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Historical perspective

From pancreatic extracts to artificial pancreas: history, science and controversies about the discovery of the pancreatic antidiabetic hormone

V: The controversy. Who discovered insulin?

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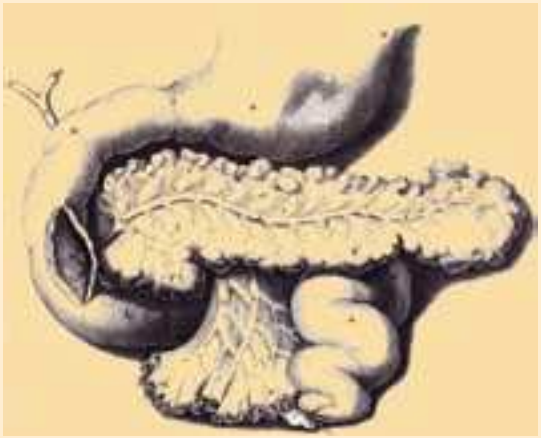

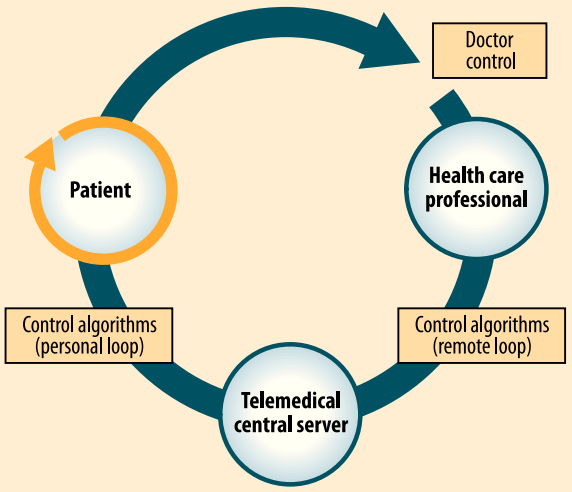

The Nobel Prize controversy

The 1923 Nobel Award of Physiology or Medicine

In April 1923, a total of 57 nominations with merits were reviewed by the Nobel Committee. The examiners concluded that the discovery of insulin was of fundamental importance. The archives of the Karolinska Institute depict that Macleod and Banting were nominated for the first time in 1923: Banting by G.W. Crile (Cleveland) and August Krogh and Macleod by G.N. Stuart (Cleveland) and August Krogh. There was also a joint nomination of Banting and Macleod from August Krogh. Written evaluations of Banting and Macleod's scientific contributions were provided by two members of the Nobel Committee: John Sjöqvist, Professor of Chemistry and Pharmacy, and Hans Christian Jacobaeus, Professor of Internal Medicine. Sjökvist arrived to the same conclusion as A. Krogh: the prize should be divided between Banting and Macleod. Professor Göran Liljstrand was the Secretary of the Nobel Committee from 1918 to 1960. He was a great friend of August Krogh. The archives of the Royal Swedish Academy of Sciences keep an interesting correspondence between Krogh and Liljestrand. The Committee concluded that although the discovery was initially Banting's idea alone, Macleod's guiding hand helped Banting's idea to reach such a happy culmination.

The Faculty members of the Karolinska Institute (Royal Caroline Institute), the Nobel Assembly, as its October 11 meeting, decided to send back the proposal to the Committee for reconsideration. The objection was to making an award on "heresy evidence" from unknown persons or on statements in the two appraisals, like "it is beyond doubt", or comments as "things that are thought as very possible"; the Assembly should take only verifiable facts. The Committee reconsidered and reconfirmed its previous recommendation. August Krogh was identified as the source of the "heresy evidence"; he emphasized that he made the joint recommendation based on his visit to Toronto.

On October 25, 1923, the nineteen Professors of the Caroline Institute, voted by secret ballot. The Nobel Award of Physiology and Medicine was jointly granted to Frederick Grant Banting and John James Richard Macleod, "for the discovery of insulin", one year before. Banting decided to share his monetary fraction of the prize with Charles H. Best; Macleod did the same with James B. Collip (figure 1).

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Figure 1. Nobel Prize Diploma to Banting and Macleod

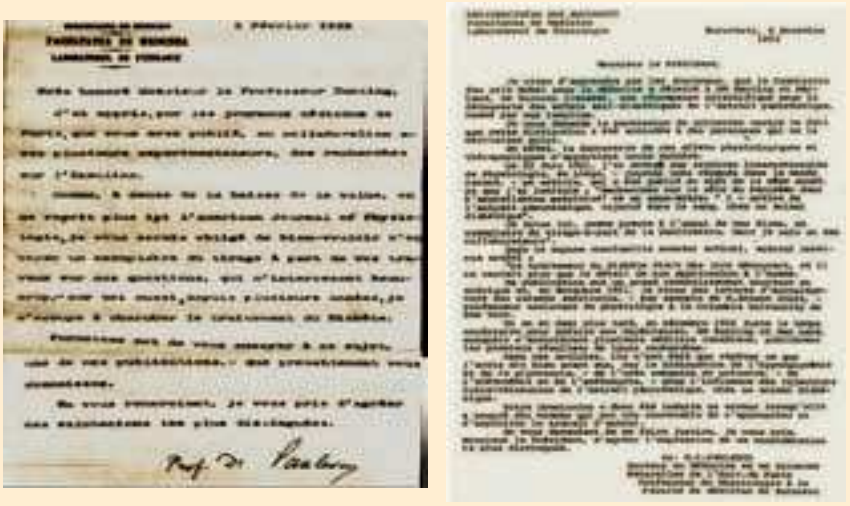

Figure 2. A) Letter from Paulescu to Banting (February 5, 1923), who did not reply. **B)** Letter from Paulescu to the Nobel Commission (November 6, 1923) (Courtesy of Dan Angelescu). Available on: http://www.library.utoronto.ca

