THE DISCOVERY OF INSULIN
and
NICOLAE PAULESCU

F. I. Dworschak

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I have tried not to be offensive and you may think I have been too mild, but I know that any criticism of the Toronto workers will be regarded as almost sacrilegious in certain quarters."

Ian Murray to I. Pavel, 4 April 1970

"He (Paulescu) was the first to describe the actions of what was later called insulin and demonstrated clearly that it was a hormone with actions on all aspects of metabolism".

Sir George Alberti

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INTRODUCTION

This essay will re-examine the contributions to insulin research and other areas of Medicine and Physiology by Nicolae Constantin Paulescu and account for his relative lack of recognition in English language historiography.[1]

One important reason was that he wrote and published exclusively in French. He also had little access to English language medical publications, likely because he could not afford them (see his unanswered letter to Banting dated 5 February 1923). As such, he was out of touch with the rapid advances in diabetes research in the Anglo-Saxon medical literature, relying exclusively on French sources. Starting in 1922 this became fatal, he was left behind and his contributions, meager at this stage also due to financial problems, became almost irrelevant. This is in marked contrast to the previous years (1920-1921) when one could rightly say that he was the leading researcher investigating the whole range of physiological properties of the "inner secretion" of the pancreas that eventually would be known as insulin. *Viewed from this angle he should be considered the discoverer of insulin as a hormone affecting practically all aspects of the metabolism.*

Unlike his personal life and his activities in politics and religion, where we have a certain body of information from his contemporaries, when it comes to his scientific work we are left only with what he published, and all this in French.

Unfortunately, we do not have the work notes of Paulescu. They were left at his death, together with all written material in the care of Dr. V. Trifu. They disappeared because of war, earthquakes, foreign occupations and ultimately because of the installation of a repressive communist regime. We know that Dr. Trifu, who was suspected by the Communist Régime and facing imminent house search, burned all material entrusted to him by Paulescu. According to their Stalinist doctrine, Paulescu was considered an "enemy of the people" (close relations with democratic and bourgeoise France, with the Church, etc.). So we cannot study the progress of his scientific research, possible failures, how much help if any he got, not to mention the tribulations, the moments of despair or of ecstasy. Dr. Trifu had started a study on Paulescu's life and work, but unfortunately again because of hostile political changes he only could write and publish a small introductory fragment in 1944.[2]

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[1] His Romanian name was Nicolae Constantin Paulescu. He often used the "French spelling" of his surname, Paulesco. We shall use Paulescu, except when it is spelled differently in quoted text.

[2] V. Trifu, "Profesorul Paulescu," in Doctorul Nicolae C. Paulescu sau Ştiinţa Mărturisitoare, ed. Răzvan Codrescu (Bucharest: Editura Christiana, 2002), p. 31-97. Originally published in 1944 by the "Fundaţia Regală pentru literatură şi artă", Bucharest, România.

Some of the more reprehensible manifestations of Paulescu's political anti-Semitism, expressed only in his writings but never in his deeds (on the contrary he always behaved in an exemplary fashion), will be discussed in the chapter "Criticism of Paulescu". But they were actually very uncharacteristic of a man otherwise devoted to the principles of charity and helping humanity. Suffice to mention here that we are firmly convinced that they were based on his religious fanaticism and an erroneous conception of the Christian religion.

In this essay, we shall concentrate on his important contributions to medical science, particularly in the field of the discovery of Insulin. His achievements become even more impressive when we consider how limited his resources were and how obsolete were the laboratory techniques at his disposal. He was competing against scientists in the West, where important new developments had rendered their task so much easier. The almost miraculous thing is that during the years 1920-1921 he managed to be the leading researcher in this field.

Obviously, he had to utilize to the maximum his superb intellectual capacity and to make the most of simpler, even obsolete methods of investigation, like for instance simple measurements of temperature. It is not often in history that one single great mind could compete against rivals with infinitely superior armamentarium. But this could not last very long. In the end, he had to give way to the genius of a bright young researcher by the name of James Bertram Collip and this we salute wholeheartedly. We should also emphasize the infinitely superior new techniques at the disposal of the latter. But unfortunately, Paulescu also became the victim of distasteful maneuvering, due either to ignorance or to malice or to both, by Frederick Grant Banting and Charles Herbert Best as we are going to demonstrate in this essay.

M. Bliss' book "The Discovery of Insulin" is without any doubt the most important work in this field.[3] He vacillates between a few words of praise for Paulescu and many unwarranted disparaging remarks (see our last chapter). It is obvious that he has a weak spot for Banting, no matter how many blunders Banting had committed. At the same time, it is equally obvious that he is too often reluctant to grant real merits to Paulescu and is even often inclined to omit essential facts that would raise Paulescu's standing in the world of science. This becomes quite obvious when he criticizes Paulescu's data based on the rather imperfect Pflüger's method for determining glucose levels in the blood especially in the upper and lower registers. The amazing thing is that in spite of being forced to work with such primitive tools, Paulescu was beyond any doubt able to achieve more than Banting was able to do prior to Collip's arrival.

Equally, when Bliss fails to quote the essential text from Macleod where the

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[3] Michael Bliss, The Discovery of Insulin, (Toronto: University of Toronto Press, 2000).

latter expresses his acceptance and recognition of Paulescu's important contributions. Or when he fails to mention the appreciative opinions of other distinguished men of science but has no hesitation to repeat Best's incompetent, at times even ridiculous evaluations of Paulescu's work, etc. We have come to the conclusion that Bliss' work, otherwise an excellent book, very rich in accumulated material and details, is unfortunately quite unfair when it comes to Paulescu's work. We say this regretfully, but after studying Paulescu's original work and other sources, we have come to this inescapable conclusion.

We should not forget that in 1993 Bliss published a stinging but very well documented critique against Best: "*Rewriting Medical History: Charles Best and the Banting and Best Myth",* 1993. His brief comments on Paulescu and Pavel will be rendered in the subchapter "Bliss and Best" near the end. They are quite positive and fair and in stark contrast to the partisan and unfair remarks in his main work "The Discovery of the Insulin".

Ian Murray among others discussed the same issues but he understood how Paulescu's data was to be properly analyzed and interpreted.[4] Murray understood that, no matter how different Paulescu's data was (considering the different methods used), compared to those from the West, they were conclusive. Also, Paulescu had covered a much wider field, and proved more facts than either Banting or Israel Kleiner did.

Bliss' work has the great merit that it is based on many documents hitherto unknown to the public and researchers alike. These include the previously inaccessible archives at the University of Toronto and also the Karolinska Institutet in Stockholm. We should also include Macleod's paper found after his death in 1948 (mentioned only but not discussed or assessed by Bliss). It is known now that it had been hidden at the University of Toronto until published by Lloyd Stevenson only in 1978. Obviously, they had been kept under lock in order to protect the glorification of Banting and others.[5] Unfortunately Bliss has very little to say about some of these sources of information. It is obvious that he is at times very selective when it comes to information stressing Paulescu's great merits. An example could be Bliss ignoring the important work by Paulescu regarding the glucogenesis in the liver or the physiology of the pituitary gland.

Bliss considers Kleiner's contributions superior to those of Paulescu. One can only have the highest respect for Kleiner, the scientist and the man. But because I

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4 Ian Murray, "Paulesco and the Isolation of Insulin", J. Hist. Med. Allied Sci. 1971, XXVI, pp. 150-157. Also: "The Search for Insulin", 1969, in Scottish Medical Journal, 1969, 14, 286; "Insulin: Credit for its isolation", Brit. Med. J. 1969, p.651; "No man an Island", Brit. J., April 1971, p.119.

5 Macleod's paper is more convincing than Banting's version and reveals some unsavory behavior by the latter.

cannot agree with Bliss' assessment, I shall have a brief chapter comparing the works of these two great scientists.

Before completing this Introduction we want to express our sincere regrets that we have to be so critical of Bliss' unjust evaluation of Paulescu, in a book that otherwise has so many merits and deserves our utmost respect. But when writing History such considerations have to give way to what one does consider historical truth such as perceived by the author.

I am very grateful to Prof. N. Hâncu[6] who provided me with a copy of Ion Pavel's work "The Priority of N.C. Paulescu in the discovery of Insulin," 1976, and to Prof. Constantin Ionescu-Tîrgoviste[7] from whom I have received many of his works and copies of Paulescu's most important texts. As such, I was able to also study "the other side" and thus arrive at my own conclusions.

I have tried to be as impartial as humanly possible and to present a work in which I allowed myself to be guided only by what in my opinion could be considered to be the historic truth. In so doing I have arrived at my firm conclusion that among the many who have contributed to this scientific discovery, the greatest contributions have come from

Nicolae C. Paulescu and James Bertram Collip,

or Collip and Paulescu, in whichever order one prefers.

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[6] Prof. Nicolae Hâncu, MD, Ph.D., University of Cluj-Napoca, Faculty of Medicine "Iuliu Haţieganu", Clinical Center of Diabetes, Nutrition and Metabolic Diseases

[7] Prof. C. Ionescu-Tîrgovişte, University of Bucharest, Director of "N. Paulescu Institute of Diabetes", "The Rediscovery of Insulin"; "Documents regarding the Discovery of Insulin", Romanian Academy Publishing House, 2005; "Insulina" and many others.

SOME INTRODUCTORY REMARKS

When analyzing the momentous events of 1920-1923 one cannot escape the conclusion that there still are few very important areas that have not been sufficiently explored.

A most intriguing aspect is the almost unbelievable fact that Pavlov's great discovery of 1899 was, and perhaps still is completely ignored in Toronto. Ivan Petrovich Pavlov, who received the Nobel Prize in 1904, together with N.P. Shepovalnikov proved beyond the shadow of a doubt that the pancreas contained only the innocuous trypsinogen. This only becomes an active proteolytic agent in the intestine under the influence of the enzyme enterokinase and only occasionally under different circumstances. Recently the name enterokinase was changed to "enteropeptidase", as it is not a true "kinase".

Seemingly, Paulescu knew this and also did Kleiner and Collip and so did Ffrangon Robert in his stinging critique against Banting. This elementary fact of Physiology was completely ignored in Toronto in 1922. Accordingly, all the work in Toronto from May to November 1921 was a waste of time, as proven by Collip's work starting in December 1921.

Equally misplaced has been all the praise heaped on Banting. Seldom in history has sheer ignorance been so glorified, as has been Banting's irrational theory that was neither new nor scientifically correct.

This pervading ignorance becomes even more tantalizing when we consider Macleod. Here we have a scientist, well informed, conscientious, who remains silent, at least as far as we know. He expresses no opinion in this regard even in his paper that he kept secret until his death, which was then kept secret in an undignified way by the University of Toronto in order to keep Banting's glory untainted as already mentioned. It is difficult to understand Macleod. Perhaps the fact that in 1913 he had predicted that the active ingredient in sugar metabolism could only be detected in the liver might give us a clue, but certainly no excuse.

The events of November 1921 again demand clarification. Neither Bliss nor Alison Li (Collip's partial biographer) give the exact date of Collip's return to Toronto. It is clear that Collip had discussions with Banting and Best in November 1921. It is clear that Collip gave them the new micromethod for measuring blood sugar (23 November). Bliss even admits: "Working several blocks away in the Pathology Building on the grounds of Toronto General Hospital, he saw Banting and Best every few days, took a great interest in their experiments, and often left with the comment, 'Well, if I can be of any assistance let me know'" (Bliss pp. 97-98).

It would be naïve to assume that Banting did not get any further advice from Collip at this stage (end of November). Particularly striking is the fact that Banting and Best suddenly overcome their inertia and abandon their sacrosanct theory of

avoiding at all costs the noxious effect of trypsin in the pancreas and instead they do the unthinkable: they use an extract from a fresh adult pancreas (December 11). The newly turned scientists successfully use whole cow pancreas (Bliss gives no date), but also extracts from other tissues (13 and 14 December with the expected negative results).

How can one explain this sudden turnabout by Banting? Bliss mentions these facts rather hurriedly and without trying to explain them. As we shall demonstrate, Macleod around this time became familiar with Paulescu's work. It would be unthinkable that Macleod did not share these new developments with his associates. As we shall see, Collip will duplicate Paulescu's tests, but as he never did make notes about his work in progress, we cannot prove this.

As to Banting, he would never admit that he borrowed anything from others, except from Barron, and even here, as we shall see he is not entirely honest. But by now (mid December 1921), because of the split between Banting and Collip, apparently with no further conversations and input from Collip they run out of inspiration and out of luck.

Perhaps one should also mention the use of alcohol to obtain their extract, as advised earlier by Macleod in May but only accepted and with success on 6 December!

Again we should also mention here that often Bliss confers such titles "important breakthrough" (6 December) or "here was another 'major advance'" (using dog's own whole pancreas 11 December) - to some well-established staples of experimental physiology.

What perhaps is a most spectacular example of scientific work are the great achievements realized by Paulescu, forced to work with relatively primitive tools and methods, but arriving at results certainly far superior to those of Banting and Best prior to Collip's arrival, or those of Kleiner, Bliss' different evaluation notwithstanding. In sharp contrast to the Toronto researchers (not including Collip), Paulescu's achievements still stand tall today, what cannot be said about Banting, Best nor about Kleiner's stylistically beautifully expressed but short-lived interpretations.

THE PIONEERS – A RETROSPECTIVE REVIEW

As all books and many articles on this subject give often a detailed list of many interesting observations of the past, going as far back as ancient Egyptian history, we shall confine ourselves in this brief presentation to the more recent, and the more important scientific discoveries in this field.

The first scientific discoveries appeared in the XIXth century. We believe that we can justly start with *Claude Bernard* (1813-1888). He studied the functions of the pancreas, the juice of which he proved to be of great significance in the process of digestion; this achievement won him the prize for experimental physiology from the French Academy of Sciences. Equally important was his study on the glycogenic function of the liver.

A third study resulted in the discovery of the vaso-motor system.
About 1851 he examined the effects produced on the temperature of various parts of the body by sectioning the nerve or nerves connected to them. He noticed that division of the cervical sympathetic nerves gave rise to more active circulation and more forcible pulsation of the arteries in certain parts of the head. A few months afterwards he observed that electrical excitation of the upper (proximal) portion of the divided nerve had the contrary effect. In this way he established the existence of vaso-motor nerves, both vaso-dilator and vaso-constrictor.

What has been called "his most seminal contribution", the "milieu intérieur" ("internal environment"), was the original concept of Bernard that to this day is of utmost importance. Conditions in the world around us constantly change, but the delicate balance of internal chemical characteristics of our bodies is not affected. It is achieved through what we call today homeostasis.

Bernard in 1865 gave us an understanding of the glycemic homeostasis. He also discovered the approximate normal values for blood glucose, the renal threshold for glycosuria (170-180 mg), and the glycogenic function of the liver. With his famous "diabetic puncture of the 4^{th} cerebral ventricle", followed by glycosuria he demonstrated the central regulation of blood glucose. He even ligated the pancreatic ducts but these experiments were inconclusive.

