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Dedicated to The 101st Anniversary, Since The Creation of Insulin: Memory in the Means of Collecting

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Abstract

This article presents the materials of a study devoted to the reflection of the memory of the creation of the hormone insulin, as well as all the scientists who took an active part in its discovery, creation, production and study of the mechanism of its action on the body, both in the norm and in the treatment of diabetes in both adults and children, who left their significant scientific and practical contribution to medical science.

Keywords: insulin, anniversary, philately, postal envelopes, blocks, numismatics, commemorative coins and medals.

Introduction

The year 2021, July 27, marks the 100th anniversary of the official discovery of insulin, and July 27, 2922, the 101st year, of this great discovery. Scientists from around the world participated in its discovery. In this case, each of them contributed to the process of both theoretical justification and practical production of this truly invaluable medicine for the lives of millions of people. It is not unimportant that the 100th anniversary is timed exactly to the time of the discovery of insulin and its isolation by Nicolae Paulescu, a Romanian scientist and researcher, as well as to the works in 1921-1922, with the subsequent production and synthesis of more "pure" insulin by F.G. Bunting, D.R. McLeod and C.G. Best [1-3, 22, 29].

For the time passed, since the moment of discovery and practical application in medicine of insulin, a considerable quantity of the most various philatelic materials devoted to these great scientists, such, in particular, as: postage stamps, envelopes and blocks, small sheets [1-3] has been issued by post offices of some countries of the world. All of them, will be presented in this article, and provided with comments.

Purpose/Aim article

To present new data about the scientists who discovered insulin and gave it practical application in medicine, through the use of collecting tools such as philately and numismatics for presentation.

Materials and Methods

When conducting this research work, we used the method of in-depth literary-critical analysis of available scientific sources of information on the issue under study, using reference books, encyclopedias, catalogs, specialized periodicals, Internet resources.

Results and Discussion of the study

I would like to begin my story with the presentation of brief data concerning the life and scientific activity of the Romanian scientist who first began to study the issues of insulin isolation from pancreatic tissues - Nicolae Paulescu (1869-1931). In 1921, Nicolae Paulescu isolated a substance from pancreatic islets ("pancrein") and discovered that its injection caused hypoglycemia in dogs [1-5, 29].

Nicolae Paulescu is the real pioneer of insulin, who developed the substance in 1916 and experimented with it on a dog. Paulescu was forced to interrupt his work because of the First World War, and he did not publish his work entitled "A Study of the Role of the Pancreas in Food Absorption" in Archives Internationales de Physiologie until August 1921, and filed a patent 6254 for his invention on April 10. 1922 to the Romanian Ministry of Industry and Trade [1-5, 29].

In 1916 he succeeded in developing an aqueous extract of the pancreas, which, when administered to an adiabetic dog, had a normalizing effect on blood sugar levels. After a break, during World War I, he resumed his research. From April 24 to June 23, 1921, N. Paulescu published four articles in the Romanian branch of the Society of Biology in Paris: "The effect of pancreatic extract injected into an animal with diabetes by injection," "The effect of time elapsed from intravenous injection of the pancreas to an animal with diabetes," "The effect of pancreatic extract injected into a normal animal through blood." An extensive article on this subject, "A Study of the Role of the Pancreas

in Food Assimilation," was presented by N. Paulescu on June 22, in Archives Internationales de Physiologiein Liège, Belgium, and was published in the August 1921 issue of that journal. [1-5,29]. This Romanian scientist did much in the study of insulin and the pathogenesis of diabetes mellitus and quite deserved to become a Nobel Laureate, but, alas, he never became one! Unfortunately, there are not many philatelic materials devoted to N. Paulescu.

Figure 1: presents philatelic materials of Romania and Ukraine (postage stamps and first-day envelopes) dedicated to this great Romanian scholar [1-5].

This Romanian scientist did a lot in the study of insulin and the pathogenesis of diabetes and, quite deserved to become a Nobel Prize winner, but, alas, did not become one! Unfortunately, there are not many philatelic materials devoted to N. Paulescu. Figure. 1, presents philatelic materials of Romania and Ukraine (postage stamps and first-day envelopes) dedicated to this great Romanian scholar [1-5].

Figure 1: A selection of philatelic materials dedicated to Nicolae Paulescu

A separate, small selection, presented, in obverse and reverse, two commemorative bronze medals dedicated to the contribution of N. Paulescu, in the study of insulin, with his portraits on the obverses [6-9,29]. In 2021, the great Romanian scientist will celebrate his 90th birthday. The National Bank of Romania issued two commemorative coins, gold and silver, dedicated to the memory of Nicolae Paulescu, with his portraits on the obverse and the insulin formula on the reverse [6-9,29].