The protests

In December 1922, Dr. F. Roberts, physiologist from Cambridge, had already reported in a letter to the *British Medical Journal* a serious criticism to Banting and Best's work in their first two publications in the *Journal of Laboratory and Clinical Medicine.*[1] Roberts claimed that the ptoteolytic enzyme (trypsinogen) existing in the pancreatic gland needs to be activated by enterokinase secreted by the small intestine; therefore, there were no physiological basis for the duct-ligation experiment.

Shortly after the announcement of the Nobel Committee's decision, various researchers claimed against such a provision. Georg Ludwig Zuelzer sent furious letters of protest from Berlin, pleading for some recognition of his priority. Ernest Lyman Scott called the attention to his experiments in the field. In his opinion, the priority of isolation and in the development of fundamental principles involved in extraction clearly belonged to the work reported from the laboratory of Chicago.[2] The method of final purification was not necessary for obtaining the active principle. John Raymond Murlin argued that he had performed, at earlier times than the researchers from Toronto, both experimental and clinical studies with the pancreatic extracts. Israel S. Kleiner made no claims.

On February 5, 1923, Nicolae C. Paulescu had written Banting, asking for mutual correspondence regarding their research activities (figure 2); Paulescu sent to Toronto his main publications of 1921. Banting did not reply. On November 6, 1923, Paulescu claimed to the President of the Nobel Commission (figure 2) that his work had been stolen by the Canadian research group, and he asked for justice. Paulescu enclosed a copy of his article "Recherche sur le rôle du pancréas dans l'assimilation nutritive" published in *Archives Internationales de Physiologie de Liège* on the 31st August 1921 (accepted on the 22 June). Paulescu's article had been published six months prior to Banting and Best's article "The Internal Secretion of the Pancreas" (*Journal of Laboratory and Clinical Medicine,* issue of February 5, 1922).

> *"Je vous demande la permission de protester contre le fait que cette distinction [Nobel] a été accordée à des personnes qui ne la méritaient point. En effet, la découverte de ces effets physiologiques et thérapeutiques m'appartient toute entière (…). Dans ces articles, ils n'ont fait que répéter ce que j'avais dit bien avant eux sur la diminution de l'hyperglycémie et de la glycosurie, de l'urée sanguine et urinaire, de l'acétonémie et de l'acétonurie, sous l'influence des injections intra-veineuses de l'extrait pancréatique, chez un animale diabétique (…)."* (N.C. Paulescu. November, 1923)

On April 10, 1922, the license application 6254, **PANCRÉINE,** was registered. In the issue of March 5, 1923, of the journal *Archives Internationales de Physiologie,* Paulescu described the various attempts to treat one male patient with "thin diabetes", and a woman with "obese diabetes". In both cases the intravenous administration of *pancréine* induced favorable outcomes regarding the symptoms, blood glucose levels and glycosuria. Nevertheless, the development of a toxic syndrome with high fever obliged to the interruption of clinical experiments afterwards.

On April 1922, the University of Toronto submitted a formal application for an USA patent granted to Charles Best and James Bertrand Collip. The USA government rejected the application, in order to protect the rights of the **ACOMATOL** patent already granted to George L. Suelzer on May 28, 1912. The process finally ended with the provision of a patent registry in November 1922, shared by the University of Toronto **(INSULIN)** and Eli Lilly **(ILETIN**) (figure 3).

Accordingly to the Bylaws of the Nobel Foundation: *"To be considered eligible for an award, it is necessary to be nominated in writing by a person competent to make such a nomination. A personal application for an award shall not be considered. Each year the prize adjudication shall embrace such nominations as have been submitted during the preceding twelve months up to February 1".*[3]

PANCREINE (N.C. Paulescu)
License application # 6254,
issued by the Romanian
Ministry of Industry. April 1922




USA Patent.
November, 1922
ISLETIN / INSULIN

F.G. Banting C.H. Best J.B. Collip J.J.R. Macleod

Figure 3.


August and Marie Krogh

Hans Christian Hagedorn

Figure 4. August Krogh, the Nobel Prize of 1923, Hans C. Hagedorn, and his wife Mary

Paulescu was never nominated. Only Banting and Macleod were nominated in 1923, Collip and Best were only nominated years later, in 1928 and 1950, respectively. Therefore, Paulescu could have never received the prize. Furthermore, the Bylaws of the Foundation also point out that once a prize has been awarded, it cannot be withdrawn, and no further Nobel Prizes can be given for the same discovery. Von Mering was nominated in 1902 and 1906. Minkowski was nominated in 1902, 1906, 1912, 1914, 1924, and 1925, but never awarded. However, the attitude of the Nobel Committee in regards to Paulescu's protest could have been different. Instead, they remained silent, probably to avoid damaging the reputation of the Nobel Prize and the Karolinska Institute.