On a broader stage, Bernard played a role in establishing the principles of experimentation in the life sciences, advancing beyond the "vitalism" and "indeterminism" of earlier physiologists to become one of the founders of experimental medicine.

Another great step forward was made by *Etienne Lancereaux* (1828-1910). In 1877, based on clinical observations and post-mortem findings, he presented two cases of diabetes with early onset and rapid progression to death. Here he found that

the pancreatic glands were atrophied, hence he called it “pancreatic diabetes” (1877). He also made the distinction between the “thin” (pancreatic) diabetes and the more frequent “fat“ variety (in 1883 and again in 1888). Again, it was Lancereaux who stated that diabetes was not a disease, but “a syndrome”. Most importantly, he discovered its pancreatic origin, contrary to Bernard’s then prevalent notion of hepatic origin. Very important in this study is the fact that Lancereaux became Paulescu’s mentor and then collaborator. Together they published the important “Traité de Medicine”, vol. I, II and III. Paulescu will later publish vol. IV, while still naming Lancereaux and Paulesco as co-authors.

In 1869, *Paul Langerhans* (1847–1888), a student in medicine in Berlin, while using a new, superior microscope, discovered that the pancreas consisted of two different cells. The majority, called acinar cells, were involved in the intestinal digestion, whereas the others, arranged in form of islands, could not be related to any physiological function at that time. Langerhans dedicated his paper to “Professor Virchow in admiration and gratitude”. These cellular clusters will be called “Langerhans islands” in 1893 by Gustave-Edouard Laguesse from Lyon in honor of their discoverer. This chapter in medical history is not only of scientific value, but it also reveals the high ethical and human values of the scientists of that era, in stark contrast to the vulgar and despicable turpitude in some circles during the 1920s.

The next great step forward took place in Strassburg. It was here that *Joseph Freiherr von Mering* (1845-1908) and *Oskar Minkowski* (1858-1931), student of Bernard Naunyn, both professors in Strassburg (then part of Germany) in 1889 for the first time in medical history conducted a pancreatectomy on a dog. At that time they were investigating the pancreatic influence on intestinal fat absorbtion. They noticed instead the clinical signs of diabetes, namely, hyperglycemia, glycosuria, and, finally, ketosis, coma, and death in 2 or 3 weeks. Thus, they proved that the pancreas was the site of secretion of an «antidiabetic» substance, now known to be insulin. Further research confirmed this fact. A memorable case of serependity.

Further they conducted experiments and found out that grafting a part of the pancreas underneath the skin prevented the development of diabetes. So they called it “pancreatic diabetes” (unaware of Lancereaux’s use of same term). One year later, Minkowski injected a “dry” pancreatic extract in a diabetic dog but this time without any success. The same extract in physiological solution fared no better.

Noteworthy are also von Mering’s studies on phlorizin-induced glycosuria. At Strassburg they had also investigated the chemical changes of diabetes and found in 1884, that formation of ß-hydroxybuturic acid with a concomitant decrease in blood bicarbonate was the cause of diabetic acidosis; they also proved that diabetic coma was accompanied by a decrease in the amount of carbon dioxide dissolved in the blood, and he introduced alkali therapy to counteract it.

Another important step forward was realized by *Georg Ludwig Zülzer.* According to A. Labhart, a group of fourteen researchers made attempts at isolating this internal secretion during the period from 1892 until Paulescu (1921) and the Toronto Group (1922) made their definitive discoveries. The most persistent of these physiologists and clinicians has to have been Georg Ludwig Zülzer. From the early part of 1903 and for twelve years thereafter, Zülzer made attempt after attempt to treat diabetes with a pancreatic extract. He called his extract "acomatol". After encouraging results on animals he succeeded spectacularly *on a man* in 1906 (21 June and repeated next day). The clinical results were astounding, but unfortunateley the sugar levels in blood in those days could not be established. Methods for detecting blood sugar were not yet available and in this particular case (Zulzer 1906) the experimental dog was also incontinent of urine and so no data about the level of urinary sugar could be obtained. Thus the experiment-treatment could not be continued as no further extract was available.

Next summer Zülzer resumed his experiments *on four patients*. With great difficulties he repeated in 1907 his experiments on a 27 year old patient, a 7 year old boy, a 37 year old patient and on a 65 year old patient. He was able to reduce the glycosuria but the reactions were too severe (fever, vomiting, convulsions) and he was forced to abandon his experiments. He published his results in 1908. Perhaps he did isolate the products of the internal secretion of the pancreas without realizing it, by misinterpreting the signs and symptoms of hypoglycemia as toxic side effects of his extract. It is unfortunate that blood sugar measurements using small amounts of blood were not available at the time of Zülzers' discovery. If they had been, possibly the discovery of insulin would have been greatly accelerated and many diabetic lives would have been saved. At least in the initial stages he thought that diabetes was caused by adrenalin.

J. Forschbach at Minkowski's clinic, now in Breslau, resumed Zülzer's experiments (three patients and three dogs but again with severe reactions, thus forcing putting an end to their experiments). It is interesting that Zülzer in 1911 applied for and obtained a patent for his discovery in the USA.

Ernest Lyman Scott (1897-1966) was born in Kinsman, OH (USA), and received his B.S. from Ohio Wesleyan University in 1902. In 1911 he earned an M.S. from the University of Chicago, and then in 1914 a Ph.D. from Columbia University, where his dissertation included the development of "the Standard Blood Test for Diabetes". It was his work in Chicago, namely his early research on isolating insulin from the pancreas for which be became best known. Scott had come to the lab of Anton Carlson, hoping to focus his research on diabetes after a close friend died of this disease. He was doing experiments on dogs that had their pancreas removed *or tied off.* When the caretaker quit because of the constant presence of flies and messy stinking urine puddles he became intrigued. This is how

Scott came to realize that the flies were attracted to the pools of urine because they contained sugar.

While doing his graduate research work he first tried unseccessfully to ligate the pancreatic duct. After he failed in his experimental ligatures of the pancreatic ducts he turned to Zülzer's method of extracting *with alcohol*, at the lowest possible temperature, from *adult beef pancreas*. In 1911 he obtained encouraging results on 3 of 4 diabetic dogs, but without biochemical proof, based only on clinical observations and urinary testing. He then tried to isolate the internal secretions from the removed pancreases.

He is considered by some to be the first to successfully separate a substance from the pancreas that aided carbohydrate metabolism. Then by using the recently introduced method of measuring glucose in blood, he also was able to study the effects of pancreatectomies on the *blood sugar* of dogs and cats and found out that the blood sugar had increased.

His results were regarded with much scepticism by his Prof. Anton J. Carlson. Nevertheless young Scott persisted, resumed his experiments but with little luck this time. For financial reasons he had to leave Chicago and to move to Kansas City[8]. He turned over his written manuscript (Scott: "Thesis T-10553, University of Chicago", 1910, written end of summer) to Carlson who will publish it in 1912 "*On the Influence of Intravenous Injections of an Extract of the Pancreas on Experimental Pancreatic Diabetes"*- Am. J. Physiol, 1912; 29:306-310). [9] This published article is riddled with altered passages of the original text, missing important elements and accompanied by many critical remarks! Nevertheless Scott's conclusions were: There is an internal secretion that can be extracted. The active ingredient is destroyed by oxidation or pancreatic enzymes. It is insoluble in strong alcohol but soluble in acidified water. It is unfortunate that he could not continue his promising experiments and so he became almost forgotten. As such, Banting had no hesitation to name him among his sources for his own publication.

We shall mention later in our text how Scott approached Paulescu (letter of 5 November 1921) in the hope of collaborating and obtaining a patent in the USA.

Another major contribution came from *John Raymond Murlin* (1874-1960), an assistant professor in physiology at the Cornell University Medical College in

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[8] Scott obtained his Master of Science in 1911 and was offered a job as lecturer in physiology with a salary of $750 yearly. As his wife was expecting he had to turn it down and accepted a position as assistant at University of Kansas with a salary of $1500 per year and as such he left for Lawrence, Kansas end of September 1911.

[9] Also: Scott E.L., "The relation of pancreatic extract to the sugar of the blood". Soc. Exp. Biol. and Med. 10, p. 101-103, 1912-1913. Also: Scott E.L. "Priority in Discovery of a Substance Derived from the Pancreas Active in Carbohydrate Metabolism", Jour. Amer. Med. Ass., pp.1303-1304, 1923.

1912[10]. Working with *Benjamin Kramer,* assistant professor in Pediatrics at John Hopkins University they succeed (1916) in producing pancreatic extracts capable of reducing glycemia even *in human beings,* but the toxic side effects forced them to abandon this avenue. They also demonstrated that a diabetic dog could utilize sugar if given an extract from his own pancreas.

They published their results in 1916.[11] Unfortunately Kramer had to leave John Hopkins and Murlin was conscripted into the army, but he returned to Rochester after the war.

Encouraged by Paulescu's results he immediately resumed his experiments (October 1921). In 1923 he will confess:

> "The immediate stimulation to recommence this research was the report of favorouble results obtained by Paulescu, which were indeed very encouraging. He had observed that i.v. injections of a sterile pancreatic extract into depancreatised dogs produced a decrease or even a temporary suppression of hyperglycemia and of glycosuria, as well as a reduction in the excessive production and assimilation of urea and ketone bodies. The effects appeared immediately and reached a maximum in about two hours and continued for about 12 hours. The method used by Paulescu appeared advantageous."

At the end of May 1922 Murlin received the visit of Banting with regard to treating one of his patients (Jim Havens). His first extract, prepared using Banting's method, proved too strong and had toxic effects. One month later he tried oral administration but with no positive results. Injection of 8 cc in the thigh led to abdominal pain and vomiting. The family finally gave up and they returned to the Toronto (Collip) extract. Murlin nevertheless continued his efforts with some good results in a few patients. Thus encouraged, he contacts Wilson Laboratories with the view to produce his extract that he called *glycopyren*.

He even contacted Scott in order to obtain a patent but apparently Scott declined. He nevertheless applied for a patent in 1923, and apparently obtained one, but by then it was meaningless. In 1925 he tried to contest Toronto's valid patent that had been obtained in January 1923.

We should not forget that he succeeded in isolating a second hormone produced in the Langerhans' cells, but far less potent than insulin, that he called *glucagon.* If insignificant in the treatment of diabetes, it was nevertheless a worthwhile addition to the understanding of the physiology of the pancreas.

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[10] "Discovery of extract that has power to restore capacity lost in diabetes is made public by Dr. John R. Murlin". p. 2, Nov.11 1922, Democrat and Chron. Rochester, N.Y.

[11] J.R. Murlin, B. Kramer, "Pancreatic Diabetes in the dog", J.Biol.Chem., p. 481-538, 1916; Murlin J.R., Kramer B., "A quest for anti-diabetic Hormone", 1913-1916, in Journal of the History of Medicine 11, pp. 288-298, 1956.

The important contribution by *Israel S. Kleiner* will be treated in a separate chapter.

For information on other researchers in this field please consult the "Appendix" at the end of this essay.

NICOLAE C. PAULESCU

The Romanian scientist Nicolae C. Paulescu was born on 8 November 1869 and died on 19 July 1931. He was born into an urban family, but with deep roots in the peasant foundation of the Romanian society at that time. In high school, he displayed an exceptional mind with a remarkable interest in natural sciences and foreign languages (Latin, ancient Greek and French). After his "baccalaureate", he decided to study medicine.

The Paris Period

In 1888, he went to Paris to enroll in the faculty of Medicine. After three years he successfully passed his exams and was then allowed to work in the Hôtel-Dieu Hospital (1891-1894) under the renowned Étienne Lancereaux, still remembered for his studies on diabetes and the pancreas, and for his celebrated three-volume Traité de Pathologie, published in 1875, among many other achievements. Soon Paulescu, working as an extern at his hospital became his trusted student and collaborator.

Lancereaux became his beloved mentor and Paulescu was his favorite disciple. In 1894 Lancereaux became chief physician at the Hôpital Notre-Dame-du-Perpétuel-Secours and he immediately chose Paulescu as his intern (1894-1897). This was the beginning of a productive collaboration and together they will become an illustrious duo. Later on in 1908, he will be named President of the French Academy of Medicine

Lancereaux had consistently argued, based on clinical and empirical observations, that diabetes had a pancreatic origin. He also introduced the term "pancreatic diabetes" as early as 1877 in a paper[12] in which he described two young patients with rapidly progressing and ultimately fatal diabetes; autopsy revealed a "fibrocalculous disease" of the pancreas. According to C. Ionescu-Tîrgovişte, Lancereaux used this term in four different publications over a period of 12 years.[13] Lancereaux had also made a distinction between the fat (*diabète gras*) and the thin (*diabète maigre*)[14] forms of diabetes mellitus in 1888, the year when Paulescu arrived in Paris, the latter form being the "pancreatic diabetes". This observation still stands today, albeit under different nomenclature (type 1 and type 2). This

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[12] Lancereaux E., "Notes et réflexions à propos de deux cas de diabète sucré avec altérations du pancréas", C. R. Soc.Biol., 4, pp.509-510.

[13] Constantin Ionescu-Tîrgovişte, Cristian Guja, Sorin Ioacara, in "Documents regarding the Discovery of Insulin and its Clinical Utilization", p.17, Bucureşti, 2005, Romanian Academy Publishing House.

[14] Lancereaux E, "Le diabète maigre: ses symptomes, son évolution, son prognostic et son traitement", Un. Méd., Paris, 1880, 29, 205-211.

likely was the first time a connection was established through clinical and pathological observations (and not only assumed) between diabetes and the pancreas and he also described diabetes as a syndrome and not a disease.

Coincidentally the term "pancreatic diabetes" was also used by Minkovsky and von Mering, based on actual pancreatectomies in 1889 and thus eliminating any doubts as to the pathogenesis of diabetes.

Lancereaux also authored many other important discoveries and publications. Indisputably Lancereaux' genius had an enormous, indelible and fruitful influence on young Paulescu and their collaboration led to many accomplishments.

It is now that Paulescu, greatly influenced by the genius of his mentor, displayed his own superb intellect and talents and quickly became known for his original and innovative work. In 1897, Paulescu obtained the title of Doctor of Medicine with his thesis "Recherches sur la structure de la Rate" ("Study of the structure of the spleen") and around the same time he was named deputy surgeon at the same hospital (Hôpital Notre-Dame-du-Perpétuel-Secours). Later in the same year, he was named editorial secretary of the *Journal de Médicine*.

This was the start of a brilliant career in medicine and physiology. Around the same time, he had entered the Faculty of Sciences obtaining a Doctor degree in Biological Chemistry in 1897 and in 1899, he earned the title of Doctor of Natural Sciences. He had already become known with his publication "Research on the coagulation properties of hepatic blood."[15] He also collaborated with other great scientists of France of that time.