Figure 2: Commemorative medals and coins dedicated to Nicolae Paulescu

Next, I would like to briefly describe Oskar Minkowski's contribution to the study of insulin and diabetes mellitus. Oskar Minkowski (1858-1931) was born in Alexothen, Russia. He studied medicine in Strasbourg and received his doctorate in Königsberg from the famous Bernard Naunin. He was looking for practical conclusions from an experimental study of metabolic disorders. O. Minkowski was curious to know if a dog could survive after removal of the pancreas, and if so, what effect this would have on the digestion of fats and proteins. This crucial study of the pancreas proved to be one of the most important and unexpected

experimental observations in the history of diabetes. This was performed with Joseph von Mering when he worked as an assistant to Naunin, in 1889. The development of massive glucosuria within 24 hours after pancreatectomy was a new discovery. Oskar Minkowski did further research to see if other lesions or injuries caused by the surgery were the cause of the glucosuria. Diabetes did not develop when the pancreas was removed from the site, with intact vascular connections to the duodenum, or when only partially removed. [Thus, Oskar Minkowski provided convincing evidence that only after total pancreatectomy did glucosuria appear, followed by death of an animal whose liver was extremely low in glycogen. His name remains one of the first among those who contributed to the understanding of the pathogenesis of diabetes mellitus and the involvement of insulin in this process [10]. Fig. 3, presents philatelic materials (postage stamps and small leaf) of Lithuania and Transkei country dedicated to this scientist [10, 11].

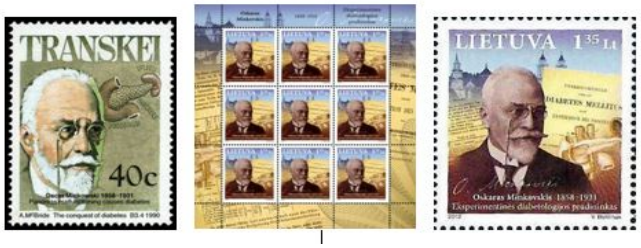

Figure 3: Philatelic materials devoted to Oskar Minkowski.

A great contribution to the study of insulin and the understanding of the pathogenesis of diabetes mellitus was made by such scientists as the Canadians Frederick Grant Bunting and Charles Herbert Best, as well as the Scottish scientist John McLeod. After the work of N. Paulescu in 1921 on the isolation of insulin, a year later, in 1922, Frederick Grant Bunting (1891-1941), Charles Herbert Best (1899-1978) and John James Richard McLeod (1876-1935) isolated the same substance and called it "isletin" - islet. Later its name was changed to "insulin. For the first time, this substance was administered to L. Thompson, a 14-year-old diabetic patient, at Toronto General Hospital in 1922. Lilly (Fig. 6) began commercial production and sale in 1923; in the same year, F.G. Bunting and C.G. Best received the Nobel Prize in Medicine for their discovery [12-25]. There is a considerable amount of collection material devoted to these scholars. First, in Fig. 4, philatelic materials devoted to them will be presented. These are both postage stamps, first-day envelopes (FD envelopes), postal blocks, cartomaxims, postal cards of different countries of the world [12-25].

Figure 4: Philatelic materials devoted to F.G. Bunting, C.G. Best, and J. McLeod.

A separate selection, in Fig. 5, there are commemorative medals dedicated to Nobel Prize winners, in the field of physiology and medicine, F.G. Bunting, C.G. Best and J. McLeod [3, 26-31,61].

Figure 5: Commemorative medals dedicated to F.G. Bunting, C.G. Best, and J. McLeod

In 1921 Frederick Bunting and Charles Best, doing research in John McLeod's laboratory at the University of Toronto, isolated a substance from the pancreas (later determined to include insulin) that lowered blood glucose levels in dogs with artificially induced diabetes. In 1922, the first patient, fourteen-year-old L. Thompson, suffering from diabetes, was injected with the pancreatic extract and thus saved his life [1-3,22,29]. In 1923, James Collip proposed a method of purification of the extract obtained from the pancreas, which later made it possible to isolate active extracts from the pancreas of pigs and cattle, allowing visible results. In 1923 Bunting and MacLeod received the Nobel Prize in Medicine for the discovery of this substance. In 1926, J. Abel and W. Du-Vigneault isolated this substance in crystalline form. A few years later Bernardo Alberto Husey (Husey) (1887-1971) (Fig. 6) demonstrated the antagonistic effect of the pituitary substance against insulin, which causes diabetes in animals, through injections of pituitary extracts. The substance was first approved by the FDA (Food and Drug Administration) in 1939. Frederick Sanger completely deciphered the amino acid structure of the hormone (1949-1954) [44]. In 1958, F. Sanger was awarded the Nobel Prize for his work in deciphering the structures of proteins and, most importantly, insulin. In 1963, artificially created insulin was obtained [44]. The first insulin suitable for humans was approved by the FDA in 1982 [32-35]. In the experiments of B.A. Usay (Usay), removal of the pituitary gland from a diabetic animal reduced the severity of diabetes, while injection of pituitary extract increased the severity of diabetes or caused a diabetic condition that had not previously existed. This interrelated hormonal effect on diabetes was clearly