In 1924, Paulescu submitted a document to the Romanian Society of Biology, in which he reviewed the chronology of his own experiments, their results, and the publications in which they appeared. He discussed the isolation of *pancréine,* and how he established a unit of measurement for it. Paulescu reviewed the work of Banting and Best which he felt inefficient, incomplete, and inadequately documented. He ended: *"it seems to me that I have the right and even the duty, to re-establish the truth and to protest against a process never permitted in science, in re-establishing the facts with total accuracy".*[4]

In 1923, Paulescu had already published the results of attempts at purification of *pancréine,* in an effort to make it suitable for use in humans.[5] He studied the effects of acidic and basic solutions, heat and alcohol, on the impurities in his extract, and found them all inadequate. In his textbook of medicine published in 1930,[6] Paulescu showed his embitterment and disappointment: *"Formerly, I used to believed taught that a scientist may work in safety, because I was convinced that the date of his publications sheltered him from any iniquity. Unfortunately, today, I am forced to acknowledge that I was completely wrong".*

August Krogh and Hans C. Hagedorn

A decisive person in the concession of the Nobel Award to Banting and Macleod, as it was mentioned before, was August Krogh, a renowned Danish scientist, who had obtained in 1920 the Nobel Prize in Physiology and Medicine for his discovery of the mechanism of regulation of capillary flow in the skeletal muscle. In 1922, August Krogh traveled to the USA with his wife Marie (also a scientist). Marie Krogh had been found a year before to have maturity onset diabetes. The renowned American diabetologist Elliot P. Joslin informed August and Marie Krogh that insulin had just been discovered and purified in Toronto. They decided to extend their trip and spent some days in Toronto (November 23-25, 1922) as Macleod's guests. Krogh met also Banting (during those days, the other members of the Toronto team were out of town).

During his stay in Toronto, August Krogh obtained a license to manufacture insulin in Denmark. He started to produce the anti-diabetic hormone immediately after he returned to Copenhagen (in fact, the first Danish diabetic patient to receive insulin was treated on March 1923). Marie's diabetes was successfully treated with insulin (she died of breast cancer in 1943). Hans Christian Hagedorn was the perso-

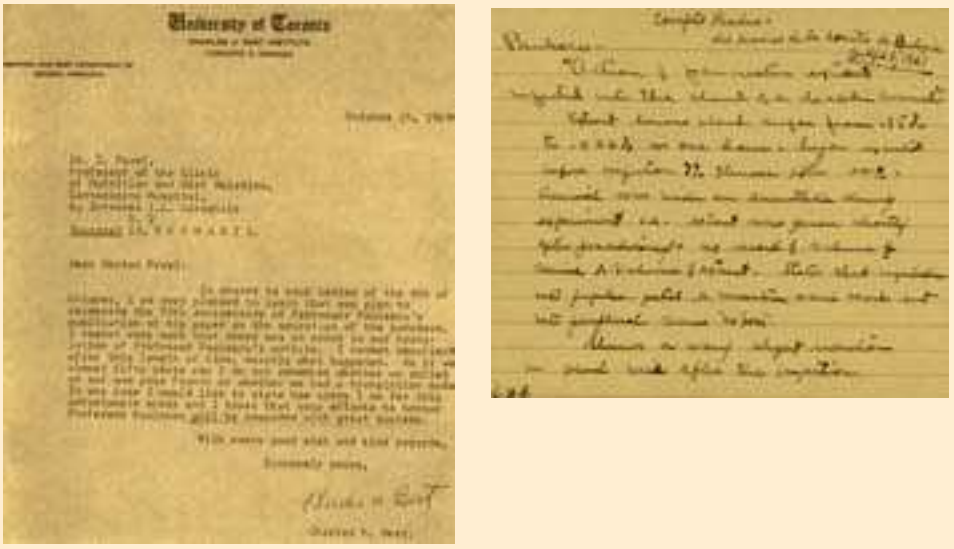

Figure 5. Letter of Best to Pavel and Blue index note card. Author: C.H. Best. Toronto, Ca. Fall 1921. Notes have been made on both sides in Best's hand. The first side is initialed C.H.B. in the bottom corner. Although Paulescu's article indicated that he was obtaining positive results using pancreatic extract, the notecard indicates that the significance of Paulescu's work was not appreciated due to a misquotation, substituting the phrase 'non bon' for Paulescu's original 'non plus'. Source: Online Library of the University of Toronto. Banting Collection. Available on: http://link.library.utoronto.ca/insulin/index.html

nal physician of Marie. Together with Hagedorn (figure 4), Krogh founded the Nordisk Insulin Laboratorium in 1923, the starting point of a successful Danish pharmaceutical company, today known as Novo Nordisk.

In 1918, Hagedorn, in joint forces with the pharmacist Bierger Norman Jensen, published a micromethod for the determination of blood glucose that has been the method of choice for more than 40 years.[7] Hagedorn invented protamine insulin in collaboration with Norman Jensen and Inger Wostrup, patented in 1936.[8] Hagedorn founded the Steno Diabetes Center in Copenhagen, and was its Chief-Physician for 26 years. He developed diabetes, gangrene and major amputation, and suffered of Parkinson's disease for many years. From 1966 became a permanent patient at the Steno. He died of coronary thrombosis in 1971.