For his brilliant activities in France, he received in 1902 the title of "Officier de l'Académie".

He published a great number of scientific contributions in the leading medical periodicals in France displaying remarkable skills in conducting physiological experiments and arriving at original, innovative results. Thus, he quickly became a respected figure in the medical-scientific community in France.

Among his many contributions were his studies of the thyroid gland[16], the adrenal glands,[17] the function and structure of the spleen, treatment of aneurysms, etc.

Perhaps the most remarkable achievement was his collaboration with Lancereaux in writing the renowned "Traité de Médicine." The first volume was printed in 1903; three more volumes followed later and have been reprinted several

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[15] "Recherches sur la coagulabilité du sang hépatique," Archives de Physiologie, January 1897, p. 21.

[16] N.C. Paulesco, "Glande thyroïde – physiologie normale et pathologique", J. Méd. Int., 1898, pp.11-14.

[17] Paulesco, "Recherches expérimentales sur la physiologie des glandes surrénales", in Journal de Médecine Interne, 1 January 1899, p. 298 (I); 1 March 1899, p. 364 (II).

times.

Another important achievement was the development of his unusual surgical skills, partly thanks to the collaboration with Paul Raynier. This is exemplified by the fact that he was the first to achieve *end to end ureteric anastomosis* in experimental animals (1897) [18]. According to Bradley Fields Schwartz, this procedure was first attempted in animals in 1906 (no name given) and Higgins first[19] applied it to humans in 1935. It would not be the first time that Paulescu is occulted in the English speaking historiography.

While collaborating with Lancereaux, they established a new concept of the nature of disease, which will later be universally accepted: *"There are no diseases of different organs, but only general illnesses of the entire organism, each one affecting one organ or another.*"

With Albert Dastre, he started his first studies on the pancreas in 1898 but will have to abandon this work as he decides to return to Romania in 1900 in spite of promising offers to join other universities in the West (Freiburg, Switzerland).

Return to Romania (1900-1916); Work on Pituitary and Glycogen.

In 1900, he settled in Bucharest, first as an assistant professor. Four years later, he became a full-fledged professor of Physiology at the Medical Faculty of Medicine in Bucharest (11 February 1905– 19 July 1931), Professor of Clinical Medicine at the Hospital St. Vincent de Paul, also in Bucharest, and a respected figure in the fields of Medicine and Physiology.

It was in 1901 that he received in Paris the title of "Doctor of the Paris University", as already mentioned, with his study of the effects of the alkaline chlorides on living tissues, published as "Study of the effects of alkaline chlorates upon living matter." [20]

Among his most important achievements were his great contributions to the study of the pituitary gland, of the metabolism of glucose-glycogen and culminating with his remarkable contributions in the field of diabetes. These will be discussed in more details later on.

Most outstanding were his experiments on pancreatic diabetes. By 1916, he had already obtained positive results by injecting depancreatized dogs with pancreatic extract and registering significant reductions in the levels of glucose and urea in blood. These early initial successes (very significant) had to be interrupted because of WW1.

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[18] Paulesco and Paul Renier, "Urétéro-anastomose", Bulletin et Mémoires de la Société de Chirurgie de Paris, July 1897 and February 1898.

[19] Bradley Fields Schwartz, Associate Professor of Urology, Department of Surgery, Southern Illinois University of Medicine on Internet.

[20] "Thèse de doctorat à la Faculté des Sciences de l'Université de Paris", 1901, p. 82.

Paulescu's studies on the pituitary gland[21] were praised by Harvey Cushing. According to S.L. Teichman and P.A. Aldea in their 1985 article[22], Cushing adopted for animal experimentation Paulescu's innovative trans-cranial, subtemporal route that resulted in a much lower mortality rate than the previously used trans-pharyngeal method.

In December 1908, Harvey Cushing presented his first paper on the pituitary gland to the American Physiological Society in Baltimore. He stated that, "*Although elaborate studies have been made upon the morphology and physiology of the gland, the only striking series of successful extirpations have been those recently reported by Paulescu*."[23] Eventually Cushing replaced Paulescu's method for surgery on humans with the trans-sphenoid approach via sub-labial incision.[24] They corresponded frequently and in 1930 Cushing, who had the highest esteem for Paulescu, invited him to the USA for a medical convention and even tried to arrange financing this trip to the USA. However, due to poor health and for financial reasons Paulescu had to decline. His contributions in this particular field will be discussed in more detail in our last chapter.

Among other important contributions by Paulescu was his work on glycogen formation in the liver[25]. This will also be described later in more details. Perhaps also interesting but without any significant follow-up were his experiments with aspirin for the treatment of fever as we are led to believe by Constantin Angelescu and Laura Sigarteu-Petrina.[26]

We have already mentioned the first volume of his Traité de Medicine written in collaboration with Lancereaux, published in 1903 (940 pages). Volume II was published in 1905 (1200 pages). Volume III followed in 1912 (1200 pages) after Lancereaux' death in 1910. Volume IV will be published much later, in 1930.

During this time he published his important works on glycogen and conceived a perfect method for performing *pancreatectomies*, including one variant that also included resection of a hepatic lobe. He also published his initial method to prepare *pancreatic extract*, we shall call it *method A*: basically consisting of:

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21 N. C. Paulescu, A) L'Hypophise du cerveau. Recherches expérimentales, (Paris: Éditeur Vigot Frères, 1906). Also B) "Recherches sur la physiologie de l'hypophyse du cerveau: L'Hypophysectomie et ses effets," J. Physiol. Pathol. Gen, 1907, 9, pp. 441-456.

22 S. L. Teichman and P.A. Aldea, "Pioneers in Pituitary Physiology: Harvey Cushing and Nicolas Paulescu," J. Hist. Med., January 1985, 40, pp. 68-72.

23 S. J. Crowe, H. Cushing and J. Homans, "Experimental Hypophysectomy," Johns Hopkins Hosp. Bull., 1910, 21, p. 130.

24 Teichman, "Pioneers Pituitary", (fn 22) p. 71.

25 Trifu, (fn 2), p.51 quoting Paulesco, "Sur la formation du glicogène dans le foie par suite d'injections de divers sucres dans la veine porte", Annales de Biologie, Paris, 1911.

26 Constantin Angelescu and Laura Sigarteu-Petrina, "Nicolae C. Paulescu", 1982, Editura Ştiinţifică şi Enciclopedică, Bucureşti.

> "Material (from dog but also from beef pancreas) hashed and mixed with sterile water (10 times its weight), stored on ice for 24 hours, filtering through tarlatan and addition of NaCl (7 per thousand), sterilizing, injecting with help of a cannula by force of gravity into the external jugular vein, 100cc over 15 to 20 minutes." (more details later on in this text).

Later he will develop a more elaborate method (B), which will be described in his Patent application (1922) and one year later in 1923 another modification, using alcohol (C).

During this period of time, he also wrote in Romanian the lesser known "Manual of Physiology" 1906, about 1000 pages lithographed with hand-written script.

Bucharest (1916-1920)

Because of WW1 and illness (hematuria), all scientific experimentation or publication became impossible during this time. The foreign occupation and use of all medical facilities for treating the wounded and the sick made any medical research impossible. So whenever he could, he wrote.

It should be remembered that this Textbook of Medicine in French became very popular in medical and university circles, and was printed in several editions. He wrote, while immobilized by war, three equally important volumes of Physiology (Traité de Physiologie Médicale). They were published later, in 1919, 1920 and 1921[27] respectively, the second volume being of extreme importance for the subject now under discussion.

Discovery of Insulin and its properties (1920-1923)

His most important works were his four communications in 1921 "Reports at the Society of Biology and its Branches, Romanian Chapter" (Comptes Rendus) *presented on 21 April, 19 May, 9 and 23 June 1921 at the Société de Biologie et de ses filiales, Section Réunion Roumaine*. They were published on 23 July 1921 in Reports of the Society of Biology of Paris (Comptes Rendus de la Société de Biologie of Paris). They were followed by the history making *"Research regarding the role of the Pancreas in nutrient Assimilation,"* received on 22 June 1921 and published on 31 August 1921 in the "Archive Internationale de Physiologie", Liège and Paris. These will be discussed in the next chapter.

With the second volume of his Textbook of Medical Physiology (1920) and

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[27] N. C. Paulescu, "Traité de Physiologie Médicale", 2110 pages published in three volumes (1919,1920 and 1921), and "Traité de Médicine", 3868 pages published in four volumes (1903, 1905, 1912 and 1928), the first three in collaboration with E. Lancereaux (died in 1911) as well as over 90 scholarly papers.

the above mentioned publications, Paulescu established his indubitable leadership in the field of Insulin Research until 23 January 1922 when Collip injected his pancreatic extract into the young Leonard Thompson. Leonard supported this new extract very well and lived into adulthood, and Collip will write a new page of glory in the history of Medicine. But the Nobel Prize in 1923 will go neither to Paulescu nor to Collip but to Macleod and…Banting! It goes without saying that this was a crushing blow to Paulescu. His reaction will be shown later in our text.
In the meantime, unaware of the events taking place in Toronto, Paulescu carried on with his experiments.

In 1923 he published in "International Archives of Physiology" two articles ("Some chemical and physical reactions following an aqueous Pancreatic extract to eliminate the protein substances present in excess."[28]) on 31 May – and "Several procedures to introduce the pancreatic extract in the organism of an animal"[29] (10 August 1923), which will be discussed later in this essay. In the following year, he will publish an article "Treatment of Diabetes", in "La Presse Médicale", 5 March 1924, pp. 202-204. Here he gives a brief but complete account of his achievements in this field since 1911.

In the first publication (1923), he mentions his new improved method (B) of extracting a more potent Pancreine, one that could even produce "aglycemia", as well as his method (C) based on alcohol extraction.

Unfortunately, for him, but fortunately for humanity as a whole, at this time the therapeutic use of insulin was already a reality and as such it rendered Paulescu's otherwise interesting observations irrelevant. History had already been made, and as we shall demonstrate, not always in a noble, inspiring way.

His 14 years of work on the discovery of insulin and its physiological properties had been falsified by two ignorant young men, without any principles of intellectual honesty and without him being aware of this. As a consequence, his name almost disappeared from the Anglo-Saxon medical literature and this was where it counted most. These unprincipled authors did not even bother to correct the record once they realized the great damage they had caused. Best did admit their grave error in a letter dated 15 October 1969 to Prof. Ion Pavel, but never did so in public. As we shall see, Best does himself no honor in a second letter.

After 1923; his tragic last years

The remaining years of his life were sad indeed. Being unfamiliar with the rules of the Nobel Committee, he regarded himself as unjustly victimized. He wrote

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[28] "Quelques Réactions Chimiques et Physiques apliquées à l'extrait aqueux du pancréas pour se débarasser des substances protéiniques en excès".

[29] "Divers Procédés pour introduire l'Extrait Pancréatique dans l'Organisme d'un Animal Diabétique".

a letter of protest to the Nobel Prize Committee that naturally was ignored. Equally, it was not accepted by the French Academy of Sciences or by the Congress of Physiology in Stockholm in 1926. It was only published by Presse Médicale on 5 March 1924. Even in his own country, he lacked the necessary moral support or acknowledgement for his 14 years of hard and genial pioneer work in this field. Nevertheless, he carried on with his research work.

In June 1924, he published in Journal d'Urologie convincing evidence that Ambard's theory about a specific constant relationship in the urinary secretion was erroneous.

Although ill, he found enough stamina to publish in 1930, under the most difficult conditions a IVth volume on Medicine entitled "Lancereaux-Paulescu, Textbook of Medicine. Pathology of the assimilating mechanisms, urinary and genital" (Traité de Medicine. Pathologie des appareils assimilateurs, urinaire et génital), 676 pages. He also wrote, in manuscript only, a fifth volume that was never published!

The personality and life of Paulescu were a tragedy indeed. Suffice to mention following crushing events:

After a brilliant career in Paris, with offers to join universities such as Freiburg in Switzerland, etc., he came back to his own country, only to have to wait four years before becoming full-fledged professor.

Even in his own country for which he had sacrificed a brilliant career in the West he was quickly forgotten. Even more so, during the communist era his name became anathema and so he simply disappeared from history, both in Romania and elsewhere.

Scientists like Ian Murray, E. Martin and Ion Pavel attempted to rehabilitate him in 1969-1971. Their effort at the 1970 meeting of the International Diabetic Federation in Buenos Aires failed. This was due to incompetent work by the appointed committee, which had put the good relations with Charles Best, a friend of the head of this Committee, above all principles of justice and fairness. We have mentioned that all his archive left after his death, which would be so helpful in studying this fascinating chapter in the history of Medicine had to be burnt in the 1950s by one of his disciples to whom he had left this treasure, but who was in grave danger of being arrested during the communist regime of that time.

Since the fall of the communist regime in Romania in 1989, there has been an attempt in this country to restore the truth and to recognize Paulescu's great merits. He has been named post mortem, member of the Romanian Academy, and the Center for Diabetes was renamed "The N. Paulescu Institute of Diabetes, Nutrition and Metabolic Diseases".

But when in August 2003 an attempt was made to unveil a plaque in his honor at the Hôtel Dieu Hospital in Paris, an organized demonstration by misled elements

of the Wiesenthal Center in Los Angeles and political bodies in Paris prevented this from happening. This plaque was meant to honor the scientist Paulescu and not his rather primitive political and religious views and the perpetrators of this odious act have only disgraced themselves. This is exemplified in an article entitled “Paris manque d'honorer l'inventeur antisémite de l'insuline” written by Nicolas Weill that appeared in Le Monde on 25 August 2003. He wrote, "If the Nobel Committee in 1923 considered Paulesco unworthy to receive the Nobel Prize, Hôtel Dieu in 2003 cannot do less by concluding that Paulescu’s brutal inhumanity nullifies all his scientific merits”. In fact, the Nobel Prize Committee never considered Paulescu for the Nobel Prize because he was never nominated. As such, he simply could not be found to be "unworthy". Also, the author implies that the Committee had considered Paulescu's social and political views in their evaluation of his scientific work, which they certainly did not. So the use of the Nobel Prize Committee in an attempt to criticize the Hôtel Dieu ceremony is ridiculous but also repulsive.

We could also add many other false allegations found on the Internet and in the press. But what is most hurtful is to see true historians treating at times Paulescu in a rather partisan and unfair way.

Paulescu died 17 July 1931 after prolonged suffering, of uremia caused by bladder cancer.

PAULESCU, CUSHING AND THE HYPOPHYSIS

In marked contrast to the revolting way that Banting and Best treated Paulescu, it is well known and documented that Cushing had the highest esteem for Paulescu's work in the field of experimental animal pituitary surgery and Physiology, as he manifested on many occasions.

Paulescu published his findings in "Hypophysis of the Brain; Experimental Research" (1906)[30], and "Research re: the Physiology of the Brain. Hypophysectomy and its effects"[31] where he reported 24 cases of hypophysectomies using his method.

