https://doi.org/10.46389/rjd-2022-1271
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2022; volume 29, issue 4, pages 485-490

Review

The fascinating history of insulin

Adela-Gabriela Ştefan [1], Adina Mitrea [2, 3], Ionela Mihaela Vladu [2, 4] *, Diana Clenciu [2, 3], Eugen Moţa [5], Maria Moţa [2], Constantin Ionescu-Tîrgovişte [6]

[1] Department of Diabetes, Nutrition and Metabolic Diseases, Calafat Municipal Hospital, Calafat, Romania

[2] Department of Diabetes, Nutrition and Metabolic Diseases, University of Medicine and Pharmacy of Craiova, Faculty of Medicine, Craiova, Romania

[3] Department of Diabetes, Nutrition and Metabolic Diseases, Clinical Municipal Hospital Philanthropy of Craiova, Craiova, Romania

[4] Department of Diabetes, Nutrition and Metabolic Diseases, County Clinical Emergency Hospital of Craiova, Craiova, Romania

[5] Department of Nephrology, University of Medicine and Pharmacy of Craiova, Faculty of Medicine, Craiova, Romania

[6] Department of Diabetes, Nutrition and Metabolic Diseases, University of Medicine and Pharmacy Carol Davila Bucharest, Bucharest, Romania

* Correspondence to: Ionela Mihaela Vladu, University of Medicine and Pharmacy of Craiova, Department of Diabetes, Nutrition and Metabolic Diseases, No. 2 Petru Rareş Str, 200349, Craiova, Romania. Phone: +40763670811; E-mail: ionela.vladu@umfcv.ro

Received: 26 September 2022 / Accepted: 4 November 2022

Abstract

This year marks 100 years since the administration of the first insulin injection, the discovery of insulin (101 years ago) representing a cornerstone in the history of medicine. This moment transformed insulin-dependent diabetes from a certain death sentence into a chronic condition associated with a high life expectancy. Tens of millions of lives or more have been saved this way. The Romanian Nicolae Paulescu contributed decisively to the discovery of insulin in 1921. In early 1922, Banting and Best administered insulin to humans for the first time, to Leonard Thompson – a 14-year-old child, his health improving considerably after the administration of purified insulin, by the Canadian team. In the same year, insulin production began in Indianapolis, later expanding throughout the world. In 1923, the Nobel Prize for Physiology or Medicine was awarded to Banting and MacLeod, for the discovery of insulin, but great controversies were triggered, not extinguished to this day. In an attempt to calm the spirits, Banting shared his prize with Best and Macleod with Collip. However, Paulescu remained excluded and died full of bitterness, being unable to accept the fact that fraud can also occur in science.

Keywords: Nicolae Paulescu, insulin, diabetes mellitus.

Introduction – the truth beyond the truth

Diabetes mellitus is a chronic non-communicable disease, its prevalence reaching epidemic proportions over the last years. Insulin treatment is probably the most complex chronic medical therapy, regarding dosage, as well as the timing and administration method, requiring individual, multifactorial adjustment.

This year we celebrate the 100th anniversary of the administration of the first insulin injection to humans, a moment that changed the history of diabetes and saved tens of millions of lives, together with the discovery of insulin just a year earlier. These events are among the most important medical discoveries of humanity. Since then, insulin has been widely prescribed as an antihyperglycemic agent in patients with diabetes mellitus [1]. The discovery of insulin thus miraculously transformed type 1 diabetes from a death sentence into a manageable chronic condition [2, 3], prolonging life for these people.

Regarding the discovery of the causes, as well as effective treatment options for diabetes mellitus, several scientists and researchers from many regions of the world have contributed, making huge efforts over numerous decades.

In 1869, the Romanian Nicolae C. Paulescu was born in Bucharest, a physician and researcher, and a great man of culture at the same time. He knew Latin and Greek, and French was like his second native language; he loved poetry, theater, music, piano playing and painting.