Upon his return to Europe, Krogh proposed Banting and Macleod for the Nobel Prize. As cited by Jan Lindsten (member of the board of the Nobel Foundation between 1979 and 1990, and member of the Swedish Royal Academy of Sciences, among other distinctions), August Krogh summarized in the following way his reasons for proposing Banting and Macleod: *"With the information which I personally have obtained in Toronto, and which also, although less clearly so, emerges from the published works, one may conclude that the credit for the idea behind the work which led to the discovery, undoubtedly goes to Banting, who is a young and apparently very talented man. However, he would definitely not have been able to carry out the investigations, which from the start and during all stages, have been supervised by Professor Macleod."*

In a letter dated February 4, 1924, to Göran Liljestrand (also referred by Lindsten), August Krogh wrote: *"I understand that the prize to Banting and Macleod ignoring other coworkers has not been met with absolute consent on the other side of the Atlantic Ocean and that especially Banting is offended by the fact that Best was not included. However, I am convinced that the correct choice was made."*

As Lindsten concluded in the mentioned article, *"it seems reasonable to assume that Krogh's nomination had some impact on the awarding of the prize to Banting and Macleod. After all he was a Nobel Laureate and had, in addition, personal knowledge of the situation in Toronto"*.[9]

The crucial misinterpretation

Banting and Best's paper, published in February 1922, mentioned Paulescu's earlier research, but reported incorrectly that the injections of pancreatic extract made by Paulescu into dogs had produced no effects. That was in fact the opposite of what Paulescu had stated. Whether they intentionally distorted Paulescu's words, or misinterpreted them because of their poor French, nobody knows well enough.

Professor Ion Pavel, from Bucharest, wrote to Charles Best complaining about the wrong paragraph included in the first article published by Banting and Best, regarding the work of Paulescu. Years later, Best apologized for the crucial misinterpretation (letter to Ion Pavel dated October 15, 1969; figure 5).

> *"I regret very much that there was an error in our translation of Professor Paulescu's article. I cannot recollect, after this length of time, exactly what happened (…). I do not remember whether we relied on our own poor French or whether we had a translation made. In any case I would like to state how sorry I am for this unfortunate error and I trust that your efforts to honour Professor Paulescu will be rewarded with great success."*

Beyond Toronto. Glory to the Canadian research team

Macleod decided to cooperate with Eli Lilly after the successful outcome of the early clinical trials. The agreement was reached in May 1922. The rabbit convulsive test devised by Collip was used for standardization; within 6 months, more than 100,000 rabbits were utilized. Shortly after the purification of insulin (Collip), the pharmaceutical company Eli Lilly started large-scale production of the pancreatic extract. The Lilly's chemist

Walden evolved a method of purification by isoelectric fractionation which significantly improved both yield and potency and made large-scale production possible. Early in 1923, the supply of insulin was adequate to meet the requirements of various institutions selected to study its clinical use, and to supply with insulin the entire North American continent. In Great Britain the patent rights were assigned to the Medical Research Council.[10]

The Toronto team was praised with honours, and received also major press coverage and publicity (figure 6). Banting achieved a sudden and outstanding fame. All kind of newspapers trumpeted his success. He was made honorary member of many medical societies. In May 1923, the Ontario Government provided him with the Banting and Best Chair of Medical Research. It included a non-teaching professorship for Banting, an annual grant of $10,000 to pay Banting's salary, and an additional amount of $10,000 for reimbursement of the discovery period; Banting gave $2,500 to Best. The Canadian House of Commons offered Banting a lifetime annuity of $7,500.

In conclusion, the Toronto's team's increasingly important reputation, not only in scientific and academic circles, but also among the general public, made it difficult to raise the question about the priority in the discovery of insulin, and the role of Paulescu in it.

Paulescu forgotten

Shortly before dying, Paulescu declared (1931):

> *"Formerly I believed and maintained that a scientist can work in perfect safety, convinced as I was that the date of his publications protected him against any injustice. Unfortunately, I am obliged to admit now that I was utterly mistaken in this regard. I am not dominated by pride and I struggle against this odious vice. Indeed, on publishing my discovery I never for one moment thought of publicity, which could have affected my modesty that I consider one of the first qualities of a scientist. But I certainly cannot accept another, more odious defect, that of the theft of someone else's scientific property."*[11]

Figure 6. An excerpt from a newspaper. Toronto star weekly [Mar 26, 1922]. Source: Online Library of the University of Toronto. Banting Collection. Available on: http://link.library.utoronto.ca/insulin/highlights.cfm

With the snap of the Second World War, the political problems that arouse in Romania and the ascension to power of the Communist party in 1947, Paulescu's figure submerged in the oblivion. The communists, who considered Paulescu an enemy of the Party, for his religious and political ideas, erased his fingerprints of the history of the Romanian science.

The reappraisal of Paulescu

There have been numerous attempts by scientists and historians to make public the scientific prestige of Paulescu and his merits.

Early Statements

- Paulescu received a letter from E.L. Scott, dated 5 November, 1921, declaring that the results of his own work with pancreatic extracts at Columbia University in 1921, and the experiments published by Paulescu in 1921, arrived at similar conclusions: *"(...) there can be little doubt of the existence of a pancreatic secretion, that via the blood stream (...) finally alleviates some of the symptoms of diabetes..."*.
- In 1923, J. Murlin wrote: *"(...) mention should be made (...) of the favorable results reported by Paulescu (1921) (...). He found that the intravenous injection of a sterile extract into depancreatized dogs brought about a diminution or even a temporary suspension of the hyperglycemia (...) and the excessive production (...) of urea and ketone bodies"*.[12] (12)
- In 1924, C. Funk declared in Paris: *"In 1920 and 1921, Dr. Paulesco of Romania, and Drs. Banting and Best of the University of Toronto, proved in a decisive manner that the pancreas contains an antidiabetic substance that has been given the name of insulin"*.[13]
- In 1926, A. Sordelli and J.T. Lewis, from Buenos Aires, wrote: *"In 1921 (...) Paulescu communicated his completed experiments with an extract prepared by aqueous maceration of the pancreas. The results are identical to those obtained by Banting in discovering insulin"*.[14]
- P. Trendelenburg, in Berlin, wrote in 1934: *"Shortly before the description of the discovery of insulin (1921) Paulesco achieved full success with extracts which lowered the blood sugar of pancreatectomized dogs within one hour of parenteral administration"*.[15]

