 2014. Available from: http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1980/index.html [accessed 31.08.15].
20. Sanger F, Thompson EOP. The amino acid sequence in the glycyl chain of insulin I. The identification of lower peptides from partial hydrolysates. Biochem J. 1953;53:353–66.
21. Sanger F, Thompson EOP. The amino acid sequence in the glycyl chain of insulin II. The investigation of peptides from enzymic hydrolysates. Biochem J. 1953;53:366–74.
22. Slatko BE, Albright LM, Tabor S, Ju J. DNA sequencing by the dideoxy method. Curr Protoc Mol Biol. 2001, http://dx.doi.org/10.1002/0471142727.mb0704as47 [chapter 7: Unit7.4A].
23. Dorothy Crowfoot Hodgkin — Biographical. Nobelprize.org. Nobel Media AB 2014. Available from: http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1964/index.html/ [accessed 03.09.15].
24. William Bragg and Lawrence Bragg — Biographical. Nobelprize.org. Nobel Media AB 2014. Available from: http://www.nobelprize.org.nobel_prizes/physics/laureates/1915/index.html [accessed 17.09.15].
25. Crowfoot D, Bunn CW, Rogers-Low BW, Turner-Jones A. X-ray crystallographic investigation of the structure of penicillin. In: Clarke HT, Johnson JR, Robinson R, editors. Chemistry of penicillin. Princeton University Press; 1949. p. 310–67.
26. Brink C, Hodgkin DC, Lindsey J, Pickworth J, Robertson JH, White JG. X-ray crystallographic evidence on the structure of vitamin B_{12}. Nature. 1954;174:1169–71.
27. Adams MJ, Blundell TL, Dodson EJ, Dodson GG, Vijayan M, Baker EN, et al. Structure of rhombohedral 2-zinc insulin crystals. Nature. 1969;224:491–5.
28. The Nobel Prize in Physiology or Medicine 1974. Nobelprize.org. Nobel Media AB 2014. Available from: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1974/index.html [accessed 15.08.15].
29. Kimball C, Murlin J. Aqueous extracts of pancreas III. Some precipitation reactions of insulin. J Biol Chem. 1923;58:337–48.
30. McGravan MH, Unger RH, Recant L. A glucagon-secreting alfa-cell carcinoma of the pancreas. N Engl J Med. 1966;274:1408–13.
31. El Nobel de Medicina Christian De Duve elige la eutanasia para morir. El País. 6 de mayo de 2013. Available from: http://sociedad.elpais.com/sociedad/2013/05/06/actualidad/1367831557_991667.html [accessed 01.09.15].
32. George E. Palade — Biographical. Nobelprize.org/Nobel Media AB 2014. Available from: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1974/palade-bio.html [accessed 13.05.16].
33. Palade GE. The endoplasmic reticulum. J Biophys Biochem Cytol. 1956;2:85–98.
34. Caro LG, Palade GE. Protein synthesis, storage and discharge in the pancreatic exocrine cell. An autoradiographic study. J Cell Biol. 1964;20:473–95.
35. Jamieson JD, Palade GE. Intracellular transport of secretory proteins in the pancreatic acinar cell. I. Role of the peripheral elements of the Golgi complex. J Cell Biol. 1967;34:577–96.
36. Claude A, Duran-Reynals F. On the existence of a factor increasing tissue permeability in organs other than testicle. J Exp Med. 1934;60:457–62.
37. Claude A, Duran-Reynals F. Clinical properties of the purified spreading factor from testicle. J Exp Med. 1937;65:661–70.
38. Albert Claude — Biographical. Nobelprize.org. Nobel Media AB 2014. Available from: http://www.nobelprize.org/nobel_prizes/medicine/lauretes/1974/claude-bio.html [accessed 13.05.16].
39. Rosalyn Yalow — Biographical. Nobelprize.org. Nobel Media AB 2014. Available from: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1977/index.html [accessed 02.09.15].
40. Roger Guillemin — Biographical. Nobelprize.org. Nobel Media AB 2014. Available from: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1977/index.html [accessed 02.09.15].

41. Andrew V. Schally — Biographical. Nobelprize.org. Nobel Media AB 2014. Available from: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1977/schally-bio.html [accessed 19.02.16].
42. Kahn CR, Roth J. Berson, Yalow, and the JCI: the agony and the ecstasy. J Clin Invest. 2004;114:1051–4.
43. Berson SA, Yalow RS, Bauman A, Rothschild MA, Newerly K. Insulin-I^{131} metabolism in human subjects: demonstration of insulin binding globulin in the circulation of insulin treated subjects. J Clin Invest. 1956;35:170–90.
44. Ganda OP, Weir GC, Soeldner JS, Legg MA, Chick WL, Patel WC, et al. Somatostatinoma. A somatostatin containing tumour of the endocrine pancreas. N Engl J Med. 1977;296:963–7.
45. Günter Blobel — Biographical. Nobelprize.org. Nobel Media AB 2014. Available from: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1999/blobel-bio.html [accessed 17.06.16].
46. Günter Blobel — Nobel Lecture: Protein Targeting. Nobelprize.org. Nobel Media AB 2014. Available from: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1999/blobel-lecture.html [accessed 17.06.16].
47. Blobel G, Dobberstein B. Transfer of proteins across membranes. I. Presence of proteolytically processed and unprocessed nascent immunoglobulin light chains on membrane-bound ribosomes of murine myeloma. J Cell Biol. 1975;67:835–51.
48. Blobel G, Dobberstein B. Transfer of proteins across membranes. II. Reconstitution of functional rough microsomes from heterologous components. J Cell Biol. 1975;67:852–62.