

CONSTANTIN IONESCU-TÎRGOVIȘTE

REDISCOVERY OF INSULIN

A Study

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Chapter 1

An Unorthodox Acknowledgement

I would like to thank first of all the unforgettable I. Pavel and Dr. C. Angelescu, who had sufficient belief in me to pass on the baton of the battle for Paulescu together with documents that help to complete the "Paulescu dossier." This baton, which they received from Ian Murray in 1974, was carried by me to the 75th anniversary of the discovery of insulin by Paulescu in 1921. In this work, the eternally youthful Prof. Ștefan Milcu, at his over 90 years, has been a permanent stimulus. He characterized my Romanian book: *"Insulin: The Medical Discovery of the Century belongs to the Romanian N. C. Paulescu"* (1996), with the following words:

"One quarter of a century ago, together with Prof I. Pavel, I began the first actions for the establishment of an indelible truth: Insulin was discovered by our great physiologist N. C. Paulescu. In our time, we won one fight but the battle continued and still continues. This work, written by one of my students, based on new and historically valuable documents is a testimony to this battle. The reader will be convinced that on the firmament of medical science of this century, Paulescu will remain a first class star."

I thank Dr. Lawrence Nwabudike, a young Nigerian doctor here in Romania to specialize in dermatology, who appeared sent by providence to help me in the English translations of this book suggesting to me sometimes to temper my intolerance against those who put many obstacles in the way of proving Paulescu's merit in the discovery of insulin. This is why the accusations of "qualified theft" against Banting, Best and Macleod against whom there insufficient proof have become a discussion of the ethics and morality of scientific research. It happened that on one of the long days spent together, he brought the book entitled *"Long Walk to Freedom"* written by Nelson Mandela which strengthened my feeling that with perseverance and wisdom, one can make the truth on a long disputed issue victorious. Just as this book was adjudged *"One of the most extraordinary political tales of the last century,"* the history of insulin will be one of the most extraordinary scientific tales of this century.

I am grateful to Prof. K.G.M.M Alberti who, in the preface of our book *"The Acid-Base Balance"* gave me an impetus when in 1978, he wrote the following:

"Romania has had previous experience of workers being bypassed by "tyche." The classic example is that of Paulesco who had insulin in his hands years before Banting and Best, but publication was delayed by the First World War. Although finally his publication preceded that of Banting and Best, it was in a French journal little known by English speaking scientists."

I am taking this opportunity to thank him for these beautiful words which he wrote almost two decades ago.

Through their interest expressed in the process of proving Paulescu's rightful place in this epic discovery, I thank Profs. R. Korec (Czech Rep.), R. Luft (Sweden), H. Lestrade and G. Cathelineau (France), L. Krall (USA), M. Berger (Germany), P. Lefebvre (Belgium) S. Bajaj (India) and many others.

I regret that despite the exchange of ideas made with Michael Bliss in our correspondence between 1989 and 1991, he did not radically changed his view about the outstanding contribution of Paulescu in the discovery of insulin. These strengthened my conviction that the lack of recognition of the priority of Paulescu in the discovery of insulin is due to the poor knowledge of the works of the great Romanian physiologist, even by Michael Bliss, who made a severe mistake mentioning somewhere in his book that Paulescu had a wrong view about the pathogeny of diabetes, which for me is a real blasphemy.