Figure 7. Ion Pavel (1897-1991)

Ion Pavel

Ion Pavel (figure 7), a Romanian physiologist, dedicated fifteen years of his life to investigate about the history of the discovery of insulin. He published a series of

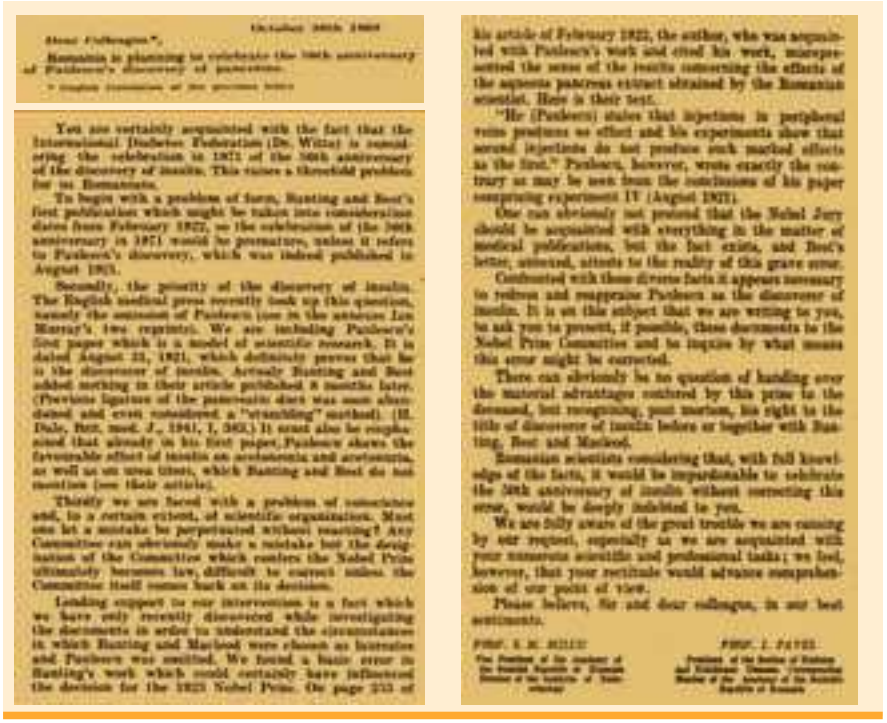

Figure 8. Letter of Pavel and Mincu on behalf of the Romanian Academy to the President of the Nobel Institute (October 1969)

articles and books where he stressed the merits of Paulescu in this field, and addressed several protests to the Nobel Committee and to the International Diabetes Federation (IDF). (For further reading, see references 16-20.)

In October of 1969, Prof. Pavel and Prof. S.M. Milcu (Vicepresident of the Romanian Academy) wrote a letter to Prof. Arne Tiselius, Director of the Nobel Institute, claiming for Paulescu's priority in the discovery of insulin (figure 8).

Tiselius' answer was the following:

"Returning to the question raised in your letter of Oct.30 1969 about the priority of the discovery of insulin, and particularly the contribution of Paulescu, I wish to say the following.

I have throughly studied the documents you have sent me and I have also discussed the case with colleagues, especially with professor Ulf von Euler, president of the Nobel Foundation and, as you know, himself a physiologist and endocrinologist of the highest reputation.

We agree that no doubt your viewpoints in connection with the planned celebration of the 50 years anniversary of the discovery of insulin to a certain extent are justified.

As you know well the Nobel Prize to Banting and Collip **[here, a mistake; Collip instead of Macleod]** *has been criticized by many, especially the fact that Best was not included. In my opinion, Paulescu was equally worth the award. As far as I know, Paulescu was not formally proposed, but naturally the Nobel Committee could have waited another year.*

The attitude of the Nobel Committee in the exceptionally difficult and controversial case of the prize for the discovery is expressed by professor Göran Liljestrand (formely secretary of the Committee) in the book 'Nobel, the Man and his Prizes' (edited by the Nobel Foundation, Elsevier Publishing Co., Amsterdam, 1964).

Unfortunately there is no mechanism by which the Nobel Committee would do anything now in this or similar cases. Personally, I can only express the hope that in an eventual celebration of the 50th anniversary of the discovery of insulin due regard is payed to the pioneer work of Paulescu.