N.C. Paulescu studied medicine in Paris, where he worked with great personalities of the French medical world, starting the long journey of discovering insulin alongside Etienne Lancereaux, being one of the complex medical personalities of the time, ready for a great discovery. The first attempts to isolate the antidiabetic "pancreatic factor" were carried out as early as 1899. Paulescu obtained, in 1916, an aqueous pancreatic extract, with which he normalized blood sugar in dogs with diabetes; his experiences were interrupted because of the First World War but were intensively resumed in 1921.

The "Birth Certificate of Insulin" was published on August 31st, 1921, in the prestigious journal Archives Internationales de Physiologie, which appeared simultaneously in Paris and Liège in Belgium, arousing great interest in the medical world, who realized that this was a great discovery; the article is entitled "*Recherches sur le rôle du pancréas dans l'assimilation nutritive*", in which Paulescu extensively presented the results of his research [4].

The Romanian scientist Nicolae Paulescu contributed decisively to the discovery of insulin so that the initiation of insulin therapy became possible only a few months later, in early 1922.

The truth about, perhaps, the most important discovery of the 20th century must be known to the whole world. Pierre Lefèbvre, former President of the International Diabetes Federation, stated that the discovery of insulin began with the Romanian Paulescu and was completed by Banting and Best in Toronto in 1921 [5–7]. An extremely important moment took place in Montreal, Canada, in 2009, at the 20th Congress of the International Diabetes Federation, where the Spanish professor Alberto de Leiva Hidalgo, in a room full of thousands of participants, monumentally ended his presentation with the slide: "Priorities in the discovery of insulin: the case of Paulescu" [6, 8], thus highlighting the work of the Romanian scientist and basically, "the truth beyond the truth".

The fascinating history of insulin discovery

The pancreatic origin of diabetes mellitus was described for the first time by Etienne Lancereaux during 1877-1883, introducing the term "pancreatic diabetes". He described two types of diabetes: "thin" diabetes (currently known as type 1 diabetes mellitus) and "fat" diabetes (currently known as type 2 diabetes mellitus), a form that develops at older ages, being frequently associated with obesity, also called constitutional diabetes, this having "indefinite" evolution [8–10].

In 1889, researchers Oskar Minkowski and Joseph von Mering discovered completely by accident, while performing a total pancreatectomy with the aim of evaluating the role of the exogenous pancreas, the fact that diabetes mellitus develops after pancreatectomy, reconfirming the role of the pancreas in the occurrence of this disease [8–11]. Minkowski fed pancreatectomized dogs with fresh pancreas, thus trying to treat diabetes, but he did not get any results. In 1890, however, he made a dried extract from the pancreas, calling it "pancreatin". Moreover, Emmanuel Hédon used the cross-circulation between a pancreatectomized dog and a healthy one, thus finding a reduction in blood sugar in dogs with diabetes mellitus. As a result of this important research, numerous attempts were initiated to extract and identify the pancreatic hormone [10]. A few years later, in 1909, Eugene Opie noted the presence of hyaline degeneration of the islets of Langerhans among patients with diabetes mellitus, a discovery confirmed a year later by Edward Sharpey-Schafer; in 1916, he described in detail the ability of the pancreatic islets to secrete a substance, which we all know today under the name of "insulin" [9, 11, 12]. Although a number of researchers have tried to isolate a product from the pancreas that could be administered to humans in order to treat diabetes mellitus, none of them succeeded before Nicolae Paulescu, who, after obtaining the pancreas extract, realized that purification was needed in order to be administered to humans. However, the contribution of each of them is indisputable. The history of insulin discovery is thus fascinating both by the way it was made and by the destiny it had [13].

Paulescu's place in the history of insulin discovery

On the ground of experimental failures and the intuitions of other researchers, Nicolae Paulescu developed his creative activity. The great scientist, being

https://doi.org/10.46389/rjd-2022-1271

prepared for an important medical discovery, began the journey alongside Lancereaux in 1899, making the first attempts to isolate the pancreatic diabetogenic factor, initiating together with Professor Dastre from the Sorbonne University the first studies regarding the internal secretion of the pancreas [5, 13]. Paulescu had to return home in 1901, where he founded the Department of Physiology at the University of Medicine in Bucharest, being actively involved in various other research projects, such as the physiological role of insulin; he developed a new method of trans-temporal approach to the pituitary gland, later being widely used after Harvey William Cushing described it as the most important achievement in this field [13]. All these studies, however, postponed the continuation of the project related to the discovery of insulin.