In including Paulescu before Banting, Best, Macleod and Collip among the "discoverers of insulin" in the chapter written by him in *"Textbook of Diabetes"* edited by J.C. Pickup and G. Williams in 1993, I believe that he partly succeeded in correcting the misrepresentation of Paulescu's role in the epic discovery that he made in his monograph published 1982. I regret that Pickup could not participate in the XXII Romanian Congress of Diabetes of 23–26 May 1996, which was dedicated to the real celebration of the 75th anniversary of the discovery of insulin. He could have also participated in the ceremony of the unveiling of the plaque on the Paulescu Memorial House which was held in an atmosphere that was unbelievably sacred for the end of this outrageous millennium. After the meeting which we shall have in Toronto (in 1996) when the hurried anniversary of the 75th anniversary of the clinical application of insulin (which should have taken place at the earliest in 1997), I hope we shall be able to synchronize our future plans in an effort to produce a Romanian-Canadian work on the Truth of the discovery of insulin. We cannot pass on this obligation (at least I cannot) to the researchers of the third millennium, who could ask why we did not do our duty which is a result of the events that took place in our century. Why should we number amongst those guilty of the delay in the establishment of the truth about this discovery when, in 2021, the centenary of this discovery will be celebrated? As Lewellyn Barker said:

"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.

I thank the young artists-in-training Anamaria Ionescu (my younger daughter) and Roberto Apati for the production of the portrait of Paulescu as well as the cover and illustrations the book. Loreta Ionescu (my older daughter recently graduated from medical school) has shown a desire to take up the baton for Paulescu's battle under

the protection of her mother and my wife Camelita Ionescu (who is a pediatric endocrinologist). Her father, Prof. Barbillian Nicolae was one of Paulescu's students and one of the only two in his group to obtain the maximum mark at the difficult physiology exam in the second year of his studies in medicine. This happened in 1915, just when Paulescu was carrying out his experiments with his pancreatic extract. I obtained a great deal of oral information from him about Paulescu and this period, but they have no place here in a book based on written documents. Also, I express my gratitude to Mr. Victor Kolleck and Mr. Nicolae Geamănu for their efforts in organising the illustrations of 12 of Paulescu's most important experiments which clearly show the physiologic effects of insulin (Pancreine).

I wish to thank Mr. Eugen Bâră, the director of Romtrans Company and BRD for their financial and technical support which made it possible for this work to be published in a short space of time and in acceptable quality.

Plea for Truth

It takes a great deal of history to produce a little literature.

Henry James

Crossing the ocean is still a means by which the historian can step back to gain perspective.

Malcom Cowley

That which is unjust can really profit no one; that which is just can really harm no one.

Henry George

Be sure you are right, then go ahead.

David Crockett

Veritatem laborare nimis saepe aiunt, extingui numquam.
The Truth is frequently placed in shadow but never destroyed.

A liar is not believed, when he speaks the truth.

One lie makes many.

Chapter 2

Introduction

The history of the discovery of insulin is interesting not only because of the tracing of the chain of events required to uncover a well hidden secret of life, but for the problems connected to ethics and to men of science as well as the lessons we can learn from the struggle which took place in Toronto for the appropriation of this great discovery.

In fact, simplifying things, this discovery was not made in a different way from other great discoveries. After long and arduous work, which was carried out with perseverance and exceptional professionalism, on 31 August 1921, the illustrious Romanian physiologist N. C. Paulescu published a great work through which he announced the discovery of the much sought after anti-diabetic pancreatic hormone which he named *Pancreine*.

All the data published by him on the physiological characteristics of this hormone was confirmed later in every detail. The conclusion of this paper was conceived in such a manner that it can be considered as the **“Birth Certificate of Insulin.”** These will be presented in Prologue 1.

The events following this great discovery were aimed at obtaining a form of insulin which is administrable in man. The struggle to achieve this took place in both Bucharest and Toronto. In Bucharest, this battle culminated on 10 April 1922, when Paulescu obtained the Patent titled **“Pancreine and the process of its production”** which we shall present in Prologue 2. Although the scope of this patent was clear, i.e., the production of a Pancreatic extract which is administrable in man, unfortunately he did not succeed in putting it into practice.

In Toronto on 16 January 1922, the brilliant biochemist Collip, under the leadership of Macleod successfully achieved the purification of an extract suitable for human administration. With this extract, Campbell, another member of Macleod's team, made the first successful human administration on the celebrated Leonard Thompson on 23 January 1922.