demonstrated by B.A. Usai in the 1930s. His work was recognized by the Nobel Committee, and he shared the 1947 Nobel Prize in Physiology and Medicine with Carl and Getty Cory for their work on the catalytic conversion of glycogen. His discoveries stimulated the study of the hormonal feedback control mechanism, which is central to all aspects of modern endocrinology, and helped later workers establish the very important role of the pituitary as the "master coordinator" and master gland for hormones produced elsewhere [32-35]. There are postage stamps dedicated to the Nobel Prize winner (1947), in physiology and medicine, Bernardo Alberto Usai, as well as CPDs personally autographed by F. Sanger, dedicated to the twice Nobel Prize winner (1958, 1980), Frederick Sanger, shown in Fig. 6 [32-35,60].

Figure 6: Collection materials devoted to Bernardo Alberto Usai

The Danish scientist Professor Schack August Steenberg Krogh, Nobel Laureate in Physiology and Medicine (1920), "for his discovery of the mechanism of capillary lumen regulation," was also involved in the work of obtaining and industrializing insulin. Scheck August S. Krogh (1874-1949), was also involved in insulin research, primarily because his wife, Maria, with whom he was involved in scientific research, became ill with diabetes, and A. Krogh, as husband and as a scientist, did everything to solve this problem. He contributed greatly to the development of insulin research and production laboratories, collaborating with Novo nordisk, a world-renowned Danish company specializing in insulin production [36-39]. Fig. 7, presents a collection of materials about Scheck Augustus Steenberg Krogh, his wife Maria, and Novo Nordisk [36-38).

Figure 7: Collection materials on August Krogh and his wife Mary

Next, I would like to tell you about Hans Christian Hagedorn (Danish: Hans Christian Hagedorn), an outstanding Danish doctor of the first half of the 20th century, a scientist-pharmacologist, the founder of the insulin laboratory of Nordisk (Denmark), after whom the group of long-acting insulin preparations (neutral protamine Hagedorn or NPH) is named [40]. Together with pharmacist Birger Norman Jensen, he developed a technique for determining blood sugar levels, which received worldwide recognition and was named after the authors, the Hagedorn-Jensen method. After Hagedorn defended his doctoral thesis, in 1921, he met Nobel laureate August Krogh, whose wife was suffering from diabetes. During a trip to Canada, in 1922, August Krogh became acquainted with the first results of the clinical application of insulin discovered by Frederick Bunting and Charles Best. In order to introduce the new drug in Denmark, H. H. Hagedorn founded the "Nordisk" laboratory for the production of insulin. Since the successful extraction of insulin from animals, scientists in different countries have been working to improve the drug and the possibility of prolonging its action. In the early 1940s, Hagedorn and a group of scientists in Toronto, Canada, obtained an insoluble preparation of protamine-zinc-insulin. In 1946, based on protamine and porcine insulin in isophane, i.e. equal amounts, Hagedorn obtained a preparation stabilized with zinc ions, later named after him, Neutral Protamine Hagedorn (NPH - Neutral Protamine Hagedorn) [40]. Fig. 8 shows, in obverse and reverse, a commemorative, bronze Danish medal, minted, in memory of Hagedorn [40].

Figure 8: Commemorative medal in honor of Hans Christian Hagedorn

Dorothy Mary Crowfoot Hodgkin (1910-1994), English chemist and biochemist, professor, won the Nobel Prize in Chemistry in 1964 for her achievements in X-ray crystallography at Oxford University. She determined the molecular structures of penicillin, vitamin B12, and insulin [4-43]. Figure 9, shows collectibles dedicated to D. M.K. Hodgkin, including an envelope with the original of her personal signature [41-43].

