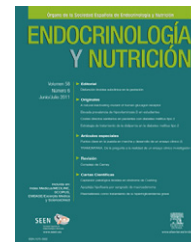




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EDITORIAL

The discovery of insulin: Continued controversies after ninety years[☆]

El descubrimiento de la insulina: continúan las controversias después de noventa años

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The introduction of insulin into the treatment of diabetes mellitus had a clinical and social impact similar to that of the introduction of antibiotic therapy. By the middle of the 20th century, patients with onset of diabetes mellitus (DM) at 10 years of age had prolonged their life expectation by 34 additional years, while the life expectations of patients diagnosed at 30 and 50 years of age had increased by 26 and 8 years, respectively.¹

On October 25, 1923, the 19 professors of the Karolinska Institutet decided by secret vote to award the Nobel Prize in Physiology and Medicine to Frederick Grant Banting and John James Richard Macleod, of the Department of Physiology, Toronto University, for the discovery of insulin, reported in 1922. Banting was nominated by GW Crile (Cleveland), FG Benedict (Boston), and August Krogh; Macleod was proposed by GN Stuart (Cleveland), and also by August Krogh.² This decision prompted claims by the German Georg Ludwig Zuelzer, the Americans Ernest Lyman Scott and John Raymond Murlin, and the Romanian Nicolae Constantin Paulescu. Years later, Charles Herbert Best, a collaborator of Macleod and Banting, would also claim the discovery.

Pioneering work conducted between 1890 and 1919 in the treatment of experimental diabetes by administering pancreatic extracts or subcutaneous implants of pancreatic tissue to pancreatectomized dogs had met with

negative results, with some exceptions.³ Rennie and Fraser, researchers at the Aberdeen Royal Infirmary, investigated the effects of islets of Langerhans from *Lophius piscatorius* and other teleost fishes, which are unique in that their islets are located separately from the pancreas. From 1902 to 1904, these Scottish researchers administered extracts from these islets to a group of five diabetic patients, by the oral route in some cases and by the hypodermic route in others. Glycosuria only disappeared in the last case, a 59-year-old female, but the researchers themselves finally attributed such disappearance to a better compliance with diet.⁴

Georg L. Zuelzer started his studies with pancreatic extracts by investigating the antagonism between the adrenal medulla and endocrine pancreas in rabbits, and estimating the potency of the pancreatic extract based on the amount of extract able to neutralize hyperglycemia secondary to administration of one unit of epinephrine (1907). He subsequently investigated the reduction in urinary glucose excretion in pancreatectomized dogs with promising results. On June 17, 1906, Zuelzer first administered a subcutaneous injection of a solution containing 3 grams of bovine pancreatic extract to a 50-year-old male diabetic patient, with known disease for at least 3 years, who had undergone major amputation of his left lower limb below the knee. While administration of the pancreatic extract was transiently associated with an apparent clinical improvement, the patient died on June 30, 1906. A 6-year-old boy admitted to hospital for malnutrition, glycosuria, and ketosis was a special case. On July 14, 1907 Zuelzer administered to him intravenously an emulsion containing 1 g of pancreatic extract. An elevation of body temperature to 38.4 °C,

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associated with vomiting, occurred immediately after injection; however, the patient showed clinical improvement, weight increase, and the disappearance of ketonuria. The same occurred on August 1, 1907 following parenteral administration of one gram of pancreatic extract, leading to almost complete disappearance of ketonuria. Unfortunately, the boy died after hospital discharge. Zuelzer also treated a heterogeneous series of patients with diabetes and noted a reduction or disappearance of glycosuria, and ketonuria when applicable, but such effects were associated with adverse effects including high fever, chills, vomiting, and sweating.⁵ In 1909, in compliance with the recommendation by O. Minkowski, J. Forschbach repeated the experiments of Zuelzer at the Breslau Clinic and confirmed the observations reported by the Berliner physician: "First (Zuelzer) to produce, successfully, from the pancreas a preparation that eliminates sugar excretion in a shorter or longer period by intravenous administration".⁶ However, Forschbach decided to discontinue treatments with pancreatic extract because of the side effects reported. In 1911, Hoffman-La Roche facilitated Zuelzer's creation of a small experimental laboratory, as well as his application for a patent of the pancreatic extract, which the German researcher called *acomatol*, adequate for the treatment of diabetes mellitus. Patent 1027790 for *acomatol* was granted on May 28, 1912. The subsequent purification process of the alcoholic extract intensified protein precipitation under vacuum and at low temperature. The disappearance of glycosuria and severe seizures, not previously seen, occurred in the pancreatectomized dogs studied. Unfortunately, Zuelzer continued to monitor glycosuria and ketonuria, but did not perform blood glucose measurements, which would have undoubtedly shown the relationship between hypoglycemia and seizures, which were instead attributed to contamination by a foreign substance incorporated into the extraction process. Subsequent observations in August 1914 showed that intravenous administration of extract decreased blood glucose to 17 mg/dL. The hypoglycemic effect only lasted a few hours and required intravenous administration of the preparation every 3 h.