As there were only five months between 31 August 1921 (the moment of the discovery of insulin) and 23 January 1922 (the first successful application in man), many researchers confused these two totally separate events, considering them to be one and the same. This confusion was ably cultivated by Canadian diabetes

historiography to the advantage of the Canadians for obvious reasons: to take all the credit for both events under the name of the discovery of insulin.

In Canada, due to the bitter “life and death” battle that had taken place in the “crab’s basket” of Toronto, things were much more complicated as we shall show in Prologue 3 and in other chapters of this book. These events were the subject of a detailed and competent analysis in Bliss’ famous book “The Discovery of Insulin.” I ask Bliss’ forgiveness if in my position as diabetologist and not historian I will bring the necessary corrections for the establishment of the Truth which cannot be but one. Bringing it to light may be delayed but in no case avoided.

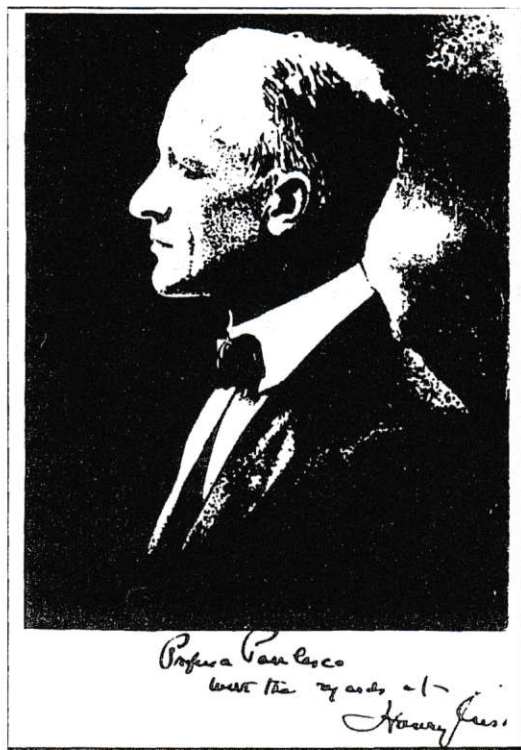
I have tried as much as possible to state my point of view either on the basis of existing documents or on the basis of the arguments Bliss has generously offered in his work. This is the reason for the numerous references I made to his work which was based on documents in Toronto to which I had no access.

Even this is not a definitive account of the discovery of insulin, but it will help to complete the “insulin dossier” with new and important documentation which Bliss, at the time he wrote his book, could not consult such as the content of Paulescu’s Patent for his “*Pancreine*” or references to Paulescu’s works made by Macleod in 1926 showing clearly that the entire Canadian team already as at the summer of 1921, knew of Paulescu’s work and realized its full significance.

New data could come to light through studying the archives of works in Paris where Paulescu worked, careful study of the few documents remaining in Bucharest after the destruction wreaked by the communist era, as well as Scott, Murlin and Cushing’s archives, scientists who all had close relations with Paulescu.

In appreciation of Paulescu’s dissertation “*The Hypophysis of the Brain*” (1908) the legendary Harvey Cushing (born in the same year as Paulescu), sent him the following beautifully autographed photograph.

Cushing considered the technique of transtemporal hypophysectomy described by Paulescu in this monograph to be the greatest contribution in the field.



Harvey William Cushing
1869–1939

Chapter 3

ESSENTIAL PROLOGUES

Prologue 1

Recently, Prof. Pierre Lefèbvre the formal president of the International Diabetes Federation stated that the discovery of insulin (*“begun by Paulescu and completed by Banting and Best in Toronto in 1921”*) is the greatest discovery of this century and one of the greatest of all time (108). However, as can be seen, to Paulescu’s name a reference from 1921 is given, but there is none for Banting and Best, as their first publication appeared only in 1922. From this point of view, this quotation is only partially correct. As the date of insulin’s discovery can no longer be changed from 1921, Lefèbvre aimed at an equivocal formulation for fear of offending the Canadians.