In 1911, Paulescu published the results of his research regarding the role of the supposed endocrine secretion in restoring liver glycogen [10, 13–15], a phenomenon later called "incretin factor". A year later, he describes "Diabetic Pancreatic Insufficiency" in the third volume of the "*Lancereaux-Paulescu Medicine Treatise*" [6, 16]. He thus went through the stages of the great discovery in a period of over 22 years.

The insulin discovery was made in the laboratories of the Department of Physiology of the Faculty of Medicine in Bucharest; during 1914-1916, Paulescu developed a method of total pancreatectomy in dogs, thus inducing diabetes mellitus. In 1916, the Romanian scientist isolated the pancreatic extract he named "pancrein", a hormone that was proven to reduce blood sugar, glucosuria and ketonuria in dogs with diabetes. The research was, unfortunately, interrupted due to the First World War, until 1920, when Paulescu published, for the first time, his work of decades, in French, in the second volume of the "*Traité de Physiologie Médicale*", proving not only the cause of diabetes but also the possibility of treatment of this disease [6, 8, 10, 17, 18]. In the chapter dedicated to diabetes mellitus, clinical, biochemical, morphopathological and etiopathogenetic data were presented, as well as his personal research regarding this condition; Paulescu demonstrated exceptional qualities as a physiologist and clinician. He described a series of previously unknown or little-known data, inducing diabetes in animals and treating them by intravenous administration of a pancreatic extract. He highlighted hyperglycemia, glucosuria and the presence of blood and urinary ketone bodies, he correlated the dose of pancreatic extract with its action, thus describing hypoglycemia. However, it is extremely important that he studied data related to the onset of insulin action, the action duration, and the reappearance of hyperglycemia symptoms [6].

In 1921, Paulescu made a synthesis of his research, presenting it in four communications at the meetings of the Society of Biology in Bucharest, later published in Paris in *Comptes rendus des séances de la Société de Biologie et de ses filiales*, in July, the entire scientific world realizing at that moment the monumental discovery [6, 19]. In August 1921, the Romanian scientist presented an extensive work in the journal Archives Internationale de Physiologie, which was published simultaneously in Paris and Liège, the synthesis entitled "*Recherche sur le rôle du pancréas dans l'assimilation nutritive*" being considered "the birth certificate of the pancreine" [5, 8–10, 19–21]. It should be noted that no work of the Canadian research group had been published to that date, their work being published starting in 1922.

On April 10th, 1922, Nicolae Paulescu obtained Patent No. 6254, entitled "*La pancréine et le procédé de sa fabrication*" [8, 22, 23].

The 1923 Nobel Prize in Physiology or Medicine

On May 17th, 1921, Banting and Best began the research project on the pancreas in MacLeod's laboratory, the resulting product being named "isletin" [9, 23–28]; that same month, Paulescu completed the fundamental work on the discovery of insulin. The two Canadian researchers prepared a pancreas extract that reduced the level of glucose, decreased the production of ketone bodies, but also the catabolic effects specific to type 1 diabetes mellitus, all these results being published starting in 1922 [6, 29], obviously after Paulescu's publications [5].

On January 11th, 1922, Banting and Best administered insulin for the first time to a child with diabetes mellitus, Leonard Thompson, aged 14 years old, who was expected to die at the time. However, the weakly purified pancreas extract produced two abscesses at the site of the administration and the injection of another dose of insulin was interrupted. The Canadian team was joined by Collip to try to purify the product in order to reduce the death rate and the risk of abscesses. The insulin extraction procedure was successful only a few days later [6, 10, 21, 30, 31]. Therefore, insulin was administered again to Leonard Thompson on January 23rd, 1922, as well as during the following period, without adverse reactions. His health condition improved considerably, with favorable evolution regarding the value