Simply put Cushing appreciated that Paulescu succeeded in allowing an exposure of the basis of the cranium in experimental animals, sufficiently large to allow gentle lifting of the temporal lobe with adequate visualization, thus rendering possible active surgical resection of the pituitary gland. As Paulescu states almost poetically, "to allow it to be plucked in its entirety as one plucks a fruit from a tree" ("de pouvoir la cueillir toute entière comme on cueille un fruit sur un arbre").

It was actually a very delicate and difficult operation, as Norman M. Dott will later attest.

Cushing presented his first paper "Is the pituitary gland essential to the maintenance of life?"[32] in December 1908 (American Physiological Society in Baltimore) and it was published in 1909. Here he clearly states according to Teichman and Aldea (22): "the only striking series of successful extirpations have been those recently reported by Paulescu". And further:

> "Hence, in our operations, we have been led to accept Paulescu's method, which possesses (….) unquestioned advantages; for the (….) technique (…) brings into play the principle of cerebral dislocation of importance in many cerebral operations on man, and (…) allows (…) the hypophysis (...) to be brought clearly into view (…) with little danger of injury to the cerebral substance and without risk of compression symptoms." Further Cushing, as quoted by Aldea, states: "we feel that the results of these observations sustain Paulescu's contention that a total hypophysectomy is incompatible with the continuance of life".

In his second paper (July 1909), "The Hypophysis cerebri: Clinical aspects of hyperpituitarism and hypopituitarism"[33] Cushing states "Our experimental

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30 "L'Hypophise du cerveau. Recherches expérimentales".

31 "Recherches sur la physiologie de l'hpophyse du cerveau. L'hypophysectomie et ses effets", 1907.

32 Harvey C. Cushing and Lewis L. Redford, John Hopkins Hosp. Bull., 20: 105-107, 1909.

33 Cushing, JAMA, 53: 248-256, July 1909.

observations, confirmatory of those of Paulescu, have shown that the procedure must be limited solely to a partial removal of the anterior lobe with careful avoidance of total removal."

In 1912 in his book "The Pituitary Body and its Disorders", Philadelphia, J. B. Lippincott, p. 12, Cushing gives full credit to Paulescu for the settlement "beyond peradventure" of the question as to whether or not the pituitary gland is essential to life.

But when he begins to operate on human patients, Cushing found that Paulescu's method was no longer the method of choice. Instead, he introduced the transphenoid approach from below through the mouth and this allowed him to proceed further in expanding the treatment of pituitary tumors in humans.

Furthermore, the authors (T & A) stress the warm relationship between these two scientists that included a prolonged correspondence, most of which is unfortunately lost. It was Paulescu who made it possible for his young Romanian protégé Dumitru Bagdasar to come to the USA and work with Cushing at the Peter Brigham Hospital during 1928 and 1929.[34] Bagdasar later became the founder of Romanian Neurosurgery. Cushing also invited Paulescu to come to the USA in 1929 to attend the Physiological Congress and when informed that Paulescu did not have the means to finance such a trip, Cushing promised to try and overcome these difficulties. Unfortunately, Paulescu's health deteriorated and this became impossible. All the above is contained in the letters of Cushing to Bagdasar (21 August 1926, 7 May 1929, and 11 July 1929, in the collection of I. Pavel according to our authors Teichman and Aldea).

We should also mention the very informative and extensive article by Norman M. Dott published in 1923[35], where he states:

> "Paulesco, who published the first really satisfactory account of experimental operations on the pituitary body, made an investigation into the anatomical possibilities of approaching the organ by surgical means. His review covered the whole vertebrate series and was made as a preliminary to his experiments. He concluded that (…) above all, the dog offered the best possibilities" (p. 242). More on this subject in our last chapter'
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> The main features of Paulescu's method are given on page 247.[36]

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[34] Bagdasar's name is not listed in Bliss' work on Cushing on page 465 where he lists European scientists trained at Brigham in Boston.

[35] Norman M. Dott (University of Edinburgh), "An Investigation into the Functions of the Pituitary and Thyroid Glands". Part I. Technique of their experimental Surgery and Summary of their Results, Q J Exp. Physiol. 1923; 13; 241-282, p. 241.

The details of Dott's "Experimental Operations on the Pituitary", basically Paulescu's method, with only few changes by the author, are given on pages 248-258 of the same work. The author states:

> "As regards the operation of Paulescu, this might appear superfluous, but the few workers who have performed it limit themselves to a brief description of its steps. They do not indicate many of the risks and difficulties, which have to be met with by the uninitiated in this particular field. Accordingly special emphasis is laid here on the operative dangers which the writer's short experience has impressed upon him."

Another highly respected author, Sir E. Sharpey from the Edinburgh University, in his work "The Endocrine Organs"[37], states quite clearly: "N. C. Paulesco was the first to state definitely that complete removal is in every case sooner or later fatal. This result was obtained with animals from all classes of Vertebrata. Most of the hypophysectomied mammals died within two or three days. Paulesco's results were also confirmed for mammals by Harvey Cushing and his fellow associates who for the most part restricted their experiments to dogs."

How does Bliss treat Paulescu's contributions in this field? Regretfully, only one mention in the 590 pages of his latest book "Harvey Cushing, - A Life in Surgery", University of Toronto Press, 2005. On p. 208 he states: *"They found that the best work was being done in Romania by the physiologist Nicolas Paulesco, who had developed what seemed to be an ideal surgical approach to the pituitary of dogs."* This is true and sounds very nice, but sadly, he adds: *"Perhaps coincidentally, it involved the same bilateral decompressive methods that Cushing had used on his 1905 patient"* (when the pituitary was not even visualized, an). We shall show in the last chapter that this was not quite the case.

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[36] "He performed complete extirpation of the hypophysis, which is fatal. He largely removed or entirely destroyed the anterior lobe, which likewise was fatal. He removed the anterior lobe, which likewise was fatal. He removed the anterior lobe partially, and the posterior lobe completely. No obvious symptoms followed. He severed the organ from the base of the brain by section of the infundibulum, which he states was equivalent to total, or almost total hypophysectomy. He separated the gland from its attachments to sella turcica, and no apparent consequences were noted. In explaining the last two effects, he mentions that in dividing the infundibulum stalk the main blood supply to the gland is cut off, while in separating it from the sella turcica only a few small vessels are severed. Paulesco makes no mentions of skeletal changes following these various lesions".

[37] "The Endocrine Organs", Sir E. Sharpey-Schafer, 2nd edition, Longmans, Green and Co. Ltd, New York, Toronto, 1926, pp. 279-80.

PAULESCU AND THE GLYCOGENIC FUNCTION OF THE LIVER[38]

In 1997 Pierre Lefèbvre, future President of the International Diabetes Federation, pronounced these eloquent words before the meeting of the same association:

> "Ninety years ago the great French physiologist Claude Bernard, discovered that the liver and muscles contain a starch-like substance, which he called glycogen, the 'sugar maker'. Every molecule of glycogen consists of a large number of grape sugar molecules, which are united together to be stored up in that form until they are needed. When needed, the glycogen disintegrates again into grape sugar, or glucose, to use a more scientific name. In this way, the glucose content of the blood can be kept fairly constant in spite of an uneven supply.
>
> Claude Bernard laid the basis for the scientific understanding of diabetes. He showed, for example, that the liver produces glucose without any requirement for alimentary ingestion, doing so by the action of a 'matière diastasique' —or as we would say, an enzyme - on glycogen, the 'glucose maker'. He also showed that the liver continues to produce glucose even after complete glycogen depletion due to prolonged fasting or severe diabetes: the first suggestion of an alternative pathway of gluconeogenesis. 'The scientific medicine which it is my duty to teach you does not exist', he told his students in 1847. 'The only thing to do is to lay the foundation upon which future generations may build, to create the physiology upon which this science may later be established. This was Bernard's achievement'."

It is surprising that prior to Paulescu nobody had produced any significant work to advance the knowledge about the role of glycogen as defined by Bernard. The most relevant but rather distant research was by Arthur Harden in 1910 when he studied the chemistry of the fermentation of sugar by yeast juice.

Between 1907 (perhaps he started even earlier) and 1916 Paulescu dedicated an enormous amount of time and energy to the study of the glycogenic function of the liver.

a) 1907-1916: He published no less than 16 articles on this subject, mostly in French medical periodicals, no less than 13 in 1913 alone.
b) 1907: In his *Handbook of Physiology"* (in Romanian)[39] he gives a surprisingly detailed historical, physiological and clinical review of the double

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[38] Here I am following very closely C. Ionescu-Tîrgovişte et al (13).

[39] "Curs de fiziologie umană", in Romanian, based on Paulescu's lectures, lithographed in handwriting by Rosenthal.

function of the pancreas, the internal and the external secretion. This is followed by a magisterial description of diabetes, mentioning the two kinds: the *pancreatic (thin) variety* and the *fat diabetes*. He arrives at the seminal conclusion: *"when the pancreas no longer exists, the liver no longer can store glucose in the form of glycogen"*.

c) 1912: In volume III of his *Textbook of Medicine* by Lancereaux & Paulescu published in French in 1912, on page 344 he clearly states (by the way for *the first time in medical history):* "the glycogenic function of the liver depends on the 'internal secretion' of the pancreas". He further states: "The original experiments by one of us (Lancereaux was already dead) appear to indicate that the internal secretion of the pancreas plays an important function in the storage of the glucose present in the portal vein, into glycogen in the liver" (p. 1020). The functions of the liver (pp. 1013-1145) and pancreas (pp. 925-927) are described with astonishing accuracy in regard to the etiology and pathology of diabetes. In the same volume, pp. 925-927, Paulescu writes:

> "The pancreatic graft and the fact that the liver and muscles of depancreatized animals, do not contain glycogen, led us to admit, until more information is available, that the internal secretion of the pancreas acts on the sugar, - that is brought to the liver by the blood of the portal vein - and makes it undergo some changes that first make it able to be assimilated. This is to be stored as glycogen in the liver, muscles, etc, - then used by the peripheral tissues. Thus, in the absence of the internal secretion of the pancreas, the blood sugar, not being any longer assimilable, is neither stored as glycogen nor used by the tissues. Accordingly it accumulates in the blood (hyperglycemia), induces osmotic effects (dehydration of tissues, polydipsia), and not being used (weight loss, increased urinary nitrogen loss, polyphagia) is eliminated in urine (glycosuria) as a foreign body".

Considering that this was published in 1912 it certainly represented the most accurate, scientifically advanced concept of diabetes at the time.

d) 1916 to 1919 he writes the *"Textbook of Medical Physiology" vol. II, based* on experiments *prior to August 1916* (the date of Romania's entry into WW1) and written between 1916 and 1919, but only published in 1920 because of the war. Here and in six articles quoted by C. Ionescu-Tîrgovişte[40] he describes the results of his exhaustive experiments.

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[40] Ionescu-Tîrgovişte (fn.7): Paulescu N.C.: 1) "Le glycogène dans le diabète par extirpation du pancréas". C.R. Soc. Biol., Paris, 1920; 2) C.R. Soc. Biol., Paris, 1913. 3) "Origines du glycogène. Substances albuminoides", C.R. Soc. Biol., 1913; 4) "Origines du glycogène. Substances grasses". C.R., Paris 1913; 5) "Origines du glycogène". C.R. Soc. Biol., Paris, 1913; 6) "Sur la formation du glycogène dans le foie, par suite d'injections de divers sucres

Paulescu studied the influence of carbohydrates, protein and lipids intake on the accumulation of glycogen in the liver. He sums up as follows:

> "The *carbohydrate* substances (glucose, sugar, lactose, maltose dextrin and starch) ingested by the dogs in doses of 50-700 gr. – after 6-14 days of fasting – represent certain sources of glycogen, which are stored mainly in the liver – almost proportionately with the quantity of ingested carbohydrates. The cardiac and muscle glycogen is slightly augmented following a similar ingestion, depending on the normal or fasting status.
>
> The *albuminoid* substances (fibrin, gelatin, casein, peptones, egg white, egg yolk, horse meat) ingested by the dogs in doses of 92 to 1020 gr. – after 5 to 7 days of fasting have a different effect as glycogen sources.
>
> In fact, the proteins from blood (fibrin), muscles (meat) or conjunctive tissue (gelatin) represent sources of glycogen.
>
> On the contrary, the proteins from milk (casein) and egg (white and yolk) are not important sources of glycogen. The peptones do not seem to represent a source of glycogen.
>
> The *fat* substances (olive oil, cotton oil, linseed oil, beef fat, pork fat, butter) ingested by the dogs in doses of 90 to 860 cc. - after 8 to 11 days fasting – do not represent a source of glycogen, neither in the liver nor in muscle.
>
> *The constituents of fat substances* – i.e. fatty acids (oleic and palmitic) and glycerol – ingested by the dogs in doses of 50 to 1085 cc – after 7 to 17 days fasting – have different effects on glycogenesis. In fact the fatty acids (oleic and palmitic) don't induce glycogen synthesis. But *glycerol,* on the contrary, is an important source of glycogen. Ingestion of ethanol did not induce the synthesis of glycogen".

In order to study the effect of *pancreatectomy* on hepatic glycogen, between 1911 and 1913 Paulescu developed an original surgical technique (see footnote 46) of total ablation of the pancreas often associated with the ablation of a hepatic lobe. Thus, he was able to prove that "Following total pancreatic ablation, the power of the liver to store glycogen is considerably reduced".

Equally important are his conclusions on the effects of pancreatectomy on the glycogenic function of the liver, the main conclusions being:

1) After the total ablation of the pancreas, the capacity of the liver to store glycogen is considerably diminished. However, this capacity is not totally abolished – because under some conditions the quantity of glycogen stored may be as high as 0.8 g or even 2.9 g per 100 g.

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dans la veine porte". C.R. Soc. Biol., Paris, 1911. "Origines du glycogène. (Hydrates de carbon)".

2) The same changes are also observed in the muscles.
3) Regarding the myocardium, its capacity to store glycogen remains normal - and remains as such until death (sixty days after the intervention).
4) To conclude, the capacity of the tissues to produce and to store glycogen is not totally abolished. This incapacity is only relative. It is a contingent phenomenon and as such it is a consequence and not a cause of diabetes. Otherwise, if the sugar cannot be stored by tissues as in normal conditions, this is due to the fact that glucose molecules – not being assimilated – cannot be used neither as a fuel nor for storage."

As the glycogenesis in the liver is so intimately connected with the glycemic pancreatic function (the inner secretion) it is no wonder that Paulescu often treats both subjects in parallel.

Most relevant to the subject of glycogenesis is the second volume, in particular the subchapter "The Assimilatory Liver", pp. 342-353. It is here that Paulescu states succinctly the most important element of this equation: *"Glycogen is stored in the cells of the liver. This storage appears to be aided by the internal secretion of the pancreas"(p. 344).*

No less important is his convincing proof that the excessive production of glucose in the liver is not the result of stimuli from the nervous system, as claimed by Kaufmann and Chauveau. He states "This entirely false concept collapses in the face of this single experimental fact- namely: after the ablation of the pancreas the animal becomes diabetic even while the liver is still fully innervated."