The discovery of insulin meant the unravelling of one of the most closely guarded secrets of life. For this, there was the need for titanic work in which numerous researchers played a part and it was marked in modern times by Claude Bernard, Langerhans, Lancereaux, Minkowski and Paulescu. The latter, in three distinct publications dated the end of 1920 (2nd vol., *“The Textbook of Medical Physiology”*), 23 July 1921 in *“Compte Rendu de Société de Biologie de Paris”* and finally on 31 August 1921 in *“Archives Internationales de Physiologie,”* brilliantly demonstrated the presence in the pancreas of the anti-diabetic hormone, anticipating in this manner, its clinical application.

As will be clearly shown, the discovery of insulin was achieved exclusively in Europe through works commenced in Paris inspired by data obtained by Lancereaux and Minkowski. They were completed in Bucharest by Paulescu through the application of impeccable physiologic reasoning and his results were finally published in Liege in one of the most prestigious physiology journals of the time.

The documents which support this assertion are incontrovertible and can be found in this work which corrects the biased presentation of Paulescu’s contribution to this great discovery written by the Canadian historian Michael Bliss in his work *“The Discovery of Insulin”* (35). This work provided me with much information about people, places and events which took place at great distances from me. I have quoted many passages which are important to the understanding of the events which preceded the discovery of insulin and especially those which followed this discovery and which have led to its application in therapy.

Here, it is appropriate to make a remark in reference to the defining of the moment of insulin's discovery. Michael Bliss made every effort to convince us that this moment coincided with the successful therapeutic use of insulin. If this were so, the anniversary of the discovery of insulin should be celebrated on 23 January 1922, because it was Collip who produced the first purified pancreatic extract and Campbell was the physician who injected this pancreatic extract for the first time as this took place at the end of January 1922.

According to the unwritten code of scientific research, a discovery is marked by the demonstration of a previously unknown structure, substance or phenomenon, defined by precise and reproducible characteristics which later become a part of classical scientific heritage. The moment of a discovery is marked by the date of its publication.

In the case of insulin, these criteria were clearly fulfilled by Paulescu's works which were published in the most widely known physiology journal of the time which also had the illustrious Maurice Arthus (1862–1945), the French Physiologist naturalized in Switzerland described in 1903, the phenomenon of local anaphylaxis (Arthus Phenomenon); Jules Bordet (1870–1961), the Belgian biologist and discoverer of many microbes and author of a serologic reaction for syphilis (Bordet-Wassermann); W. Einthoven (1860–1927) the Dutch physiologist and Nobel Laureate for his description of the electrocardiographic technique; Louis Lapique (1866–1952), the French physiologist who made great contributions to the study of the electrical excitability of nerves; LP. Pavlov (1849–1936) the Russian physiologist and Nobel Laureate for his studies in the field of conditioned reflexes; Charles Richet (1850–1935), the French physiologist and Nobel Laureate for his studies on humoral immunity and many others on its editorial board. Eugen Gley and Emmanuel Hedon whose contribution to the basis of the endocrine pancreatic secretion we will discuss in detail later were also on this board, alongside Paulescu who was a member of this board from 1921 to 1931. Could such a journal then be an obscure or second rate one as the Canadians attempted to make us believe?

As regards the quality of the papers published by Paulescu in his monumental work *“Research on the Role of the Pancreas in Nutrient Assimilation,”* it exceeds all that had been written in the field of endocrine pancreatic secretion not only up to 1921, but even till 1923. An aspect of Paulescu's genius which was easily ignored was that of the demonstration of the effect of the pancreatic extract on all intermediate metabolisms—proteins, carbohydrates and lipids as is presently known. This is the source of the inspired title of his writings. No scientific panel will ever be able to invalidate even one of Paulescu's assertions. They are made on the basis of clear and precise experiments. From the point of view of basic research related to the physiologic and pharmacodynamics characteristics of insulin, all the Canadians' work—published in 1922 and 1923—cannot characterize the endocrine pancreatic