It is, therefore, not surprising that Zuelzer protested after the Nobel Prize was awarded to Banting and Macleod: "I am now entitled to state my claim to priority in this discovery. . . because in the German literature, partially from ignorance, the role that fell to me in the discovery was not always perceived quite correctly" (*Medizinische Klinik*, 1923;47:15551-2). Georg Zuelzer emigrated to the United States in 1934 as a Jewish refugee, and practiced medicine there until he died in a New York old people's home at 79 years of age.

Ernest L. Scott, a researcher at the Department of Physiology of Columbia University, argued in a letter he sent to the editor of *JAMA* in 1922 that the administration of pancreatic extract from adult animals reported by Banting and Best⁷ reproduced his own experiments.⁸ E.L. Scott prepared aqueous and alcoholic extracts of animal pancreas and administered them to pancreatectomized dogs by the intravenous route. He observed some transient reduction in glycosuria, which he attributed to a toxic rather than therapeutic effect upon confirmation of the adverse reactions previously reported by Zuelzer and other researchers.⁹ Influenced by Leschke's (1910) and Hédon's (1911) reports,

Scott used higher temperature and alcohol concentrations in an attempt to destroy the hypothetical activity of digestive pancreatic enzymes to destroy internal pancreas secretion. His additional experiments with cats not only showed no hypoglycemic action of the pancreatic extract, but also revealed an increase in blood glucose levels by approximately 20%.¹⁰

John R. Murlin and Benjamin Kramer, researchers at the Laboratory of Physiology of Cornell University, initially thought that the decreased urinary glucose excretion found with their preparations containing pancreatic extract and a dual extract of pancreas and duodenal mucosa was due to changes in renal tubule permeability, rather than to a hormonal effect.¹¹ Years later, they noted that the disappearance of glycosuria ran parallel to a decrease in blood glucose levels and concluded that the pancreatic extract actually contained the internally secreted active ingredient.¹² Pancreatic extracts caused tissue toxicity with ulceration at the injection sites, resulting in death in some dogs.¹³ Murlin published, in cooperation with C. Sutter, the clinical report of a diabetic patient with ketosis treated at the Rochester General Hospital in July 1922 with pancreatic extract, which was administered through a gastrointestinal catheter and by the oral and subcutaneous routes. Only in this latter case could glycosuria and ketonuria be decreased. On July 26, 1922 blood glucose decreased from 513 mg/dL to 241 mg/dL.¹⁴

Israel S. Kleiner and S.J. Meltzer, from the Department of Medical Research of the Rockefeller institute, investigated the effects of intravenous injection of a pancreas emulsion into intact and pancreatectomized animals, and published their results in 1915. They reported that, in the group of healthy animals, venous blood levels became equal to those seen before glucose administration at 90 min of infusion of isotonic glucose. In untreated pancreatectomized animals, however, glucose levels 90 min after glucose administration were more than two times higher than the original value. In a third group of animals, the addition of pancreatic extract allowed for a very close to normal response. These experiments suggested that internal pancreas secretion contributed to the rapid disappearance of circulating glucose.¹⁵ In 1919, Kleiner published a set of experiments conducted between 1915 and 1919 supporting the existence of internal pancreas secretion and showing beneficial effects for the treatment of experimental diabetes. Intravenous administration of pancreatic emulsion achieved a highly significant blood glucose reduction in most of the 16 dogs with diabetes after pancreatectomy which were investigated. Submaxillary gland emulsions, which were experimentally administered to the control group by the intravenous route, did not change blood glucose levels. Surprisingly, no relevant toxic effects occurred, which was attributed to the high dilution and slow administration of the pancreatic extract. At the end of the manuscript discussion, Kleiner commented: "The fact that these pancreas emulsions lower blood sugar in experimental diabetes without marked toxic effects indicates a possible therapeutic application in human beings. . . Finally, the search for the effective agent or agents, their purification, concentration, and identification are suggested as promising fields for further work".¹⁶ Unfortunately, Kleiner left the Rockefeller Institute, and as a result, this interesting research area, in 1919.