of blood sugar, glucosuria and ketonuria [6, 29–33] and the administration was continued for another 13 years until Thompson died of pneumonia at the age of 26 years old [6, 9, 10, 12, 21, 34]. The results were presented by Macleod on May 3rd, 1922, in Washington DC and were published later that same year [6, 29, 31]; the huge role of the Canadian team regarding insulin purification and its administration to humans, without adverse reactions being more than obvious, but not regarding the discovery of insulin. The Canadian researchers were aware of Paulescu's work regarding the effects of pancreatic extract on carbohydrate metabolism, but also on protein and lipid metabolism, being cited in their first publications. Thus, the role of the Canadian team in insulin purification, its first administration to humans, but also the immense role played by the vision and prestige of the University of Toronto, which quickly disseminated the importance of insulin therapy, gathered around researchers, great medical personalities, pharmaceuticals companies, must be recognized, so that the access of patients with diabetes to insulin therapy quickly became a reality [6, 27, 35].

In 1922, the Eli Lilly company started insulin production in Indianapolis in collaboration with the University of Toronto, becoming the first insulin producer in the world [9, 10, 36]. The chemist of the Eli Lilly company, Walden, contributed to the refinement and purification of the pancreas extract, this being a very important step for the mass production of "Iletin" as the insulin produced by Lilly was named, patients from all over the world benefiting from this treatment [9, 21, 37, 38]. The Eli Lilly company received the right to manufacture in South and North America and Connaught in Canada. In 1923, insulin production began in Nordisk Insulinlaboratorium in Denmark, the company being later named Novo Nordisk [9, 12, 21, 37, 38]. Also, in 1923, the German company Hoechst started producing insulin [9, 12, 39]. The phenomenon started spreading in 1924 in Hungary, Argentina and Australia [9, 12]. During the next period, huge efforts were made in order to obtain pure insulins, increasing the quality of life of patients with diabetes and saving tens or perhaps hundreds of millions of people.

In 1923, Banting and MacLeod received the Nobel Prize for Physiology or Medicine [40]. However, great controversies were triggered, not extinguished even 100 years later, Best, Collip and Paulescu being excluded. To calm the spirits, Banting shared the prize money with Best and Macleod with Collip, but not the glory [6, 12, 29, 37, 41, 42]. However, Paulescu remained excluded. According to Alfred Nobel's decision, the prize is awarded only for an important discovery and cannot be shared by more than three people who must be alive at the time of the award [27].

Moreover, the regulations of the Nobel Foundation do not allow either the withdrawal or the completion of the list of prize winners [6]. The Romanian professor Ionel Pavel tried for over two decades to restore the truth about the discovery of insulin, partially succeeding when the International Diabetes Federation and the Nobel Foundation recognized Paulescu's merits through correspondence with him, but they never widely informed the scientific community [6, 43]. Professor Pavel handed over the baton to the academician Constantin Ionescu-Tîrgovişte to continue the fight to find out the truth and to honor the Romanian scientist N.C. Paulescu [6].

Unfortunately, Paulescu could never accept the fact that fraud can also occur in science and he died full of bitterness, but not before warning the scientific community about the danger determined by the development of an immoral and aggressive attitude in scientific research [6].

Conclusions

The insulin discovery is more than a landmark in the history of medicine, it is a stage that represents a real lesson with ethical and historical implications. Although the context was not favorable for Paulescu, he played a crucial role in the discovery of insulin, an event that transformed and saved the lives of tens of millions of patients over time. The idea of discovering insulin and saving the lives of patients with diabetes excited the medical world and researchers, but not only them, being regarded as a miracle. However, the nominations for the Nobel prize were rushed, without studying, according to the regulations, who had the essential contribution to the true insulin discovery. On the other hand, no one proposed the Romanian scientist N.C. Paulescu for the Nobel prize, this being a mandatory condition, although his role could have been investigated more carefully and a proposal could have been induced. The celebration of the centenary of insulin discovery in 2021 could have restored the truth, even with a delay; however, this official fact was not realized, but dozens of articles were published, most of them recognizing the capital role of Paulescu. "There is in insulin enough glory for all, both for Paulescu, the discoverer of insulin and for the meritorious Canadian Team, that put into practice this great discovery".

https://doi.org/10.46389/rjd-2022-1271

Conflict of interest

The authors declare no conflict of interest.