Figure 9: Philatelic materials dedicated to Dorothy Hodgkin

Figure 10, is a collection of materials dedicated to a married couple of scientists, husband and wife Gertney, who contributed to the study of diabetes and the biochemical processes that occur in it and its treatment. Carl Corey and Gertie Corey, in the United States, served as professors in the Department of Pharmacology and later in the Department of Biological Chemistry at the University of Washington. They were nominated by the Nobel Committee, for their work in elucidating the synthesis and degradation pathway of glycogen, now known as the Cory cycle, which proceeds through the key intermediate α-D-glucose-1-phosphate, now known as Cory ester. Later, Gerty studied various diseases of glycogen accumulation and found a relationship to specific enzyme defects, in particular defects in the enzyme that breaks down glycogen, that lead to irreversible glycogen accumulation with short outer branches, one form of which is called, you guessed it, Cori disease. After Gerty's death, Carl did similar research on the clinical manifestations of glucose-6-phosphatase deficiency, called von Hirke disease (also glycogen accumulation disease) [45,62,63].

Figure 10: Collectibles dedicated to Carl and Gertney Corey

Rosalyn Sussman Yalow (1921-2011), in collaboration with Solomon Berson, was involved in the development of the method of radioisotope detection of biological blood components. Initially, they developed a method for the extremely sensitive detection of insulin in human plasma. The radioimmunological method developed became widely applicable to hundreds of other minor blood components, such as hormones, vitamins, and enzymes, which could not be measured before because of their low concentrations in the blood [47,49]. In 1950. R.S. Yalow began working with Solomon A. Berson. Combining Berson's knowledge of clinical medicine, physiology, and anatomy with R.S. Yalow's expertise in mathematics and physics, the two researchers began joint scientific experiments that lasted 23 years. They used radioisotopes to measure blood volume, study the distribution of serum proteins in body tissues, and diagnose thyroid disorders. Scientists soon became interested in diabetes mellitus, and research on this disease developed the radioimmunological method (RIM), which involved using radioactive substances to measure the content of various substances in blood plasma and

other body tissues [47,49]. At that time, insulin was quite available, and R.S. Yalow and S.A. Berson knew that it could be easily labeled with radioactive iodine. Radioactive labeling could be used to measure the rate at which insulin disappeared from the bloodstream (plasma) in diabetes by counting in a radioactive meter the radioactivity of plasma samples obtained at various intervals after the administration of radioactive insulin. It was believed that the intake of insulin from the pancreas in adults and children with diabetes was reduced and any insulin available was quickly utilized by the body. However, Yalow and Burson found that the rate at which insulin disappeared from plasma in such patients was unexpectedly low. They hypothesized that in adults with diabetes, antibodies to the foreign insulin molecule are formed, which inactivate insulin and lead to a slower release of insulin from the plasma. In 1959, R.S. Yalow and S.A. Berson published a description of RIM during their research on diabetes mellitus. Since that time, the method has been used in laboratories around the world to measure low concentrations of hormones and other substances in the body not previously determined. The method can also be used to determine substances in body fluids or tissues, to detect hepatitis virus in donated blood, for early cancer diagnosis and to establish the level of neurotransmitters (substances involved in nerve impulse transmission in synapses) or hormones in tissue or plasma [47,49]. In Figure 11, there are collection materials dedicated to the Nobel Prize winner in Physiology and Medicine, R.S. Yalow [45-49].

Figure 11: Philatelic materials devoted to R.S. Yalow

There are quite a lot of philatelic materials devoted to insulin, its discovery, crystal form and structural volumetric formula, represented on postage stamps, PACs, and postal blocks, of different countries of the world. A selection of philatelic materials, including postage stamps, PDAs, and postal blocks, devoted to insulin are shown in Fig. 12. [50-54].

Figure 12: philatelic materials devoted to the discovery and production of insulin

Also, there are philatelic materials that tell about the use of insulin by people of different age groups, and their everyday life, including physical training and sports. These materials are presented in Figure 13. [54-57].

Figure 13: Practical use of insulin by patients with diabetes mellitus in the reflection of philatelic materials [58].

Figure 13: philatelic materials of Finland on pigs, the source of pig insulin

Эта статья, является одной, из серии статей, посвящённых юбилейным датам в медицине, отмечаемым в 2021 году.

And, to conclude the article, Fig. 14 shows a Canadian $100 banknote, the reverse of which bears an image of a vial of the first insulin developed by Bunting and Best, with a working image of a woman scientist behind a microscope in her laboratory [59,60].

Figure 14: Canadian banknote and lottery ticket commemorating the creation of insulin and one of its authors

This article is one in a series of articles on medical anniversaries celebrated in 2021-2022.

Conclusions

1. This article, in a creative, non-standard way, presents interesting information dedicated to the 100th anniversary of the creation of insulin, illustrated, with a presentation of various means of collecting - philately, numismatics and bonistics, in all their completeness and diversity.
2. The materials of this article can be used for classes in the history of medicine, endocrinology and several other disciplines in medical and biomedical higher educational institutions.
3. The data presented in the article, including the extensive illustrative (collection) material, may be of interest not only to collectors, but also to teachers, university students, and all interested readers.

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