Nicolae C. Paulescu (1869–1931) started his research on endocrine pancreas secretion in the Hôtel Dieu (Paris), in the laboratory of the Department of Internal Medicine (Prof. Etienne Lancereaux), and at the Sorbonne (Albert Dastre). At the age of 31 years he returned to Bucharest to organize the Laboratory of Experimental Physiology. Paulescu made significant progress in surgical procedures for pancreatic ablation. During his enforced retirement due to the wartime occupation of Bucharest by German troops, he wrote, and later published in French in 1920, a text of medical physiology (*Traité de Physiologie Médicale*) describing in detail the effects of the administration of pancreatic extracts to pancreatectomized dogs.¹⁷ In 1921, Paulescu presented papers at meetings of the Romanian Society of Biology on April 21 (in Iasi), May 19 (in Bucharest), and June 23 (in Cluj). This resulted in the publication of a series of studies in the issue of July 23, 1921 of *Comptes rendus des Séances de la Société de Biologie*.¹⁸ In his initial experiments, he reported the effects caused by complete pancreas ablation in dogs (elevated levels of glucose, urea, and ketone bodies in blood and urine) and the temporary suppression of hyperglycemia which occurred after the injection of pancreatic extract into the external jugular vein (and also into portal vein branches), followed by hypoglycemia and the suppression of glycosuria. In seven subsequent experiments, Paulescu showed the resultant decrease in blood and urine urea levels, ketonemia, and ketonuria, the duration of the biological actions of the pancreatic extract (almost immediate start of action, peak at 2 h, and disappearance at 12 h), and the dose-dependent nature of the effects observed (depending on the weight of the pancreatic fragment used to obtain the extract). These effects were also reproduced in non-diabetic animals. On August 31, 1921, Paulescu published a long article (accepted on June 22), entitled “*Recherche sur le rôle du pancréas dans l’assimilation nutritive*”, in the journal *Archives Internationales de Physiologie*. There, he reported multiple experiments illustrating the hypoglycemic effect of the pancreatic extract, the reduction in glycosuria and ketonuria in pancreatectomized dogs, and the induction of hypoglycemia in normal dogs.¹⁹ The metabolic effects of the administration of pancreatic extract were not seen in control experiments (using saline, splenic extract, and intraspinal injection of sodium nucleate). Paulescu made unsuccessful efforts to purify the pancreatic extract in order to avoid the side effects, consisting mainly of febrile accesses and local swelling at the injection site,²⁰ and showed in a limited number of diabetic patients that the extract was effective when administered by a parenteral (intravenous and subcutaneous) route, but had no effect when it was administered orally or through an intestinal cannula.²¹ He called pancrein the active pancreatic extract, for which he filed a patent application to the Romanian government on April 10, 1922.²²

On February 5, 1922, Frederick G. Banting and Charles H. Best published the article “The internal secretion of the pancreas” in *The Journal of Laboratory and Clinical Medicine*.²³ The results reported were essentially the same as those previously published by Zuelzer, Kleiner, and Paulescu. The authors administered at least 75 doses of extract from “degenerated pancreas” (in the surgical procedure used, following Barron, they tied the pancreatic ducts so that supposed degenerative changes in acinar