With my kindest regards,
Sincerely yours,
Arne Tiselius"

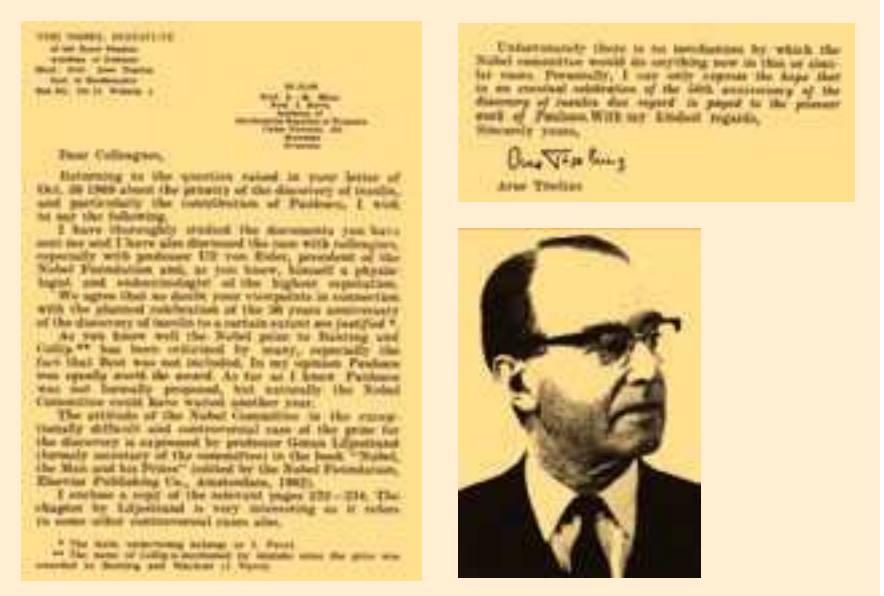

Figure 9. Arne Tiselius (1902-1971) and his answer

Ian Murray

Prof. Ian Murray (figure 10), Professor of Physiology at the Anderson College of Medicine in Glasgow, Scotland, Vice-president of the British Association of Diabetes, and founding member of the International Diabetic Federation, claimed that Paulescu was the true discoverer of insulin.

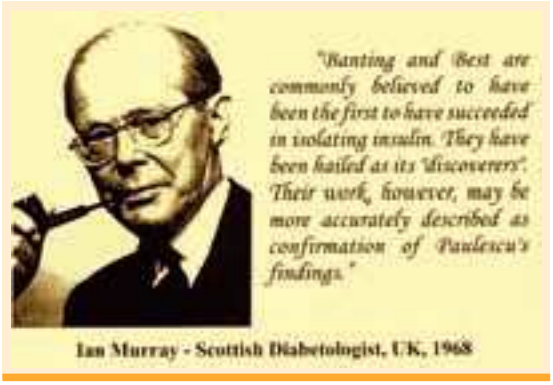

Figure 10. Murray I. Paulescu and the isolation of insulin. (Ref. 21: Journal of the History of Medicine and Allied Sciences. 1971;26: 150-7)

In an article for a 1971 issue of the *Journal of the History of Medicine and Allied Sciences,* "Paulescu and the Isolation of Insulin",[21] Murray wrote:

> *"The fascinating story of the discovery of insulin still provokes controversy (...). Insufficient recognition has been given to Paulescu, the distinguished Romanian scientist, who at the time when the Toronto team were commencing their research had already succeeded in extracting the antidiabetic hormone of the pancreas and proving its efficacy in reducing the hyperglycaemia in diabetic dogs (...). His results, published in August 1921, proved convincingly that he had succeeded in isolating the antidiabetic hormone of the pancreas and demonstrating its action in lowering the blood sugar in both diabetic and normal dogs (...). Banting and Best are commonly believed to have been the first to have succeeded in isolating insulin. They have been hailed as its 'discoverers'. Their work, however, may more accurately be construed as confirmations of Paulescu's findings (...). There can be no doubt that pancréine and isletin were identical. Unfortunately both these extracts caused such local irritation when injected subcutaneously that administration by this route was impossible."*

During years, Murray maintained written correspondence with Pavel (letters included in Pavel's book "Correspondence Lending Support to the Priority of N.C. Paulescu in the Discovery of Insulin"). Some lines from this correspondence explicit the thoughts of Murray about the Paulescu affair.

- Murray to Pavel (November 11, 1969): *"It is satisfactory to have his (Best's) admission that they were so wrong in their reference to Paulesco's work. The explanation on their error, however, seems to me somewhat naïve".*
- Murray to Pavel (February 29, 1972): *"My suggestion is that IDF should institute a Paulesco Memorial Lectureship. The lecture at each triennial meeting would be given by someone of merit".*

Eric Martin

For Eric Martin, Professor of Medicine, University of Geneve, *"it is beyond denial that Paulesco 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 Paulesco, 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".*[22]

IDF Report of the Special Committee set up to present to written summary of work leading up to the discovery of insulin, 1971

In the VII Congress of the International Diabetes Federation celebrated in Buenos Aires (August 1970), a Special Committee was created to devise a summary on the research developments related to the discovery of insulin. Initially, Dr. Witte (Secretary of the IDF), had invited Romania to send a delegate to the meeting, and Rachmiel Levine, President of IDF from 1967 to 1970, had suggested the name of Prof. Pavel.

In a letter to Murray, Pavel wrote: *"I will raise the problem at Buenos Aires. I intend to find some scientists ready to support our point of view which is: the Nobel Prize cannot cover a 'forgetting' whether it is inadvertent or erroneous. An international tribunal is able to correct history without reducing the honor of its perpetrators. This means therefore that if it is not possible to condemn the Nobel Prize jury for ignoring a pioneer, it will be the same for those who, 50 years later, would pass by the works of the true discoverer. We must understand that this is not a question of pushing aside those that have been rewarded with the Nobel Prize – Paulescu himself would not have sought that– but only of placing he who showed the way beside them, if not before them".*[10]

In the end, though, no Romanian was included in the Committee, which was formed by: F.G. Young (UK), President of the Committee, elected also as President of the IDF at the end of the Buenos Aires Congress, and Best's personal friend (Best was still alive and had a great influence in scientific circles). The other members of the Committee were: R. Haist (Canada), who worked with Best, and successor to the Chair of Physiology in the Toronto University; W.J.H. Butterfield (UK); Rolf Luft (Sweden), and P. Rambert (France).