He also rejects the theories of Lépine and other authors, proponents of the theory whereby the presence of a glucose-reducing enzyme in the blood reduces the consumption of glucose. He states: "As we shall demonstrate later, if glucose is no longer utilized, this is due – not to the absence of a glycolitic enzyme in the blood, but to the fact that it is no longer assimilable. The non-consumption of glucose is the effect – and not the cause- of the defect in assimilation – that is, of diabetes."

Before moving on to the role and function of the pancreas in diabetes, we should discuss here Paulescu's physiological concepts of "absorption" and "assimilation". May I be allowed to remind the readers that these concepts were formulated based on experiments during the years 1906-1916. The research ended in August 1916 when Romania entered the war and was occupied by the Central Powers. During the war and immediate postwar era, he could not conduct any experiments (all facilities were used for war-related activities) nor could he publish anything because of censorship at home and isolation from the western countries. While his articles were written during 1916 and 1919, they could only be published in 1919, 1920 and 1921 respectively.

As such, during this period of relative "inactivity" he wrote the three volumes of his "Textbook of Physiology". It is here, in vol. III, pp. 283-288 that he discusses

"*The phenomena of absorption*" stating that the monosacharides (glucose, levulose, galactose) enter the blood after "*some modification while passing through the intestinal walls, since the blood contains only glucose"*. Furthermore, the blood glucose, but not the lymphatic glucose, is greatly increased after ingestion of glucose.

In the chapter "*The Phenomena of Assimilation*" (chapter 4, starting p. 289) Paulescu introduces the concept of "Assimilation Apparatus", including the endocrine pancreas, the liver, the thyroid, adrenals, hypophysis, thymus and spleen. Some of his conclusions have already been mentioned.

It is also here that he introduces what he calls his personal hypothesis according to which under the influence of the endocrine pancreas secretion the absorbed elements would form a glyco-lipid-protein complex that he named Plasmine. According to this hypothesis, without the endocrine pancreatic secretions, the three nutritive components "remain dissociated and can no longer nourish the tissues". Obviously, we now know, this hypothesis is scientifically incorrect. But this does not invalidate all the other correct conclusions in this remarkable work of the years 1916-1920. It is peripheral and presented by the author as just a hypothesis.

However, M. Bliss in his otherwise remarkable work, regretfully resorts to almost sarcastic remarks that are totally uncalled for.

First, Bliss mentions this towards the end of his work (p. 267, note 79), while discussing Paulescu's articles of 1923 and thus creating the wrong impression that this was still Paulescu's understanding in 1923.

Secondly, Kleiner had expressed similar notions in 1919, without drawing any criticism from Bliss (see our chapter on Kleiner). Thirdly, and most important is the fact that this erroneous interpretation by Paulescu is an isolated one, and even more important, an honest interpretation. There is no comparison with the ridiculous and outright dishonest assertions by Banting in his first paper published in February 1922[41] where he claims that he had proven that the "pancreatic Trypsin" was destroying the "internal secretion" of the pancreas. This is almost unbelievable considering the fact that his own previous experiments had proven the opposite; and after Collip had successfully treated a patient using this dangerous Trypsin (actually Trypsinogen) containing extract. Even more damning is the fact that in the same paper he falsifies Paulescu's data, for which in today's world he could face serious legal consequences – but these fallacies are not mentioned.

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[41] "The Internal Secretion of the Pancreas", in the Journal of Laboratory and Clinical Medicine, February 1922.

Finally may I say that if Paulescu erred in this respect in the years 1916-1920 he more than anybody else has helped to shed light on this complex problem with his brilliant work done in 1920-1921.

C. Ionescu-Tîrgovişte remarks (7): *"It is almost unbelievable that all the texts written by Paulescu more than 80 years ago retain all their validity even today.* Diabetes is causally related with the pancreas by the internal secretion of the latter, a secretion that has the role to render assimilable all the nutrients in the human body: carbohydrates, lipids and proteins". Further the author, quoting Paulescu, states that he arrived at the following hypothesis: "If diabetes and its biochemical changes are due to the absence of the internal endocrine secretion of the pancreas, then the extraction of the active principle from a normal pancreas and its injection into a diabetic animal should be followed by *both the suppression of the clinical symptoms of the disease and of the biochemical changes of carbohydrates (hyperglycemia, glycosuria), lipids (blood and urine ketone bodies) and proteins (blood and urinary urea)."*

Certainly, his studies on the glycogenic function of the assumed hormone of the pancreas were a huge step forward in this area of research[42] and required an enormous effort.

[42] It will be later in the 20s that scientists like Robinson and Embden and particularly Otto Frtiz Meyerhof and Archibald Vivian Hill will make significant discoveries on this subject (glycogen). Robison-Embden will establish the connection with phosphoric acid and Meyerhof will show that glycogen is converted to lactic acid in the absence of oxygen, whereas in the presence of oxygen only a small portion of lactic acid is oxidized and the rest is converted back to glycogen. Accordingly, less glycogen is consumed in muscle metabolism in the presence of oxygen than in its absence (Pasteur-Meyerhof effect). Meyerhof and Hill won the Nobel Prize 1922, for their analysis of the lactic acid cycle.

PAULESCU AND THE STUDY OF PANCREAS IN DIABETES PRIOR TO 1920[43]

It was in Paris that Paulescu worked under and later collaborated with the renowned Étienne Lancereaux. It was Lancereaux who consistently argued for a pancreatic origin of diabetes, and introduced the term *'pancreatic diabetes'* as early as 1877, in a paper in which he described some young patients with diabetes and a fibrocalculous disease of the pancreas. He had succeeded (1887) in convincing Claude Bernard, mentioned in the previous chapter to conduct pancreatectomies in order to solve this important problem especially considering the fact that Bernard had all the necessary facilities to conduct such experiments. Unfortunately, due to Bernard's death (1888) this project could not be realized.

Unabated, Lancereaux continued his work and accumulated sufficient proofs that were published in three further papers. The last paper was published in 1888, one year before Oskar Minkowski and Joseph von Mehring[44] in Strassburg (Germany at that time) confirmed this fact with their history making experiments (first experimental pancreatectomies performed in Medicine). Interestingly, they also used the term "*pancreatic diabetes"*.

Furthermore, it was Lancereaux who characterized diabetes as a syndrome rather than a disease for obvious reasons: cause unknown, course very variable and lack of constant anatomical lesions. It was again Lancereaux who first made the distinction between the "thin diabetes" and the "fat diabetes".

We have already mentioned the close working relationship between Lancereaux and Paulescu so it is no wonder that the problem of diabetes became important to the latter. As such, he commenced working together with Professor Albert Dastre on how to isolate the active substance of the internal secretion of the pancreas (1899), which however came to an abrupt end with his return to Romania in 1900.

There he resumed his work on the pancreas *as early as 1906.* In 1907 in his book lithographed in Romanian "*Physiology Handbook*", he states about the pancreas: "apart from this (external secretion), it also plays an important role as a gland with internal secretion." As already mentioned Lancereaux discovered this function (1877) in diabetic patients when the autopsies revealed changes in the pancreas.

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[43] C. Ionescu-Tîrgoviste (fn 7), pp.17-23.

[44] Von Mering, J., Minkowski, O., "Diabetes mellitus nach Pankreasextirpation", Arch. Exp. Path. Pharma., 1890, 26, 371-387.

In 1912, in the third volume of "Lancereaux-Paulescu Textbook of Medicine", published in Paris, Paulescu described the dysfunction in diabetes already mentioned in the previous chapter[45].

> "In the absence of the internal secretion of the pancreas, the glucose not being assimilated any longer, it is neither stored in the form of glycogen, nor consumed by the tissues. It is accumulated in the blood (hyperglycemia) leading to the symptoms mentioned above (dehydration of tissues, polidypsia, weakening, loss of nitrogen, polyphagia and glycosuria)

Although written at this very early date (1912) there is not much today to be added to this classical description of diabetes. Paulescu already had a clear picture of the pathogenesis and symptomatology of diabetes.

His *"Textbook of Medical Physiology vol. II" (1920)* is of extreme importance when studying this subject. It was based on work conducted before August 1916 (Romania's entry in WW1), and written during the war years 1916-1919 but could not be published until 1920**.**

It is here on page 60 that we find this classical description of diabetes by Paulescu:

> "Total extirpation of the pancreas is immediately followed by an intense and very grave diabetes". Its symptoms are mentioned above.
>
> "Although the animal has an exaggerated appetite and eats rapidly and in large quantities, it loses weight progressively and soon becomes a skeleton and ends up dying of emaciation, covered with scabs.
>
> Very frequently, the operation wounds (such as those for laparatomy) suppurate in spite of all rigorous aseptic precautions. Whatever the case may be, they heal slowly and poorly.
>
> Partial ablation of the pancreas does not bring about diabetes if the remaining fragment is greater than a tenth of the gland. If this fragment does not reach these dimensions, nutritional disturbances that are more or less pronounced and especially a nutritional glycosuria appears.
>
> Experiments show once again that the pancreas does not intervene – as a digestive gland – in the genesis of diabetes.
>
> Indeed, ligature with resection of the excretory pancreatic canals – as well as obstruction of these canals through the injection of coagulant substances – does not produce glycosuria.
>
> Also, extirpation of the duodenal portion of the organ does not lead to diabetes either. Clear proof was offered by Minkowski and Emmanuel Hédon. These experimenters grafted a portion of the pancreas subcutaneously and removed

[45] pp. 925-927

the rest of the gland and diabetes did not appear. This syndrome however appeared when the graft was removed.
These experimental facts prove at the same time that neural trauma – produced during the extirpation of the pancreas – has nothing to do with the genesis of diabetes."

These history making conclusions, which still stand today, unlike Kleiner's speculations or Banting's wrongly conceived notions about diabetes, were the result of many years of experimentation and struggle. Much of the work on liver and glycogen described in the preceding section relate, as demonstrated to the diabetes problem.

Even before 1916 (Romania's entry in WW1) he was able to conduct experiments using his own method for performing complete pancreatectomy[46] *in*

[46] "Ablation of the Pancreas, Textbook of Medical Physiology, 1920" p. 313:"An experimental condition that is a "sine qua non" is that this *ablation must be complete*. In order to fulfill this postulate, we have designed a different procedure that has proven quite satisfactory. We shall sum it up here and describe it later in greater detail in another chapter. We start with the removal of the splenic end of the pancreas, separating it with the finger from the fine surrounding peritoneum. This splenic end goes in quite deeply. It is connected to the spleen vessels by lax connective tissue that gives way upon light traction on the gland. In this cellular tissue, there is an arteriole and one or two veins that supply the pancreas. These must be ligated and severed under direct vision. To the jejunal end of the pancreas is attached the arteriole and the vein – that originates from the intestinal vascular network and has to be detached. In order to free the body of the pancreas – that is attached to the duodenum – we must first separate, using a hollow probe, the two sheets of peritoneum (anterior and posterior) at the level where the gland comes into contact with the intestine – while taking care not to damage the small vessels that are present here in large numbers. It is possible to remove the gland's parenchyma in small pieces by pulling on the lobules that become detached en masse leaving the superficial vessels behind. These vessels originate from the artery and vein (the pancreatico-duodenal). They travel together, deep inside the gland, in its posterior aspect, very close to the intestine. They must be detached from the parenchyma and remain intact in order to prevent necrosis of the duodenum. They feed a quite large vein at the level of the superior part of the body of the pancreas – and two other veins also rather large close to the Wirsung canal. These three veins must be ligated and sectioned. The other arterioles and venules are too fine and are obliterated as result of the traction to which they are subjected during this procedure. There are here and there several glandular lobules that are easily recognized by their white color and they can be easily be removed with the fingers or a dissecting instrument. Once the pancreas has been extirpated, the abdominal wall is sutured in three layers followed by applying a cotton dressing at the end. The operation lasts about half an hour – that is 5 minutes to remove the hepatic lobe; 15 minutes for the removal of the pancreas; 10 minutes to the end of dressing the wound. In order to be able to operate in good conditions, young dogs must be used that weigh 8-12 kg – this is because their pancreatic lobules are very fragile and their connective tissue is not very resistant and may easily tear. Even more, in these animals the splenic end of the gland is not very profoundly located and can be removed without much difficulty."

order to obtain a pancreatic extract and was able to demonstrate the effects of his pancreatic extracts, but only on carbohydrate and protein metabolism. He thus proved the glucose reducing capacity of the pancreatic extract. Unfortunately, war intervened and he was unable to publish in France from enemy-occupied Romania. Nevertheless, he was able to write the three volumes of his Textbook of Medical Physiology that were published after the war ended (1919, 1920 and 1921).

This is how Paulescu, describes this episode:

In the Textbook of Medical Physiology (vol. II), before presenting his results Paulescu states:

"The war surprised us while trying to test the hypothesis we presented before, regarding the role of the pancreas in nutrient assimilation. We are now in the process of reconfirming the results and completing our research on this topic. We give here a summary of some of the experiences that illustrate the direction of our investigations".

The chapter of 7 pages entitled "personal research" (pp. 321-327) starts with the topic "*Injection of pancreatic extract into peripheral vein".*

Prior to describing the results of his experiments following complete pancreatectomy Paulescu gives us his results from studying the diabetes induced by injection of phlorizin (diabète phlorizinique). It was von Mering who had discovered the diabetogenic property of phlorizin. He gives us the results based *on only two* of his many such experiments (he will present his results in a similar fashion in all future presentations). Here his surgical intervention consisted of only the removal of a hepatic lobe following an injection of phlorizin.

His conclusions are: In "*phlorizin induced" diabetes*, the capacity of various tissues to retain the glycogen remains intact, contrary to the results obtained in experimental diabetes caused by removal of the pancreas. Following ingestion of sugar (after surgery and injection of phlorizin), the urinary sugar content increases. Again, he emphasizes that the war had put an end to this research.

The next chapter ("Personal Research, Injection of pancreatic extract into a peripheral vein")[47], pp. 321-327 begins as follows:

"If – in an animal rendered diabetic by the ablation of the pancreas – a pancreatic extract is injected into the external jugular vein, we can notice a temporary suppression of hyperglycemia and glycosuria, as well as a considerable diminution of blood urea and also of urinary urea."

This chapter continues with the description of Method and Technique. As he will conceive two other improved methods in 1922 and 1923, we have designated this as *"Method A".*

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[47] Recherches personelles – Injection d'extrait pancréatique dans une veine pérpihérique.

"In order to obtain a pancreatic extract, as sterile as possible, we take a young and vigorous dog – after dosing the glucose and urea in blood and urine, - and the pancreas is completely removed (see p. 313). After this, taking rigorous aseptic precautions, the gland is minced into a Latapie mincer, which was previously sterilized. Subsequently we add to the minced pancreas ten times its weight of distilled water, - and after repeatedly shaking the mixture, everything is put on ice.