tissue, attributable to trypsinogen and/or its derivatives, would not affect the pancreatic islets). The “complete degeneration of exocrine tissue” was not completed until at least 10 weeks had elapsed. In pancreatectomized dogs, the “extract of degenerated pancreas” caused partial reductions in glucose levels in blood and urine. The authors therefore felt justified in stating that this extract contained internal pancreas secretion. Banting and Best used the Myers-Bailey method, reported in 1916, to estimate glucose levels. The administration of a hepatic or splenic extract using a similar protocol, or of a heat-treated fresh pancreatic extract, did not result in changes in glycemia and glycosuria. Intrarectal administration, as an alternative to intravenous administration, was also ineffective. The Barron hypothesis, accepted by Macleod and Banting,²⁴ ignored the fact that Heidenhein had already demonstrated that fresh pancreas extracts had no proteolytic activity and contained a zymogen which would only generate an active ferment under various circumstances.²⁵ Langley, Bayliss, and Starling had confirmed this finding by showing that the proteolytic enzyme trypsin was present in fresh animal pancreas as an inactive precursor (trypsinogen).²⁶ Because of the pessimism of the first few months, in which the mortality rate of the operated animals was high, and they experienced extreme difficulty in inducing experimental diabetes in animals, Banting and Best decided on August 3, 1921 both to replace the Hédon procedure and to perform pancreatectomy. They subsequently developed extracts with a higher activity because they were obtained from fetal sources and used new procedures (discontinuation of ligation of pancreatic ducts, acidulation of the alcoholic extract, washing with toluol, use of the Berkfeld filter). Despite such changes, the pancreatic extract still contained significant concentrations of impurities, including an excess content of protein, which caused the occurrence of “sterile abscesses” at the injection site. Banting could not calm the anxiety that caused him to delay in starting clinical trials. Despite the initial refusal of Prof. Duncan Graham, Head of the Department of Internal Medicine of the Toronto General Hospital (TGH), to authorize Frederick Banting to have direct contact with inpatients, mediation by Macleod allowed for administration of the first dose of pancreatic extract prepared by Banting to an admitted patient. On January 11, 1922 the resident physician Ed Jeffrey obeyed the order of the consultant physician Walter Campbell, coordinator of the medicine hospitalization ward of TGH, to administer a 15 mL dose of the pancreatic extract of Banting (a turbid, light brown fluid), divided in two 7.5 mL injections, one in each buttock, to the patient Leonard Thompson, a 14-year-old boy diagnosed with DM in December 1919. Leonard had been admitted to the TGH on December 2, 1921, as a charity patient. He was on the standard 450 kcal dietary therapy, including fluid (fat-free broth, water, clear tea), 50 g of lean meat, vegetables, and fruit, with a total carbohydrate provision of approximately 100 g. The patient was emaciated and had extreme glycosuria, severe ketonuria, hypotension, and a urine output of approximately 4 L in 24 h. Response to administration of the pancreatic extract consisted of reductions in blood glucose from 440 to 320 mg/dL and in 24-h glycosuria from 92 to 84 g. Ketonuria remained unchanged. A “sterile abscess” rapidly developed in one of the injection areas. The experience was considered a clinical failure,

and it was decided not to administer additional doses of the preparation. James Bertram Collip, a 29-year-old doctor of biochemistry and professor at Alberta University, was at the time in Toronto as an assistant professor on a sabbatical supported by the Rockefeller Foundation. At Banting's request, Macleod asked James B. Collip for help in extract development. Collip started to work in his own laboratory on December 12, 1921. From the beginning, Collip used calf pancreatic extracts. On the evening of January 19, 1922 Collip made a crucial observation: the alcohol concentration limit that determined precipitation of the active ingredient in the extract was higher than 90%. Using this threshold, he was able to remove most protein contaminants, which precipitated at concentrations lower than 90%. He thus achieved isolation of the active ingredient, still with impurities, but with a much higher potency as compared to previously tested preparations.²⁷ The Collip extract was first administered to Leonard Thompson on January 23, 1922 and caused an immediate clinical improvement. Blood glucose decreased from 520 to 120 mg/dL, glycosuria from 71 to 9 g in 24 h, and ketonuria disappeared. The patient experienced a clearly improved well-being, recovering his mobility and activity. This was the first successfully treated patient. In February, 6 patients were treated using the same protocol as for Leonard Thompson, with successful results in all cases. The administration protocol of the Collip extract was directly supervised by W.R. Campbell and A.A. Fletcher. Patients were maintained on a constant diet. Blood glucose was measured by the Folin-Wu method, glycosuria by the Benedict method, ketone bodies by the Van Slyke procedure, and respiratory quotient using the Tissot-Haldane method. The results achieved were: a dramatic decrease in blood glucose, elevation of the respiratory quotient, substantial symptom improvement, a marked reduction or even disappearance of glycosuria, the abolition of ketonuria, increased muscle strength and the general well-being and vigor of the patients. The preliminary report first appeared in the March issue of the *Canadian Medical Association Journal*, which had little dissemination outside Canada but guaranteed immediate publication.²⁸

Joseph Pratt, Professor of History of Medicine at Harvard University, stated in 1954 that Banting and Best had not advanced our understanding of the pancreatic extract beyond that achieved by Zuelzer in 1908. Both the pancreatic extract of Zuelzer and that of Banting and Best had a similar toxicity that ruled out its use for treatment of patients. For Pratt, it was the expertise of Collip that actually led to the advance of the Toronto team in the therapeutic use of insulin.²⁹ In January 1922, the researchers of Toronto University signed a cooperation agreement with Connaught Antitoxin Laboratories, and on April 12, 1922 the research team and J.G. Fitzgerald proposed to the university a patent to be registered under the names of Best and Collip. They gave the pancreatic extract the final name of insulin, being unaware of the fact that the Belgian J. De Meyer had already proposed in 1906 the name of "insuline" and E.A. Sharpey-Schafer had proposed the name of "insulin" in 1916.^{30,31} On May 30, 1922, an agreement was signed between the university and Eli Lilly. The pharmaceutical company would invest in insulin production, acquiring its exclusive rights in the United States and Central and South America. Lilly agreed that the term "insulin"