References

1. Mathieu C. Minimising hypoglycaemia in the real world: the challenge of insulin. Diabetologia 64: 978-984, 2021.
2. Nathan DM. Realising the long-term promise of insulin therapy: the DCCT/EDIC study. Diabetologia 64: 1049-1058, 2021.
3. Batista TM, Haider N, Kahn CR. Defining the underlying defect in insulin action in type 2 diabetes. Diabetologia 64: 994-1006, 2021.
4. Paulescu NC. Recherche sur le rôle du pancréas dans l'assimilation nutritive. Arch Int Physiol 17: 85-109, 1921.
5. Mota M, Catrinoiu D. The Nobel Prize for the insulin discovery. Diabetes Res Clin Pract 180: 108950, 2021.
6. Moţa M. Locul lui Paulescu în istoria descoperirii insulinei. In: Diabet zaharat 2021. Centenarul descoperirii insulinei (1921-2021). Mihalache DD (ed). Viaţa medicală: Medichub Media, Bucharest, pp 12-14, 2021.
7. Lefèbvre P. L'insuline: 1921-1996 [Insulin: 1921-1996]. Rev Med Liege 51: 88-89, 1996.
8. Ionescu-Tirgoviste C, Buda O. Nicolae Constantin Paulescu: the first explicit description of the internal secretion of the pancreas. Acta Med Hist Adriat 15: 303-322, 2017.
9. Moţa M, Ştefan AG. Istoria insulinoterapiei. In: Diabet zaharat 2021. Centenarul descoperirii insulinei (1921-2021). Mihalache DD (ed). Viaţa medicală: Medichub Media, Bucharest, pp 28-32, 2021.
10. Ionescu-Tîrgovişte C. Diabetul zaharat: epoca modernă dintr-o perspectivă istorică. Practica Medicală 3: 217-225, 2015.
11. Alam S, Eqbal K, Patel I, Mulla I, Ansari S, Ayesha B. The history of diabetes: From olden days to discovering insulin. International Journal of Unani and Integrative Medicine 1: 25-28, 2017.
12. Vecchio I, Tornali C, Bragazzi NL, Martini M. The Discovery of Insulin: An Important Milestone in the History of Medicine. Front Endocrinol (Lausanne) 9: 613, 2018.
13. Ionescu-Tîrgovişte C. Fascinanta istorie a descoperirii insulinei. In: Diabet zaharat 2021. Centenarul descoperirii insulinei (1921-2021). Mihalache DD (ed). Viaţa medicală: Medichub Media, Bucharest, pp 8-10, 2021.
14. Paulescu NC. Sur la formation du glycogène dans la foie, par suite d'injections de divers sucres, dans la veine porte. Annales de Biologie, Paris, v I, pp 228, 1911.
15. Paulescu NC. Origines du glycogène. C R Seances Soc Biol Fil, Paris, 1913.
16. Lancereaux - Paulesco. Traité de Médecine. Bailleres&Fils, Paris, 1912.
17. Trăilescu A, Şerban V. Diabetul zaharat: istoric şi importanţă. In: Tratat român de boli metabolice vol 1. Şerban V (ed). Editura BrumaR, Timişoara, pp 63-68, 2010.
18. Paulescu NC. Traité de Physiologie Médicale vol II: Phenomenes de Nutrition. Cartea Românească, Bucharest, 1920.
19. Paulesco NC. "1.Action de l'extrait pancréatique injecté dans le sang chez un animal diabétique. 2.Action de l'extrait pancréatique dans le sans d'un animal normal. 3.Influence de la quantité de pancréas employée pour préparer l'extrait injecté dans le sang diabétique. 4.Influence du laps de temps écoulé depuis l'injection intraveineuse de l'extrait pancréatique chez un animal diabétique. Communications faites à la branche de Bucarest de la Société de Biologie (séance du 23 juillet 1921)". C R Seances Soc Biol Fil 85: 555-558, 1921.