After 24 hours, we filter through a sterile double gauze compress and we add 7/1000 saline solution.

The extract is subsequently placed in a sterile 'Mohr burette' that communicates through a rubber tube with a 'cannula'. The extract is introduced by the force of gravity into the external jugular vein with an average speed of 100 cc over a period of 15 to 20 minutes.

Before the injection we draw 24 cc. of blood from the carotid artery for the dosage of glucose, - and 10 cc of blood for the dosage of urea.

We also take 25 cc and 10 cc of blood from the carotid immediately after the injection, - then one hour later, and so on.

Separation of glucose from the blood is made using 96 degrees alcohol. Its dosage in blood is made according with the method indicated before (vol. I, p. 99).

Separation of urea from blood is made in the same manner as that for glucose. Its dosage is made by using sodium hypobromide."

This was in 1916 but the preliminary work had begun in 1914.

This introduction is followed in Paulescu's text *by a presentation of four experiments (12 November, 29 November, 20 December, and 29 December). Here he includes pertinent tables showing his data indicating levels of glucose in blood and urine and that of urea in urine (first three experiments) or only the levels of urea (4th experiment).* This is followed by "Conclusions":

I

"The pancreatic extract injected into a peripheral vein produces:

1) A diminution and even a temporary suppression of diabetic hyperglycemia, which may be replaced by hypoglycemia;

2) A diminution or even a temporary suppression of glycosuria;

3) A diminution of blood urea;

4) A diminution of urinary urea

In other words, the intravenous injection of the pancreatic extract causes the disappearance of diabetic symptoms.

II

> The attenuation of the diabetic syndrome begins immediately after the injection. It reaches a maximum after 2 hours – and it lasts for about 12 hours. This discovery – which shed a bright light over the pathogenesis of diabetes, gives us also the key for the treatment of this syndrome".
> "At this moment we shall try to put into practice this opotherapeutic method and we shall present the results of our researches in a future edition of this Textbook".

We remind the readers again that all the above was achieved by *Paulescu before August 1916* when Romania became involved in WW1. The war explains why they could only be published in his three volumes of Traité de Physiologie in 1919, 1920 and 1921 respectively**.** We also wish to remind our readers that his archive was destroyed in the 1950s during and because of the communist Regime in Romania at that time.

Nevertheless, we can say that even before completion of his celebrated work in 1920-1921, Paulescu had discovered an immense body of knowledge as to the physiological dynamics of diabetes, long before Kleiner did his important work. *And he presented at the same time a far superior understanding of the nature of diabetes*. Actually, in 1907 he had already shown a surprising insight into the nature of diabetes. All these assertions of ours have been amply demonstrated in this chapter. And no less important have been his impressive discoveries on the role of pancreas on the formation of glycogen in the liver, already discussed.

We should also keep in mind the fact that Paulescu's work was an incredibly arduous undertaking, and he worked practically alone. He performed the operations on his dogs, oversaw the laboratory work and devised his own surgical method[48] of pancreatectomy used as early as 1907. He also devised his own method of preparing his tissue extracts using aqueous and later alcohol solutions,[49] and established the course to follow as demonstrated above. He used pancreatic extracts on dogs as early as 1913-1914. After encouraging results in 1916 using an aqueous extract that resulted in quick but only temporary lowering of the glucose and urea levels, he had to abandon his work because of World War I and the enemy occupation of Bucharest.

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[48] Nicolae Paulescu, "Traité de Physiologie Médicale", v. II, (Paris: Vigot, 1920), p. 313.
[49] Ibid., p. 321.

WORK ON DIABETES BROUGHT TO CONCLUSION 1920-1921
Victory, but no Glory!

After World War I Paulescu resumed his experiments and his positive results proved insulin's anabolic effect on all intermediate metabolisms, including proteins, carbohydrates and lipids. His findings of 1916 were amplified by new, additional experiments. According to his custom, he published nine experiments, out of a series of many others. These were presented in Bucharest in a succinct but sufficiently detailed form at four meetings of the Romanian Chapter of the Société de Biologie de Paris on 21 April, 19 May, 9 and 23 June 1921. They were subsequently published as four Presentations ("Comptes Rendus").[50] In addition to the data published in 1920 concerning the effect on glucose and urea (1916), Paulescu also gives his results on the effect upon ketone bodies and on glucose in blood and urine in a *normal animal* (9th experiment).

In the first Report ("Compte Rendu"), "The effect of pancreatic extract injected into the blood of a diabetic animal," he describes the three main effects of a total ablation of the pancreas: a) the rise of glucose level in blood and its presence in urine, b) the rise of the level of the urea in blood and urine and c) the rise of the ketone bodies in blood and urine.

It is in this Report that we find the text that became notorious thanks to the ignorance of Banting and Best. We quote the text in the original French version in order to eliminate any doubts (English text in the footnote).

> "*Si, chez un animal, diabétique par ablation du pancréas, on injecte dans une veine jugulaire, un extrait pancréatique, on constate une diminution, ou même une suppression passagère, de l'hyperglycémie, qui peut être remplacée par l'hypoglycémie, et aussi une diminution ou même une suppression passagère de la glycosurie. L'expérience suivante, prise entre plusieurs semblables, servira de preuve".* Also*: "Les mêmes effets, c'est-à-dire une diminution ou même une suppression passagère de l'hyperglycémie et de la glycosurie, s'observent aussi lorsqu'on injecte l'extrait pancréatique, non plus dans une veine périphérique, mais dans une branche de la veine porte, par exemple :*

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[50] N. C. Paulescu, "Comptes Rendus des Séances de la Société de Biologie", Tome LXXXV, No. 27, pp. 555-559, 3 juillet 1921, Paris, Mason et Cie, Editeurs:" Action de l'extrait pacréatique injecté dans le sang chez un animal diabétique, Influence du laps de temps écoulé depuis l'injection intraveineuse de l'extrait pancréatique chez un animal diabétique, Influence de la quantité de pancréas employée pour préparer l'extrait injecté dans le sang chez un animal diabétique" and "Action de l'extrait pancréatique injecté dans le sang chez un *animal normal*." (based on 9 experiments an.)

dans une veinule mésaraïque ou dans une veinule splénique. Cela montre que le passage à travers le foie n'entrave pas l'action de l'extrait pancréatique."[51]

In addition he demonstrates the reduction of urea and ketone bodies following the same injection (Experiments 1, 2, 3, 4 and 5)).

In the second Report: "Influence of the time elapsing after intravenous injection of a Pancreatic Extract into a Diabetic Animal,"[52] he proves that the hypoglycemic effect starts immediately, it reaches a peak at about two hours and lasts apprimately 12 hours (Exp. 6 and 7).

A third Report titled "Influence of the amount of pancreas used for preparing the extract injected into a diabetic animal"[53] proved that this effect varies with the amount of glandular tissue used in preparing it (Exp. 8).

The fourth Report, "Action of the Pancreatic Extract injected into the blood of a normal animal,"[54] proved that the hypoglycemic effect is significantly present also when injected in a normal animal.

Although the text is brief, these papers (comptes rendus) are extremely important. *They indicate for the first time in the historiography of diabetes the effect of the pancreatic extract on the lipid metabolism (in addition to the protein and glycemic metabolism already demonstrated in 1916 and published in his Traité de Physiologie).* In addition, in a prominent footnote on first page he refers the reader for further details to his more detailed, historical article "*Research on the role of the pancreas in nutritive assimilation*"[55] as well as his, *Traité de Physiologie*, v. II, p. 321. Naturally, Best preferred to ignore this information and instead engaged in a totally unfounded and base critique.

The same year Paulescu submitted to the Archives Internationales de Physiologie (Liège and Paris) a more comprehensive and detailed presentation titled

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[51] "If in an animal rendered diabetic by ablation of the pancreas, a pancreatic extract is injected into the jugular vein, a diminution is observed, or even a transient suppression of hyperglycemia, and a diminution or even a transient suppression of glycosuria. The following experiment, chosen from among other similar experiments, serves as a proof. The same effects, that is diminution or even transient suppression of hyperglycemia and glycosuria are likewise observed after injection of the pancreatic extract, not only into a peripheral vein, but also into a branch of vena porta, for instance: into a mesenteric venule or the splenic vein. This shows that passage through the liver does not prevent the action of the pancreatic extract".

[52] "Influence du laps de temps ecoulé depuis l'injection intraveineuse de l'extrait pancréatique chez un animal diabétique".

[53] "Influence de la quantité de pancréas employée pour préparer l'extrait injecté dans le sang chez un animal diabétique".

[54] Action de l'extrait pancréatique injecté dans le sang chez un animal normal".

[55] Paulescu, "Recherches sur le rôle du pancréas dans l'assimilation nutritive," Arch., Int., Physiol., 1921, 17, pp. 85-103.

"Recherches sur le rôle du pancréas dans l'assimilation nutritive" mentioned above, that was received on 22 June and published on 31 August and is also included in his book by C. Ionescu-Tirgoviste.[56]

I) He mentions the use of his personal method of complete ablation of the pancreas as described in his "Textbook of Medical Physiology" (Paulesco, Traité de physiologie médicale, II, p. 313, Paris, Vigot éditeur).[57]

II) He describes his method of obtaining a sterile pancreatic extract.[58]

He repeats the three main changes observed following pancreatectomy that had already been described in his "Comptes Rendus":

1) Increase in the concentration of glucose in blood and urine;
2) An increase in the concentration of urea, both in blood and urine;
3) An increase in the concentration of ketone bodies in blood and urine.

Under "Method and technique", he mentions: prior to the injection, 25 cc of blood taken from a carotid artery or from a jugular vein to determine the blood glucose. Immediately after the injection, another 25 cc blood taken for same purpose. This is repeated after 1/4 h, 1/2 h, 1 h, etc. and again after 25 hours. *The separation of glucose from blood is made with 96% alcohol*. The determination of blood sugar is made using the Pflűger method (Textbook of Medical Physiology, vol. I., p. 99). For determining the urinary sugar he uses the method of Claude Bernard (ibidem, p. 98).

Following which he described in detail, clearly and judiciously 12 experiments between 12 November 1920 and 14 May 1921 (as already mentioned *he had conducted numerous other experiments with positive results, some going as far back as 1907 but records of them were lost in the 50s*). He gives precise details about the condition of the dogs, frequent temperature measurements, the amounts of injected extracts and of excreted urine and the autopsy results.

He takes his blood samples from the carotid arteries or the jugular veins and injects his extracts in the *jugular veins* with the exception of experiment VI when it is injected into the splenic vein. In experiments I and II he clearly specifies "*the external jugular vein"*.

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56 Ionescu-Tîrgoviste, (fn. 7), pp. 39-56.

57 N.C. Paulescu, "Traité de Physiologie", v. II, p. 313. See also our note (42).

58 Pancreatic Extract (A): "Material (from dog but also from beef pancreas) hashed and mixed with sterile water (10times its weight), stored on ice for 24 hours, filtering through tarlatan and addition of Na Cl (7 per thousand), sterilizing, injecting with help of a cannula by force of gravity into the external jugular vein, 100cc over 15 to 20 minutes". See also chapter Paulescu and the Study of Pancreas in Diabetes prior to 1920. Method (B) is described in his Patent text and Method C in his 1923 text (Quelques Réactions Chimiques et Physiques Apliquées à l'extrait aqueux du pancreas pour se débarasser des substances protéiniques en excès).

The results were also presented in the form of tables (but no diagrams) and conclusions. Here are the results of his 12 published experiments on depancreatinized dogs, following injection of his extract into the jugular veins and presented in his history making "Recherches sur le rôle du pancréas dans l'assimilation nutritive", usually presenting "one among other similar cases".

Experiment I (12, 24 and 25 November) proves a temporary decrease of the hyperglycemia or even hypoglycemia and suppression of glycosuria, diminution or even a transient elimination of glycosuria. He adds that passage of the extract through the liver (see experiment VI where the extract is injected into a branch of the portal vein) does not interfere with its efficiency.

Experiments II (29 November, 2, 3, 4, 5 and 6 December), proves that the glycemia and glycosuria begin immediately after injection, the effect reaches a maximum after 2 hours and lasts approximately 12 hours.

Experiment III (19, 23, 24, 25 and 26 February): same as above.

Experiment IV (20, 22, 23 and 24 December) proves that the effect of the pancreatic extract on glycemia and glycosuria depends on the quantity of gland used in its preparation. Using two thirds of the pancreas produces greater decrease of hyperglycemia and glycosuria when compared with using only one third of the organ.

Experiment V (29, 30 and 31 December and 1 January) proves that same extract leads to a considerable decrease of glucose *and urea in blood* as well as urine. He was using the sodium hypobromide solution method after separating the urea from blood with 96% (10 vol.). He also refers to Paulesco Traité de physiologie médicale, II, p. 569.

Experiment VI (17, 21, 22, 23, 24 January), using same method but with the pancreatic extract being injected into the *splenic vein*, produces similar results with regard to both glucose and urea in blood and urine.

Experiment VII (13, 14 and 15 April) using the very intricate Denigès procedure (see G. Denigès, Chimie analitique, 1913, p. 1192), the pancreatic extract caused a significant reduction of *ketonemia and ketonuria* in addition to the glucose lowering effect.

Experiment VIII (17, 18, 19 and 20 April) confirms these results, but dog dies during a bout of fever ("accès fébrile")

Experiment IX (12, 14, and 15 May) reveals that the pancreatic extract causes decrease of *glucose and urea*, in blood and urine of a *normal animal*. He is using this time an extract from *beef pancreas*.

Experiment X (31 March, 1, 2, 3 and 4 April) proves that injection of physiological saline (NaCl 0,9%) has no effect on the glucose content in blood nor urine, in experimental diabetes.

Experiment XI (26, 27, 28 and 29 January) proved that an extract of splenic tissue had no effect on the hyperglycemia, or the glycosuris of a depancreatinized animal. Experiment XII (24, 25, 26, 27 and 28 April) proved that inducing fever by injecting sodium nucleinate into the sub-arachnoid space with a "fever peak" 1 hour later had no effect on the hyperglycemia or glycosuria in experimental diabetes. This way Paulescu has proven that the fever caused by the impurities (diastases) in the pancreatic extract had no effect on the blood sugar level. Actually, the urinary urea was checked in practically all his experiments with results similar to those in experiments V and VI.

With the results of his experiments, Paulescu could rightly conclude:

1) In an animal with diabetes induced by a total ablation of the pancreas, followed by injecting pancreatic extract into the jugular vein we observe:

a) A decrease and even a temporary suppression of hyperglycemia, which can be replaced by hypoglycemia and a diminution or even temporary suppression of glycosuria;
b) A considerable diminution of blood and urinary urea;
c) A marked diminution of ketonemia and ketonuria.