Frank George Young (1908-1988)'s work about diabetes began under J.J.R. Macleod at Aberdeen, and then C.H. Best at the University of Toronto. In 1935 he returned to University College, London. Then he was appointed to the Scientific Staff of the Medical Research Council's National Institute for Medical Research, under the Directorship of Sir Henry Dale, mentor and friend of Charles H. Best (as a matter of fact, Dale had proposed Best for the Nobel Award, in 1950). Young was a Vice-president of the British Diabetic Association from 1948, President of the European Association for the Study of Diabetes (1965-1968), and President of the International Diabetes Federation (1970-1973).

The report was published in 1971 (fifty years after the discovery of insulin) with the title "Report of the Special Committee set up to present to written summary of work leading up to the discovery of insulin". It started with a foreword from Young, and an introduction that established that: *"There was no intention to detract in any way from*

the contributions of Banting, Best and Macleod in Toronto in 1921-1922 but rather to pay tribute to others whose published observations formed part of the background in which the investigations of the group in Toronto began fifty years ago".[11]

The report stressed above all the importance of the clinical application of insulin carried out by the Toronto team, without paying too much attention to the importance of the physiological step. Therefore, the work of Paulescu and the other pioneers was diminished, and the report ignored the chronology of events. The following extracts of such a report are reproduced in the following paragraphs:[12]

EXTRACTS:

If the isolation of a substance involves the preparation of it in pure form, as indeed the word isolation does imply, Banting and Best did not isolate insulin. What they did was to produce for the first time pancreatic extracts containing that substance which were suitable for subcutaneous injection into animals and man, such treatment being highly effective in controlling the symptoms of diabetes mellitus in diabetic dogs and human patients…

There can be little doubt that Paulesco, as well as Banting and Best, obtained a pancreatic extract which contained insulin, and that the pancréine and the insulin present in the crude extracts in which the hormone was first obtained, are the same substance.

Undoubtedly, Professor N.C. Paulesco should be given special credit for the successes with which his experimental observations were crowned. But more than experimental physiology was needed if insulin was to become available in the form, and on the scale, in which it was quickly needed for the therapeutic use. The resources required involved not only the large-scale production of material of a refinement that ensured no irritant reaction on subcutaneous injection into a human being, but also the biological standardization of the hormone and the extensive clinical testing of the standardized product.

The Nobel Prize that was given to Banting and Macleod was awarded for work which the Professorial Staff of the Caroline Institute considered to be of great importance, theoretically and practically. The practical importance of the investigations initiated by Banting and Best is witnessed by the fact that since 1922 countless numbers of diabetic people have been able to live normal lives.

For further reading about the 1970 Report of the IDF, consult the works of Pavel,[19] Ionescu-Tirgoviste and Dworschak.[23-27] Pavel maintained a long time and intensive correspondence with both Murray and Young in defence of the priority of Paulescu's achievements.[17] In one of these letters, Young openly showed to Pavel his personal relationship with the researchers from Toronto, as well as his attempts to be as objective as possible in the contents of the IDF official report.

Young to Pavel (June 23rd, 1971): "It was my loss that I could not have known personally Prof. N.C. Paulesco. As a young research student I spent a period in Abardeen with the late Prof. J.J.R. Macleod, and in Toronto with Prof. C.H. Best. In Toronto I also came to know Prof. J.B. Collip and Dr. F.G. Banting. I knew Dr. C.-H. Best most intimately and am a great admirer of him personally and of his research activities (...). In my capacity of Chairman of the International Committee which has now submitted its report, I attempted to be as objective as possible and to ignore all but evidence published in medical and scientific journals at the time of the discovery of insulin, or shortly afterwards".

Recent statements

- Prof. R. Luft, when participating in an anniversary symposium on insulin, in 1972, described Macleod as a manager and promoter who *"put Collip and Lilly Company into business"*.[28] A former Chairman of the Nobel selection Committee told the NIH that in his view, the 1923 award to Banting and Macleod was the worst error of the Commission.[29]
- James Theodore Nicolas emphasized the misquoting in the English translation by Banting and Best of the Paulescu's statement which appeared in his major French publication, to provide a directly contrary meaning. In relation with this incident, he remembered the thought of Wilfred Totter, expressed as his Hunterian Oration in 1932 (one year after Paulescu's death): *"With the process of time it will become increasingly difficult to separate the commemoration of the dead from the responsibility for their treatment during life, or to believe that posthumous honour is in any real sense a reparation for the dead, or a discharge of the liability of the living (...). 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"*.[30]
- John Waller declared: *"(...) It became clear that Paulesco had performed essentially the same experiments as Banting and Best. The only difference was that he started earlier and, by working with much more care, achieved greater success. It was also undeniable that the Romanian had published his data months before the Toronto team had even written their first paper"*.[31]

Figure 11.
Michael Bliss

Among others, important attemps to resurrect Paulescu's work have been undertaken by Prof. Nicolae Hâncu (Cluj-Napoca University in Romania), Prof. Constantin Ionescu-Tirgoviste (University of Medicine and Pharmacy Carol Davila in Bucharest, Director of the Institute N. Paulescu of Diabetes, Nutrition and Metabolic Disease, and member of the Romanian Academy), and Francisc I. Dworschak, that have devoted several books to the subject. Other scientists and physicians that have stressed the merits of Paulescu in the discovery of insulin are E. Sharpey-Schafer, Jean Pirart, Dorothy Hodgkin, and in Spain, L.F. Pallardo and J.L. Rodríguez Miñón.