20. Paulesco NC. Action de l'extrait pancreatique injecté dans le sang, chez un animal diabétique. C R Seances Soc Biol Fil 85: 555-559, 1921.
21. Brink SJ. Insulin Past, Present and Future: 100 Years from the Nobel Prize. Accessed at https://cdn.ymaws.com/www.ispad.org/resource/resmgr/1__ispad_resources_new_/resources_/2021/brink_2021__insulin_past_pre.pdf on 14th of November 2022.
22. Paulescu NC. La Pancréine et le procéde de sa fabrication. Brevet d'invention Ministère de l'Industrie et du Commerce de Roumanie No. 6254 du 10 Avril, 1922.
23. Dorchy H. Nicolae Constantin Paulescu: co-découvreur oublié de la découverte de l'insuline il y a 100 ans. Rev Med Brux 43: 74-80, 2022.
24. Eknoyan G, Nagy J. A history of diabetes mellitus or how a disease of the kidneys evolved into a kidney disease. Adv Chronic Kidney Dis 12: 223-229, 2005.
25. Barach JH. Historical facts in diabetes. Ann Med Hist 10: 387-401, 1928.
26. Macleod JJR. History of the researches leading to the discovery of insulin. Bull Hist Med 52: 295-312, 1978.
27. Rydén L, Lindsten J. The history of the Nobel prize for the discovery of insulin. Diabetes Res Clin Pract 175: 108819, 2021.
28. Fralick M, Zinman B. The discovery of insulin in Toronto: beginning a 100 year journey of research and clinical achievement. Diabetologia 64: 947-953, 2021.
29. Banting FG, Best CH, Collip JB, Campbell WR, Fletcher AA. Pancreatic Extracts în the Treatment of Diabetes Mellitus. Can Med Assoc J 12: 141–146, 1922.
30. Banting FG, Best CH. The internal secretion of the pancreas. J Lab Clin Med 7: 251-256, 1922.
31. Brink SJ. Insulin Past, Present, and Future: 100 Years from Leonard Thompson. Diabetology 3: 117-158, 2022.
32. Bliss M. The Discovery of Insulin. University of Chicago Press, Chicago, 1982.
33. Marshall SM. Celebrating 100 years of insulin. Diabetologia 64: 944-946, 2021.
34. Collip JB. History of the discovery of insulin. Northwest Med 22: 267-273, 1923.
35. Bolli GB, Porcellati F, Lucidi P, Fanelli CG. The physiological basis of insulin therapy in people with diabetes mellitus. Diabetes Res Clin Pract 175: 108839, 2021.
36. Collip JB. The original method as used for the isolation of insulin in semipure form for the treatment of the first clinical cases. J Biol Chem 55: 11-41, 1923.
37. Rosenfeld L. Insulin: discovery and controversy. Clin Chem 48: 2270-2288, 2002.
38. Hegele RA, Maltman GM. Insulin's centenary: the birth of an idea. Lancet Diabetes Endocrinol 8: 971-977, 2020.
39. Bosnyak Z, Korn M, Bielohuby M, Wohlfart P, Tennagels N. Nearly a Century of Insulin at Sanofi: Looking Back Over the Decades of Production and Development. Pediatr Endocrinol Rev 17(Suppl 1): 161-169, 2020.
40. Chast F. La découverte de l'insuline. Ann Pharm Fr 80: 782-802, 2022.

41. Sims EK, Carr ALJ, Oram RA, DiMeglio LA, Evans-Molina C. 100 years of insulin: celebrating the past, present and future of diabetes therapy. Nat Med 27: 1154-1164, 2021.
42. Bliss M. The history of insulin. Diabetes Care 16 Suppl 3: 4-7, 1993.
43. Pavel I. Corespondenţă în sprijinul priorităţii lui N.C. Paulescu în descoperirea insulinei. Editura Academiei Republicii Socialiste România, Bucharest, 1986.

https://doi.org/10.46389/rjd-2022-1271