2) The effect of pancreatic extract on glycemia and glycosuria varies with the interval of time following the injection, beginning immediately after the injection, reaching a peak after 2 hours and lasting about 12 hours. The effect also varies with the amount of pancreas tissue used for preparing the extract.

3) A venous injection of pancreatic extract in a normal non-diabetic animal results in an important diminution of glycemia, blood urea and urinary urea.

4) Similar effects influencing especially diabetic hyperglycemia and glycosuria are not produced by either:

a) An intravenous injection of saline solution;
b) An intravenous injection of an extract of an organ other than pancreas;
c) An intra-rachidian injection of a sodium nucleinate solution causing a bout of fever.

As can be seen Paulescu did not confine himself to the hypoglycemic effect only. He rather than Banting and Best in Toronto or Kleiner in the USA was the first to describe the actions of his "pancréine" on all aspects of metabolism (carbohydrates, lipids, proteins, etc.) and this was a huge step forward. By demonstrating its hypoglycemic, anti-ketonic and anabolic (lowering the urea) function, in diabetic but also in normal animals, Paulescu has proven the so important physiologic role of insulin.

His great merit is that he proved the actions of insulin at the level of global human metabolism.

His publication of "Recherches sur le rôle du pancréas dans l'assimilation nutritive" was the most advanced, factual and convincing work in the field of Insulin

at that time.[59] It certainly compared favorably with Kleiner's work (1919) and certainly by far surpassed Banting's embarrassing ulterior presentation on 30 December 1921 in New Haven or the latter's subsequent paper "The Internal Secretion of the Pancreas"[60]. In the latter, Banting quite irresponsibly extols his genial discovery that the insulin is destroyed by the harmful "Trypsin" in the pancreas! Paulescu's achievement was only equaled by the historic presentation of Collip's breakthrough of 23 January 1922[61] by Prof. Macleod on 3 May 1922.

It is important to note that Paulescu's observations on the protein metabolism will gain great significance decades later.

Before discussing Paulescu's further works, a few words on *Paulescu's patent for Pancreine***,** obtained in Bucharest on 10 April 1922. We know that Zűlzer had obtained a similar patent in 1912 in the USA. In my view this type of patent granted before satisfactory proof that the extract was safe, effective and reliable in humans, had little value if any. The Toronto group received their patent after their insulin had been tested on humans according to stringent rules, and this represents a great difference. Certainly today, the requirements are even more stringent.

Paulescu's patent is important in my view only because it gives us his *new method (B)* for preparing his extracts that we reproduce below. After the usual preparatory steps, Paulescu describes his method as follows:

> "*Following the usual method, under most aseptic conditions, the tissue (dog or bovine pancreas) is hashed and mixed with sterile water (10 times its weight), stored on ice for up to 24 hours. The minced pancreas is filtered through a sterile double gauze compress in order to remove the very voluminous solid parts.*
>
> *This filtrate is cloudy and more or less rose in color and to it is added pure hydrochloric acid – 10 p.p. 1000 – that brings on a slight protein precipitate.*
>
> *Under the influence of this acid environment, lasting up to 24 hours, the extract does not lose its hypoglycemic property.*
>
> *The gray precipitate is separated with a sterile gauze filter and, and the acid liquid is neutralized using "caustic soda" (NaOH).*

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[59] E. Martin, "Problèmes de priorité dans la découverte de l'insuline", in "The Priority of N. C. Paulescu in the Discovery of Insulin", ed. I. Pavel (Bucharest: Editura Academiei Republicii Socialiste România, 1976), p.125.

[60] F. G. Banting and C. H. Best, "The Internal Secretion of the Pancreas", "J. Lab. Clin. Med., February 1922, 7, pp. 256-271. It includes the false assertions about Paulescu and states that pancreatic juice destroys the active principle of the extract.

[61] F. G. Banting, C. H. Best, J.B. Collip, W. R. Campbell, A. A. Fletcher, J. J. R. Macleod, and E. C. Noble, "The Effects Produced on Diabetes by Extracts of Pancreas", Trans. Assoc. Am. Physicians, 1922, pp.1-11.

Thus, a new and abundant protein precipitate is produced. The liquid still contains small quantities of proteins.
The new precipitate is separated using a Berzelius sterilized paper.
The filtered liquid is clear and transparent, still gives a positive protein reaction and maintains its physiological properties. By contrast, the precipitate is inactive.
Finally, the volume of this liquid is reduced by evaporation at a temperature, which must not exceed 50C."

The above represents the essential elements of the new method used by him in 1922-1923, quite a significant departure (treating the extract with hydrochloric acid followed by NaOH) from his original purely aqueous extract.[62]

In 1923, Paulescu published the two already mentioned articles in "Archives Internationales de Physiologie". "Some chemical and physical reactions following an aqueous pancreatic extract to eliminate the protein substances present in excess."[63], apparently received on 5 March and published 31 May 1923 – and "Several procedures to introduce the pancreatic extract in the organism of an animal"[64] received 7 June 1923 and published 10 August 1923 (1923A and 1923B in Bliss' work).

In the first publication (May 1923) he describes again his new (B) improved method of extracting a more potent Pancreine that could even produce "aglycemia". It incorporates the separation of the potent liquid filtrate from the inactive precipitate. He describes in detail Experiment XIII where he uses *beef extract* - and reaches the stage of aglycemia. This is how Paulescu describes it:

"After injecting the thus obtained limpid extract, we have encountered an unexpected and very remarkable result. Such an extract has not only diminished the hyperglycemia to a level below normal, but it has even produced a state of real aglycemia, by reducing the glucose to zero. In other words the blood of the diabetic animal that prior to the injection contained 2-3 gm glucose per 1000 cc, no longer contains any glucose. Such transient aglycemia is never observed in a normal state, when the blood has between 1 gm and 0,3 gm of glucose in 1000 cc. This important phenomenon will serve as starting point for a theory of diabetes that we shall expound shortly".

This is all he says, no interpretation whatsoever, quite unlike what Bliss will later claim. Beef extract is also used in experiments XIV, XV, XVI, XVII, XVIII,

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62 See chapter "Paulescu and the Study of Pancreas in Diabetes prior to 1920."

63 "Quelques Reactions Chimiques et Physiques Appliquées à l'extrait aqueux du pancreas pour se débarasser des substances protéiniques en excès"

64 "Divers Procédés pour introduire l'Extrait Pancréatique dans l'Organisme d'un Animal Diabétique".

XIX and XX.

His conclusions: Treating the extract with HCL followed by "caustic soda" (NaOH) removes impurities and is potent (XIII). Not so when the extract is subjected to a temperature of 100° (XVII), or 90°(XVI) and even to only 50° (XVII). The liquid portion of an alcoholic extract subjected to below 50° retains its glucose lowering properties. The precipitate itself however is inactive (XIX and XX).

In his experiments XIX and XX he uses pancreatic extracts obtained *with alcohol* (*method C)* as follows:

> *"Hashed beef pancreas (10gm) are added to 100 cc distilled water, then kept on ice for 24 hours. Alcohol 96° is added up to 250 cc. This causes formation of a precipitate. Next day it is filtered and the filtrate is exposed to evaporation, thereafter is kept at a temperature between 65° to 75° and thus the filtrate is reduced to 25cc. Distilled water is added up to 100 cc."*

He uses this method in experiment XIX with good result (blood sugar drops from 2.18 to 1.66).

In experiment XX, again using method C with alcohol but using this time the solid precipitate, no beneficial result is obtained.

The second publication (10 August) gives an overview of the various methods of administering the pancreatic extract. He again describes his previous method of extracting the pancréine (B), but he also adds his newer method using alcohol (we have called it method C) that is less likely to cause fever and abscesses. He came to the conclusion that the oral route (Exp. XXI) and the anal route (enema) using a 90 cm tube (Exp. XXII, XXIII, XXIV, XXV) had no effect, contrary to the intravenous route (XXI, XXIII and XXV). In Experiment XXVI, he uses the *subcutaneous and intravenous routes subsequently and with decisive and equal results*. No side effects following subcutaneous injections are mentioned in this experiment.

In Appendix I, he relates the further results in Experiment XXI four days later, by which time the dog is quite weak. On 31 January subcutaneous administration of pancreatic extract, followed by intravenous administration fail to show any effect.

Accordingly, he assumes that administration of pancreatic extract helps only in incipient cases but fails in advanced cases.

In Appendix II he relates two failures following administration by enema, in one case to a man with "diabète maigre" and then to a lady with "diabète gras".

Unfortunately, for him at this time the therapeutic use of insulin by subcutaneous route was already a reality and this renders Paulescu's otherwise interesting observations irrelevant. History had already been made, and as we shall demonstrate, not always in a noble, inspiring way.

On 6 November 1923, he writes to the President of the Nobel Foundation complaining bitterly about the grave injustice and ends with these words: "Your committee was therefore misled in honoring some people who felt proper to exploit

and appropriate someone else's work. In demanding that you accord me justice, Mr. President please accept my highest regards".

In 1924, he published "Traitement du Diabète" (La Presse Médicale, V, 19, 5 mars, 1924, pp. 202-204) which again proved irrelevant as in Toronto insulin was already being used extensively on human patients. In 1930, he succeeds in publishing the 4th volume of his Traité de Médicine in an obscure printing facility belonging to the Army (Imprimeria Şcoalei Militare in Sibiu, România). A fifth volume in manuscript form has never been published.

Paulescu's earlier publications (1921), unlike Banting's work at that time (1921-1922) were appreciated by researchers like John Murlin and Harry Clough at the University of Rochester.[65] Murlin was even sufficiently encouraged by Paulescu's results to resume his own research work.[66] Equally impressed were Ernest L. Scott,[67] professor at Columbia University in New York and Sir E. Sharpley-Schaffer,[68] professor of Physiology at Edinburgh University.

However, Macleod, Banting and Best succeeded in drawing the attention of Dr. George H.A. Clowes, research director of the Eli Lilly Company. Clowes played a very important role later on in helping the Toronto team to purify the extract and produce insulin on industrial scale. Eli Lilly in turn would use the services of George Walden, working as a chemist for the company, who will further purify Collip's pancreatic extract using the "isoelectric method". Most important is the fact that by February 1923 Eli Lilly would be able to mass-produce insulin.

I. Pavel provides valuable information on this exciting chapter that cannot be ignored but he puts too much emphasis on the element of priority[69]. Certainly, priority plays an important role when considering the merits of a scientific discovery. But in so doing, he does not stress enough the superior, more comprehensive nature of the study achieved by Paulescu. He also reduces the race to isolate the insulin to only two rival camps, Banting in Toronto and Paulescu in Bucharest. Thus he ignores all others, among whom Israel Kleiner who certainly could have gained the distinction of "discovering" insulin (1919), if "priority" in animal experiments and their publication had been the only criteria.

Paulescu's considerable merit is the undeniable fact that he succeeded in

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65 J. Murlin, Harry D. Clough, C.B.F. Gibbs and Arthur M. Stokes, "Aqueous extracts of Pancreas: I. Influence of the Carbohydrate Metabolism of Depancreatized Animals", J. Biol. Chem., 1923, 56, pp. 253-96.

66 Bliss, (fn 3), p.145.

67 Trifu, (fn 2) p. 52. It is stated that Scott wrote to Paulescu on 5 November 1921 and asked for permission to patent his new Insulin extract in the USA. Also mentioned in Paulescu, "Traitement du Diabète", 1924.

68 Ibid. p. 54.

69 I. Pavel, The Priority of N. C. Paulescu in the Discovery of Insulin, Bucharest: Editura Academiei Republicii Socialiste România, 1976.

producing effective pancreatic extracts. This enabled him to present to the world the new hormone he called pancréine, with its physiological global effects on all the body's metabolisms. These discoveries are still valid today, as are all his discoveries of 1920-1921, even if some authors have expressed quasi-sarcastic remarks.

TORONTO 1921-1922; BANTING AND COLLIP

For good reason the year 1922 is regarded in the history of Medicine as a very memorable year because it was then, on 23 January, that Collip realized one of the most important successes in both the sciences of Medicine and Physiology, and in the clinical treatment of Diabetes. Macleod officially announced to the world on 3 May 1922 the great triumph at the University of Toronto, the purification (partial, but sufficient) of Insulin by Collip and its successful use in clinical medicine.

The most comprehensive study of this great event and the efforts leading to this great success is unquestionably Michael Bliss' work *"The Discovery of Insulin"* (see note 3). It is a fine and impressive model of scholarly research of facts, events and participants to this great saga in the history of medicine, with only few exceptions: he fails to recognize the great merits of Paulescu (Paulescu, see note 12) and only to a certain extent those of Collip. Again the obvious fact that in spite of Bliss' at times devastating criticism of Banting's unbelievable ignorance, lack of proper orientation and failure in attaining his goal, Bliss in the final analysis gives him too much credit for various "discoveries" without mentioning the fact that same discoveries had actually already been realized by others before him. Hence the words "new discovery", or "another breakthrough" abound when describing his work, in lieu of simple "steps forward" that would have been more appropriate.

His dissection of Banting is objective and at times merciless, but still, when it comes to the final conclusions, the scholar Bliss gives way to the man. He cannot hide the fact that he admires Banting who, in spite of an enormous string of errors, improper behavior and even dishonest intellectual deeds emerges as Bliss' hero in the drama of the discovery of Insulin. This should not be taken as malicious critique, perhaps just one more reason to respect the author, who after all is also a human being. I myself started with similar feelings when I approached this subject.

Banting was not a true scientist. As such the often-quoted "great idea", as we shall demonstrate, should be just an anecdote in medical folklore, instead it is indelibly entrenched in history. Interestingly many enthusiastic authors regard every small step forward by Banting as a "new discovery". They were "new" only to the small ignorant group in Toronto, while to other scientists they were already well-established facts. Banting and Best knew or ought to have known that I. Kleiner (December 1919) and N. Paulescu (July 1920-1921) had successfully conducted experiments using extracts of whole pancreas. Accordingly when they ran out of steam by mid-December 1921, they were certainly in no way further ahead than the other precursors (Kleiner, Paulescu, etc.) and actually in certain aspects, when compared to Paulescu, they had obviously achieved less.

By contrast there was Collip, who like Paulescu exemplified the true scientist, acquainted with the pertinent facts, but also up-to-date with recently available,

modern methods of research. He also was experienced in the field of extracting various substances from tissues[70], and had a genial gift for interpreting the facts confronting him and resolving the ensuing problems. As such, he was able to establish a plan that following logic and known facts would reach its goal in only 42 days, whereas Banting after 7 months was a spent force.

In my opinion, there were two distinct periods during the work on insulin in Toronto: the period before and the period after Collip's arrival on the scene. Without any doubt, James Bernard Collip made by far the most significant scientific contributions in Toronto to the study of the actions of insulin on many aspects of metabolism, confirming Paulescu's findings. This culminated with its purification and introduction as the first effective drug for diabetes.