would be assigned to the generic product, and that the alternative term "iletin" referred exclusively to the specific Lilly product. The Collip-Best patent was rejected by the patent office of the United States because of the conflict of interest with the patent previously granted on May 28, 1912 to Georg Zuelzer. Subsequently, on January 23, 1923 the American patent was granted to both the Toronto and Lilly methods. George Walden, a chemist researcher at Lilly, developed a purification method using isoelectric fractionation which allowed for the large-scale manufacture of insulin, increasing stability and purity up to 100 times as compared to the previous product. From February 1923, insulin production allowed for provision of the hormone to various institutions selected for its clinical use. Because of the refusal by Duncan Graham to accept Banting as a consultant at the Department of Medicine, Banting founded a private clinic which was attended by many patients because of the celebrity of the group. Finally, the management of the Toronto General Hospital decided to grant the refused privilege to Banting, who joined the staff and conducted patient treatment in cooperation with Campbell and Fletcher. In November and December 1922, the Department of Medicine published three articles of great clinical relevance in the *Journal of Metabolic Research*. In the first of these, the Canadian team thoroughly reported nine cases of diabetic patients treated with insulin.³² In the same issue of the journal, Walter R. Campbell made highly revealing clinical observations about the first 14 cases of diabetic coma treated at the medical clinic of Toronto General Hospital. In addition to the clinical description of each case, the manuscript reviewed the causes of death, mainly of an infectious nature, the insulin doses administered, the comparison of intravenous and subcutaneous insulin administration, the significance of intravenous glucose administration, the pros and cons of bicarbonate administration, and so on.³³ The third manuscript, signed by Almon Fletcher and Walter Campbell, contained a wonderful description of insulin-induced hypoglycemia including its clinical signs in both the adrenergic and neurogenic stages.³⁴ In November 1922, August Krogh (Nobel Prize in 1920) and his diabetic wife, Marie, visited Macleod in Toronto. A few days later they returned to Denmark with the license for exclusive use of insulin in Scandinavia. Krogh and Hagedorn, personal physician of Marie, founded the Nordisk Insulin Laboratorium in 1923.

In his report to the Nobel Committee, August Krogh would state that his decision was mainly based on the visit he had made to Toronto, where he had seen at first hand the research that was underway there. Best and Collip were not nominated. When Banting found out that Macleod, with whom he had strained relations, had also been awarded the Nobel Prize, he was furious. His first instinct was to reject the prize, but he then decided to share the Nobel Prize money with Best. Macleod did the same with Collip.

Paulescu had written to Banting on February 5, 1923 and sent him his publications of 1921. He asked Banting to maintain mutual correspondence on their research activities. Banting never answered him. By contrast, Paulescu would obtain the support of some pioneers in research into pancreatic extracts. He received a letter from E.L. Scott, dated November 5, 1921 recognizing that both his own experiments at Columbia University in 1921 and those of Paulescu,

also done in 1921, confirmed the existence of a pancreatic secretion that would relieve symptoms of diabetes through the bloodstream. J. Murlin also wrote in 1923 that mention should be made of the favorable results achieved by Paulescu in 1921, showing that intravenous administration of a sterile extract to pancreatectomized dogs decreased or even transiently suppressed hyperglycemia and excess production of urea and ketone bodies.³⁵ In 1924, C. Funk declared in Paris that Paulescu had decisively shown in 1920 and 1921 that the pancreas contained an antidiabetic substance which Banting and Best would call insulin.³⁶ For A. Sordelli and J.T. Lewis, who worked at Buenos Aires, Paulescu reported in 1921 complete experiments with an extract prepared by aqueous maceration of the pancreas in which results identical to those obtained by Banting upon insulin discovery were achieved.³⁷ In 1932, Wilfred Totter said (according to the verbatim transcription by James Theodore Nicolas) in his Hunterian Oration one year after the death of Paulescu: "...His research was the culmination of years of experimental work of precursors, colleagues and himself. This great advance, perhaps equivalent in some respect to the discovery of the therapeutic virtue of penicillin, remains unacknowledged".³⁸ In 1934, P. Trendelenburg wrote in Berlin: "Shortly before the description of the discovery of insulin (1921), Paulescu achieved full success with extracts which lowered the blood sugar of pancreatectomized dogs within one hour of parenteral administration".³⁹ Nicolae C. Paulescu wrote a letter to the chairman of the Nobel Committee, dated November 6, 1923 to which he enclosed a copy of his article published in 1921 in the journal *Archives Internationales de Physiologie*, entitled "*Recherche sur le rôle du pancréas dans l'assimilation nutritive*", and protested in vain at the granting of the award to Banting and Macleod, emphasizing the priority of his 1921 publications; for him, the Toronto team had not respected his intellectual property rights. The reply of the Nobel Committee was to send him a booklet entitled "The 1923 Nobel Prizes" including the speech by J. A. Sjöquist quoting the Banting and Best article of February 1922. Paulescu also wrote to the French Academy of Medicine, but his attempts to proclaim his priority in the discovery of insulin were unsuccessful. Weeks before his death in 1931, Paulescu once again expressed his disappointment and sadness when recalling how his whole scientific activity relating to the discovery of the antidiabetic hormone had been ignored by the international scientific community. With the tragic events of World War II, the political problems in Romania, and the accession to power of the Communist Party in 1947, the figure of Paulescu fell into oblivion. The communists, who considered Paulescu, a fervent catholic and a member of the Romanian right, an enemy of the party, wiped out any trace of his achievements from the history of Romanian science.