Michael Bliss

Michael Bliss (figure 11), Professor of History of Medicine at the University of Toronto, published in 1982 "The Discovery of Insulin", where he describes in de-

tail the experiments carried out by the Canadians, highlighting above all Macleod and Collip's contribution.[32]

Eleven years after the publication of "The Discovery of Insulin", Bliss published an article in the *Journal of the History of Medicine and Allied Sciences.*[33] We copy here some revealing fragments.

"This essay traces the continuation and elaboration of the Banting and Best myth after Banting's 1941 death. Best then became the chief spokesman for the view that the two young researchers had discovered insulin on their own in 1921, and had been deprived of their full share of the consequent glory because of the machinations of Macleod, Collip and their friends. During the next thirty years Best and his friends championed a Banting-and-Best version of the discovery of insulin which featured a substantial enlargement of Best's part in the story. Their version of historical correctness became increasingly convoluted and difficult to maintain as the years went by, however, because of outsiders' interest and the obstinate refusal of the fourth party in the research, J.B. Collip, to play ball. Charles Best himself seems to have had a deep psychological hunger for recognition as a discoverer of insulin. Ironically, by the end of his life, the view of Banting and Best as insulin's discoverers was beginning to backfire, because it had established the pre-conditions for other historians to deny any Toronto researchers a significant role in insulin's discovery.

(…) By 1956 Best was involved in several projects design to secure his role in the insulin adventure. On one occasion he literally asked the director of the Connaught Laboratories to rewrite the history of the discovery of insulin published in one of its handbooks.

(…) J.B. Collip died in 1965. Throughout all of these controversies Collip had refused repeteadly to be drawn in or offer written comment. He had always maintained that the truth about the discovery of insulin was to be found in the scientific publications of those years and that perhaps someone would be able to piece it together after they had all died. Collip's friends were deeply upset at the way in which Best was able to continue his campaign of self-aggrandizement.

(…) From time to time in the 1960s Charles Best would received letters from Romania, inquiring into Banting and Best's research and its relationship to that of a distinguished Romanian physiologist, N.C. Paulesco, who had published his results just before Banting and Best began their work. Best politely replied to the queries but by now was unable or unwilling to enter into renewed controversy. Perhaps it was just as well, for Paulesco's chief admirer, I. Pavel, had substantial evidence to show that rigorous application of the standards of evidence being used by Best to justify the claim that he and Banting had discovered insulin in the summer of 1921, would very likely lead to the realization that priority in the discovery of insulin belonged to Paulesco. Through the 1970s, the argument for Paulesco's priority gained strength and recognition, until by the early 1980s it was on its way to becoming a new orthodoxy in medical history and endocrinological circles. The Paulesco case was based on the realization that, in fact, Banting and Best had not produced results more impressive than Paulesco'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. The final irony of the Banting and Best myth was that it could not meet its own incomplete criteria; 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 form medical history.

Asked about the Paulesco affair in 1971, Best dismissed all of his and Banting's predecessors with the comment that 'none of them convinced the world of what they had. This is the most important thing in any discovery. You've got to convince the scientific world. And we did.' The decision of the Nobel Committee in 1923 showed that the world was convinced that insulin had been discovered in Toronto, as the result of a collaboration building on the original work of Banting and Best. Throughout his later life Charles Best worked very hard and with considerable temporary success, to convince everyone of his and Banting's claims to be the sole discoverers of insulin. In the long run he failed.

(…) At time Best's distortions of the historical record seem to amount to a deliberate, unethical exercise in falsification which verges on scientific fraud. In the later years of his life Charles Best appears to have had a profound psychological hunger for recognition, a serious ego-problem, many thought, which overwhelmed his good sense."

Figure 12. Paulescu's statue near the Faculty of Medicine, University of Bucharest

Glory to Paulescu, 2001

Paulescu was elected posthumously member of the Romanian Academy in 2001. A bronze statue in honor of the Romanian scientist was inaugurated in Bucharest (figure 12), on the occasion of the 80th anniversary of the publication of Paulescu's paper on his discovery of **pancréine.** To the ceremony came, among others, Ion Iliescu, President of Romania at that moment, and Sir George Alberti, President of the IDF. After the ceremony, Alberti published an article in *Diabetes Voice* in which he declared: *"I recently had the enormous honour to unveil a large bronze statue of Nicolae Paulescu in Bucharest together with the President of Romania. The occasion was the 80th anniversary of the publication of Paulescu's seminal pa-*

per on his discovery of insulin (…). My own view is that Paulescu's observations were fundamental to our understanding of insulin, but the Canadians were the first to treat patients successfully. Sufficient credit was not given to the oustanding work of Paulescu".[34]

Conclusion

We conclude that the bestowal of the Nobel Prize to Banting and Macleod was done with very great haste and without due deliberation and that Paulescu's merits were forgotten and diminished for a long time. Banting and Best's article from February 1922 was just a confirmation of Paulescu's results. If just only some people should receive the credit for the discovery of insulin ought to be Paulescu, for his definition of the physiological properties of the pancreatic extract and his experimental research on animals, and Collip, who purified the extract and made possible the clinical utilisation in man. ■

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