We owe our recovery of the figure of Paulescu and his contribution to the discovery of insulin to Ian Murray (1899–1974), a Scottish diabetologist who was Professor of Physiology at the Anderson College of Medicine (Glasgow). Upon retirement, Murray set out to write a book on the history of insulin to celebrate the fiftieth anniversary of its discovery. Murray documented how the Romanian scientist had as early as in 1916, before Banting and Best, experimentally observed that parenteral administration of

an aqueous pancreas extract induced immediate symptom relief in pancreatectomized dogs. In his textbook of medical physiology published in 1920 and his publications in 1921, Paulescu showed in a very rigorous and convincing way that he had been able to successfully isolate from the pancreas the antidiabetic hormone, which he called pancrein. Banting and Best later reached conclusions similar to those of Paulescu. In the first publication (1922), the Canadian authors erroneously interpreted the original findings by Paulescu and stated that after the first successful injection, intravenous administration of subsequent doses was not able to reproduce the effects (the exact opposite to what Paulescu had reported). Thus, for I. Murray there was no doubt that pancrein and iletin/insulin were one and the same thing. Determined to investigate the subject, Murray sent in October 1968 a letter to the Professor of Physiology of the Bucharest School of Medicine. He had no reply, and subsequently wrote to Prof. Ion Pavel (1897–1992), who had been a pupil of Paulescu in 1916–1917, asking him for information. From that time, Murray and Pavel maintained a warm correspondence until the Scottish physician died in 1974. Thus, on November 11, 1969 Murray wrote to Pavel: "It is satisfactory to have his (Best's) admission that they were so wrong in their reference to Paulescu's work. The explanation of their error, however, seems to me somewhat naïve". Murray also wrote to Pavel on February 29, 1972: "My suggestion is that IDF should institute a Paulescu Memorial Lectureship. The lecture at each triennial meeting would be given by someone of merit". Years later, Pavel published these letters together with other communications. Based on his inquiries, Murray wrote a series of articles in several British and American medical journals.^{40,41} Pavel also devoted a great part of his life to investigating the history of insulin, and published various articles and books about Paulescu.^{42–45} According to Eric Martin, Professor of Medicine at the Geneva University, "It is beyond denial that Paulescu was the first to provide an exemplary demonstration of the antidiabetogenic and antiketogenic effect of a pancreatic extract... We should stress the cardinal importance of the discovery of Paulescu, a discovery known to the Canadian physicians but poorly interpreted by them, with the result that determinative studies of the Romanian physiologist have been left in the shade".⁴⁶

In their already mentioned article published in February 1922, the Canadians had wrongly quoted the Paulescu report. Pavel wrote to Charles H. Best to find out why. In a letter dated October 15, 1969, Best replied that almost 50 years later he barely recalled the facts, but recognized that there had been a mistake in the translation. It was Pavel who disclosed the letter, as Best never admitted his mistake in public. Also in October 1969, Pavel wrote, together with Prof. S.M. Milcu, vice-president of the Romanian Academy, to Prof. Arne Tiselius, Director of the Nobel Institute. They enclosed the Paulescu articles and the letter from Best, and asked the Nobel Committee to grant Paulescu the post mortem title of discoverer of insulin together with or before Banting, Best, and Macleod. The reply by Tiselius arrived two months later. He said that Paulescu deserved the prize, but the Committee could be nothing on this matter because Paulescu had not been nominated and, according to the standing rules, the Nobel Prize can only be awarded to those who have been nominated.

Finally, a prize already awarded cannot be taken away. A few months later, Pavel sent information relating to Paulescu to the committee of the International Diabetes Federation (IDF). A special committee was created in the 7th Congress of the International Diabetes Federation, held in Buenos Aires in August 1970, to prepare a report on all research related to insulin recovery. Contrary to the expectations of the members of the Romanian Academy of Science, the report by the special committee was not favorable to the claim of Paulescu, which was virtually ignored in the statement of the committee. For neutral observers, the membership of the committee was inadequate. It was initially decided to include in the committee a member representing Romania. Prof. Rachmiel Levine, IDF chairman in 1970, suggested the name of Ion Pavel, but no Romanian was finally included in the research team. Both the chairman of the committee, Frank George Young (1908–1988) (United Kingdom), and the vice-chairman R. Haist (Canada) were very closely related to the Toronto team. Young had worked under the direction of J.J.R. Macleod in Aberdeen, and later in Toronto with C.H. Best, of whom he was a personal friend (by then, Best was the only member of the Toronto group alive, and had become a legend in diabetology). In addition, Young was elected chairman of the IDF at the end of the congress. Haist had previously worked with Best, and succeeded him as head of the Department of Physiology of Toronto University. The other members were W.J.H. Butterfield (United Kingdom), Rolf Luft (Sweden), and P. Ranbert (France). The final report⁴⁷ had many mistakes, and although it mentioned Paulescu and several forerunners in the discovery of insulin, it did not do justice to his achievements. In 1971, Ian Murray stated: "...insufficient recognition has been given to Paulescu, the distinguished Romanian scientist, who at the time the Toronto team were commencing their research had already succeeded in extracting the antidiabetic hormone of the pancreas and proving its efficacy in reducing hyperglycemia in diabetic dogs...".⁴⁸ R. Luft described Macleod in 1972 as a manager and sponsor who "...put Collip and the Lilly Company into business".⁴⁹ In his view, granting the 1923 Nobel Prize to Banting and Macleod had been the worst error the committee had ever made.⁵⁰ After the deaths of Murray and Pavel, Constantin Ionescu-Tirgoviste, a professor at Bucharest University, devoted two books^{51,52} to the figure of Paulescu. Michael Bliss, Professor of History of Medicine at Toronto University, published in 1982 "The Discovery of Insulin", a book that gives a detailed account of the experiments made in Toronto, particularly emphasizing the contributions of Collip and Macleod.³ Eleven years later, Bliss published an article where he stated: "...The Paulescu case was based on the realization that, in fact, Banting and Best had not produced results more impressive than Paulescu's. Indeed, as Banting had had the honesty to write of the first clinical test of their extract, the results had not been as impressive as those produced by another predecessor, Zuelzer, in 1908... Banting's and Best's research was so badly done that, without the help of Macleod and Collip, and a much more subtle view of the constituents of the discovery of insulin, the two young Canadians would be fated to disappear from medical history... At times Best's distortions of the historical record seem to amount to a

deliberate, unethical exercise in falsification which verges on scientific fraud...".⁵³

In 2001, the Romanian Academy paid tribute to Paulescu and posthumously elected him as its member. On the occasion of the 80th anniversary of the Paulescu publication (1921), a statue was unveiled in his honor in a location close to the school of medicine. The inaugural ceremony was attended by the Romanian prime minister, Ion Iliescu, and the chairman of the IDF, Sir George Alberti. In 2002, the Romanian Academy of Sciences, the European Association for the Study of Diabetes (EASD), and the International Federation of Diabetes (IFD) decided to jointly organize various academic events to pay homage to the Romanian physiologist. One of the events was the announcement of a Paulescu International Prize to recognize research excellence in areas related to insulin. Professor Zvi Laron (Israel) was designed chairman of the evaluating committee. Among the four candidates presented, the committee unanimously decided to award the Paulescu International Prize to Geremia Bolli, Professor at Perugia University (Italy). The IDF planned, in collaboration with the EASD and the Romanian Academy of Sciences, an academic homage to Paulescu to be held at the Hotel Dieu in Paris on August 27, a few days before the start of the 2003 IDF Congress. The event would consist of the placement of a commemorative plaque and busts of Paulescu and Lancereaux, followed by an award ceremony at which the NC Paulescu International Prize would be presented. Professor Geremia Bolli, from Perugia University, the award recipient, would then give a lecture to conclude the event. On August 22, the Simon Wiesenthal Center (SWC) issued a news release directed to the French Minister of Health (Jean-François Mattei) and the Romanian ambassador in France asking that this homage to Paulescu be cancelled.⁵⁴ In that release, Dr. Shimon Samuels, Director of International Relations of the SWC, accused N.C. Paulescu of publicly known anti-Semitic activities. On August 26, Nicolas Weill published an editorial article in *Le Monde* quoting the titles of anti-semitic publications written by N.C. Paulescu and confirming the decision of the Romanian embassy, in agreement with Professor Gérard Slama, Head of the Department of Diabetes, Hotel Dieu, to cancel the ceremony.⁵⁵ Nicolas Cajal, chairman of the section of medical sciences of the Romanian Academy and president of the Jewish community in Romania, held a press conference of August 31, 2003 where he defended this recognition of the scientific work of Paulescu and emphasized the need for making a distinction between his academic contributions and his anti-semitic views. According to Cajal (whose father was a disciple of Paulescu and admired and respected him although he knew his anti-semitic ideas), "...nobody should exert the right to deny the scientific merits of Paulescu and his special contribution to the benefit of the health of citizens...".⁵⁶ On September 29, 2003, the chairman and the vice-chairwoman of the Romanian Academy, Eugene Simoin and Maya Simonescu respectively, protested in a letter to Pierre Lefèbvre, chairman of the IDF, against the decision to cancel both the ceremony and the presentation of the Nicolae C. Paulescu International Prize. "Prof. Paulescu did publish several articles against the Jews, which are regrettable from all points of view... Nevertheless, Nicolae Paulescu's personal opinions did not result in any violent actions in the social sphere, and he himself never

participated in any action that might have brought accusations of guilt. No real offenses could be charged on him...". It should be noted that, by analogy with the matter in dispute, the letter stated that: "We cannot judge the work of the great writer Céline based on his political ideas...", a statement that would prove to be unintentionally ironic, as in this same year (2011), on the 50th anniversary of Céline's death, the French Ministry of Culture has decided to delete his name from the list of official commemoration. In October 2003, Professor Gérard Slama justified the cancellation of the ceremony in a letter published in *The Lancet*.⁵⁷ Two months later, George Alberti and Pierre Lefèbvre (IDF) published another letter in *The Lancet* referring to the Slama letter and concluded by saying: "...The IDF is now collecting the appropriate writings of Paulescu. These will be scrutinised by an independent committee. The IDF does not wish to mix science and politics. But more information is needed before we can internationally laud an individual who has undoubtedly made a major contribution, but who might have espoused a morally unacceptable position later in life".⁵⁸ Doctors Christos S. Bartsocas, Spyros G. Marketos, George Alberti, Jorn Nerup, Jon Alivisatos, Stefano Geroulanos, and Sotiris Raptis organized an international expert symposium at Delphi on September 8, 2005 on the occasion of the annual meeting of the European Association for the Study of Diabetes (EASD). The title of the symposium was: "Who discovered insulin?". The different speeches by Torsten Deckert, Alberto de Leiva, Constantin Ionescu-Tirgoviste, John Dupré, Jay Skyler, and Paolo Pozzilli agreed that international organizations had ignored the scientific merits of Paulescu, which should be recognized. However, in the closing lecture Zvi-Laron angrily denounced the anti-semitism of Paulescu and his influence on the terrible events of the Romanian holocaust. At the end of the meeting, the organizers did not issue an official statement about the symposium's contents. The vote, announced in the program, was cancelled. In that same year (2005), the IDF executive committee decided that: "The IDF does not want to be associated with the name of Paulescu. Therefore, the Paulescu Lecture would not be included in world congresses, even if requested". Three years later, Prof. Laron published an article giving a personal and scientific description of the Romanian researcher entitled "Paulescu, scientist and politician". For Laron, it was unquestionable that Paulescu deserved no homage. By contrast, he should be criticized for his contribution to the darkest pages of Romanian history.⁵⁹

Nicolae Paulescu was in many aspects a follower of creationism. He was opposed to both spontaneous generation and Darwinism; an Orthodox Christian, he expressed anti-masonic and anti-semitic viewpoints.⁶⁰⁻⁶³ Large segments of the Romanian population shared these anti-semitic ideas in the inter-war period. While it is fair to criticize Paulescu for his aberrant political views, his extraordinary contribution to science should not therefore go unrecognized.

The Romanian Ministry of Health has devoted the Bucharest Institute of Diabetes and Metabolic Diseases to the memory of Nicolas Paulescu. Its director, Prof. Constantin Ionescu-Tirgoviste, a biographer of Paulescu, has spent a lot of time attempting to vindicate the Romanian researcher before the international community. Ninety years after the discovery of insulin, the controversy continues.

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