A) Before Collip

No one can deny that Banting initiated this splendid adventure that led to Collip's breakthrough. He did not realize how lucky he was to be able to capitalize on newly improved techniques for laboratory testing and purification. By sheer luck, the time was right for isolating insulin and using it in medical treatment and his willpower and passion pushed the work forward. He was at the right place, the University of Toronto with adequate facilities for animal experimentation and with the right advisor in the person of Prof. Macleod, a renowned authority on carbohydrate metabolism.

The story of the triumph of the Toronto team (Frederick Banting, John James Rickard Macleod and Charles Herbert Best) is well known, their names having been immortalized in books on the history of diabetes, in movies and having received all possible honors. James Bertram Collip (1892-1965) joined the team later (December 1921).

This is the story of two young men, idealists, attempting to do what nobody had been able to do before: to isolate the "internal secretion" of the pancreas and use it in the medical treatment of diabetes.

They finally, like some other researchers in this field, came very close to their goal in spite of their initially meager financial means, working hard and sweating during the hot summer months of 1921. This is all true and for this they deserve all credit.

What often is not mentioned is that they actually were quite ignorant in this field of study. Best was simply a bright student with no experience, but an exceptional mind, who later will pursue a great scientific career on his own. As

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[70] Alison Li, J. B. Collip and the Development of Medical Research in Canada, McGill-Queen's University Press, Montreal & Kingston, 2003, p. 17, "During research of the action of adrenaline – he prepared extracts of many mammalian tissues – heart, lung, spleen, liver, brain, cord, pancreas, thyroid, and parathyroid".

such, he was the junior member of the group and had to bow to the decisions made by Banting. His relationship with Banting after a brief initial strife was good until after the insulin fireworks were over. Later their relations deteriorated markedly.

Banting on the other hand was a more complex person. He was an honest man of his word, loyal, straightforward and had character, and we want to stress this at the outset. For example, he spontaneously split the money from his Nobel Prize with Best. He and Best first reciprocally injected themselves with the extract they were going to inject into Leonard, their foolish human experiment. Also, he initially refused to have his name on the patent for their discovery, in the true Hippocratic spirit. Later on, he had to give in, in order to protect the rights of everybody, including the public.

He excelled with his unflinching dedication to a great cause, and his tremendous willpower proved unstoppable.

But once he became involved in an arena with competitors, or potential rivals, his character began to show many flaws. According to Bliss he felt insecure, suspicious and quickly got involved in fights, on one occasion even physical assault (against Collip) or almost (with Duncan Graham).[71]

His scientific training and knowledge was almost non-existent; for example, he intended to do his research by testing the sugar in urine only. I assume that this is what was taught in medical schools during his study-years. Somehow, he was initially ignorant of the availability of tests for determining the blood glucose (introduced around 1910). But on the other side, his will power and ambitions knew no limits and he had conviction. Certainly, the first few months at the University of Toronto were hard, with no income and little sense of direction.

His "great idea" of ligating the pancreatic ducts and thus removing the destructive influence of trypsin, not only was at that time already without any scientific foundation (as proven by Pavlov and associates in 1899 already) but had been probed by many others long before him. The only difference is that Banting followed this long and unnecessarily tortuous pathway at a time when important advances in science (laboratory and otherwise) had made possible the isolation of insulin. So we can only speak of perfect timing and naturally of his great luck[72].

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[71] M. Bliss, (fn 3), pp. 200-201.

[72] His luck was legendary. He was accepted to work at Prof. Macleod's clinic with its excellent facilities for experimenting with animals. He had the privilege of being guided with unbelievable patience by Macleod, although such a thought never entered his mind. Newer methods became available to determine sugar in urine and blood and also new, superior methods of producing better extracts from various tissues. The immense boost from Macleod's entire faculty later in the game, in lieu of being kicked out for his impertinent ways and at last but not at least, the immense and deciding contributions by Collip. And we could also add the way history treated him, nobody mentioning the so obvious fact that Banting himself had

The time was ripe for isolating the insulin. What is unbelievable is the fact that an ignorant like Banting was to reap the benefits of this unique conjuncture in the progress of medical sciences.

Banting's innovative skills as a researcher were not very impressive. It is true that after reading (16 November) the article by G.E. Laguesse, who had found that the concentration of Langerhans' islets was higher in newborn calves, he conceived the idea of using fetal pancreas (rather than from newborn calves) from slaughterhouses. He conducted accordingly a successful experiment on 17 November. This certainly represents a genuine innovation by Banting and a step forward (as the son of a farmer he knew the farmers used this trick to make cows heavier prior to selling). But it wasn't in the right direction, which would have been using whole adult beef (or pork) pancreas.

His initial concept of ligating the pancreatic ducts came from an article written by Moses Barron in 1920[73]. In this article, Barron described the case of a pancreas with a congenital absence of the Santorini's canal, while the main duct, the Wirsung duct was blocked by a stone. As a result, all acinar cells had disappeared and only the Langerhans cells were present.

By reading this article, Banting must have learned that similar results had been obtained experimentally in 1884 by ligating these ducts, among others by Charles Louis Xavier Arnozan and Louis Vaillard. He also certainly learned from Barron's article about Ssobolow's (and many others) experiments with ligating the pancreatic ducts in 1901, because Barron described this in great detail in his article read by Banting.

Did he know that Scott in New York and many others had already tried it without success?[74] Perhaps, as he eventually quotes him. Actually, this ignorance was his strength. Unaware of the difficulties to be expected, he just plowed ahead. Was he aware of the fact that in the meantime science had realized significant advances, much improved laboratory techniques, better, more sterile extraction methods, etc., and as such what had been impossible years prior, might be possible now?

What is certain is that his knowledge of physiology was rather rudimentary to put it mildly and not up to date. As such, he was totally unaware of this simple but very important fact, that in the pancreas the Trypsin was in the form of the innocuous

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added nothing new to science, nothing that had not been proven earlier by Kleiner, Paulescu or others.

[73] Moses Barron, "The Relation of the Islets of Langerhans to Diabetes with Special Reference to Cases of Pancreatic Lithiasis", in Surgery, Gynecology and Obstetrics, November issue, 1920.

[74] Experiments with ligature of pancreatic duct were done without success also by D'Arnozan et Vaillard on rabbits, 1884; Vassale, 1891; Katz & Winkler 1898; Schulz 1900; Leonida Ssobolew (1902) with preservation of Langerhans islands for some weeks, etc. (see Appendix);

Trypsinogen and that accordingly all his complicated procedures to avoid the dangers of the "perilous Trypsin" were absolutely unnecessary. This fact, as mentioned above, had been established in 1899 by Ivan Petrovich Pavlov and N.P. Shepovalnikov (see our footnote 129) of Russia and had been accepted universally by all those who were trying to keep abreast in the field of physiology (see also more on this subject in the chapter "Banting; Further Criticism").

To quote Louis Rosenfeld, "Banting and Best were not experienced and knowledgeable enough to have achieved success without input and other help from an experienced investigator like Macleod"[75]. The immediate chilling of the pancreatic material, as suggested by Macleod, stopped self-digestion of the fresh pancreas by the activated enzymes. According to Michael Bliss, "Banting and Best's research was so badly done that, without the help of Macleod and Collip, the two young Canadians would be fated to disappear from medical history". Although duct ligation played no essential part in the discovery and was not the way to go, it indirectly set the stage for eventually making extracts directly from the whole pancreas. Many of the extracts were potent enough to convince Macleod that there really was an internal secretion that could be extracted, and accordingly he added new resources and additional staff.

As such, his "intuition", in reality the facts (including ligatures of pancreatic ducts) revealed in Barron's article, was only important in convincing him to invest all his boundless energy towards this great goal, the isolation and clinical use of the insulin in clinical medicine. But it led him down a blind alley for nearly six months.

Certainly, this could not be called another case of serendipity, he knew what he was after, but he so pathetically lacked the necessary scientific training. He likely would have gotten nowhere with his animal experiments without Macleod. Likewise, without Collip the purification and clinical use in the treatment of diabetes in humans would have never materialized, at least in Toronto.

In brief, he has his "revelation" in November 1920, based on false and not quite honest premises, as he simply copied Barron - without mentioning this until after having received the Nobel Prize (see chapter Banting; Further criticism). He sees Prof. Macleod on 7 November and again on 15 March 1921, who finally allows him to use the Faculty's facilities for his experiments on animals on 17 May 1921. He also gives him a young student, Charles H. Best, as an assistant, teaches them how to extirpate the pancreas (Hédon's method in two stages) and about one month later, after giving them plentiful valuable advice, leaves for England. Left alone they start their experiments.

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[75] Rosenfeld L., "Insulin: Discovery and Controversy", in Clinical Chemistry, 2002; 48: 2270-2288

The beginning is disastrous, most dogs die, the operations on dogs with ligature of the pancreatic ducts fail, the catgut used had dissolved so they replace it with silk. On 30 July a first, partial success with dog 410, which dies the next day, but not after having revealed a drop of the glucose level in the blood from 0.20 to 0.12. Another step forward occurred on 3 August when they successfully performed a total pancreatectomy in only one stage, as Paulescu, Kleiner, etc. had previously done.

On 17 August, they try an extract (dog # 92) from whole pancreas (undigested). The results are superior, glucose levels drop from 0.30 to 0.17 in one hour, but they in a most incomprehensible, yes I would say stupid way, disregard this because they had not eliminated the trypsin, and this conflicted with their theories. This is a first indication of a lack of intellectual integrity in our view. Blindly they start to experiment with trying to exhaust the pancreas of its trypsin with the use of the enzyme "secretin". Then they try experimenting in test tubes. No reasonable person could consider Banting a "scientist". He was simply a fanatic capable of overcoming any obstacle provided he was properly guided.

On 21 September Macleod returns from England, is relatively pleased, and rewards Banting (after some complaining) with a position at the Faculty with a monthly salary of $250 as a lector in Physiology while Best becomes a "demonstrator".

On 17 November, they tried successfully fetal pancreas. On 23 November, they adopted the vastly improved and recently published Shaffer-Hartman micro-method for measuring glucose levels in blood that was brought from the States by Collip. Equally they adopted the use of the more sterile Backfield filter (introduced by Henry Doulton already in 1906), and the use of Tricresol as preservative for their extracts, but we do not know where these innovations originated. Shortly the research staff will be increased with new additions: Clarke Noble, John Hepburn and A. A. Fletcher.

On 6 December they, with Macleod's help, use alcohol in extracting the insulin (as previously advised by Macleod), and this worked well on 7 December (same method used prior by Zülzer and Scott and others, but considered a "breakthrough" by Bliss). Unfortunately, it did not work as well the following day.

On 8 December, they decide to use an extract of a whole adult pancreas, from the same dog they had depancreatized and using alcohol for this purpose. They and Bliss fail to mention that this was exactly what Kleiner and Paulescu had done previously. So on 11 December they inject into dog # 35 this extract (somehow similar to the experiment on 17 August), again with good results. But this time they realize their "major advance" and can relish in their "new discovery" (again Kleiner and Paulescu are conveniently forgotten; but we know that Collip was in town).

The following 10 days or so suddenly become obscure in Bliss' book (p. 101) when it comes to Banting's work, nothing is precise. Perhaps, because as Bliss points out there were conflicting reports. "Whole cow pancreas injected intravenously also seemed potent" (Bliss, p. 101). But who suggested this idea so contrary to Banting's fanatical notion that the trypsin had to be eliminated at all costs? Certainly Collip was using whole beef liver, so this seems the logical explanation, but why not say so? This is very important to know. It is not fair to deprive Collip of his dues. Then they are "experimenting" with dialysis and washing with toluene (ibidem). An extraordinary success on 15 or 16 December follows the injection of "a dried extract the size of a match – redissolved in 10 cc. of saline" (ibidem). What kind of extract? This seems to be their last successful experiment as further attempts fail.

What seems to indicate that whole bovine pancreas was unsuccessfully used (and this sounds rather strange indeed) on 18, 19 and 20 December, is the information by Bliss (p. 101) that they possessed large quantities of this material. Perhaps this was also used on 15 or 16 December when they tasted for the last time what they considered victory, their "new discoveries".

Again, what cannot be established with certainty is how much interaction had taken place between Collip and "the Banting group" (Banting, Best, Macleod) between 23 November when they adopted Collip's new Schaffer-Hartmann method for measuring the glucose in blood[76] and 12 December. Also, how relevant is Bliss' observation that "in making the extract for Thompson, Banting and Best had apparently adopted the improvements Collip had worked out in December, notably the use of a vacuum still and the technique of not evaporating all of the alcohol".[77]

The successive failures following their initially successful experiments brought to an end their so promising beginnings. There will be one more unfortunate attempt on a human diabetic on 11 January, after which Collip will be the only significant player on this stage of real drama and hope. Banting and Best would do no further experiments on animals between 22 December and 13 February. From this point on Banting will be just a technician providing pancreas tissue.

As already mentioned some authors use words like "discovery" and even "breakthrough" when describing any step forward realized by Banting, which is true only in the narrow, relative sense of these words, meaning that it was "new" only to them, but not to the scientific community as a whole. The genuine breakthroughs will soon come from Collip and only then Toronto will take the lead in this field.

It is obvious that Banting and Best had so far discovered nothing really new and whatever they did find was only after using unnecessarily tortuous, complicated

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[76] Li, J.B., Collip, (fn 70), p.17, Collip adopted this method while at Wood's Hole Marine Biological laboratory in Cape Cod in summer 1921.

[77] Bliss, (fn 3), p.114.

methods. The real new discoveries in Toronto will begin only with the arrival of Collip.

B) After Collip's Arrival

Now let's see what happened after Collip "officially" arrived on the scene around 12 December. In my opinion, prior to Collip's arrival Paulescu was by far ahead of his colleagues in Toronto. Perhaps Paulescu's laboratory data based on different methods raised some eyebrows in Toronto, but all his interpretations and conclusions were correct and he showed an understanding of how insulin acted on all aspects of metabolism, a huge step forward that apparently many do not realize.

Unlike Banting, Collip is not as well known to the general public nor is he mentioned in schoolbooks. Even after this so important contribution to the discovery of insulin, he carried on with great discoveries that explain how he became a legend in Canadian Endocrinology. He was honored for all these accomplishments that he fully deserved. But he is seldom mentioned in connection with the discovery of Insulin, and yet, it is here that he achieved his most brilliant feat, not only of his career, but also in the entire field of Canadian Medicine and Physiology. In my opinion, one could say that this achievement was Canada's greatest gift to the whole of humanity.

Let's not forget that he was an accomplished scientist. He published his first article at the age of 21. When joining the Toronto team he already had 23 publications to his credit. After leaving Toronto at the end of May 1922 his scientific accomplishments in the field of Medicine and Physiology will be without equal in Canadian Medicine. M. Bliss states that in the end "Collip made himself by far the dominant figure in the history of endocrinology in Canada".[78] Suffice to mention here his discoveries (1923, Glucokinin) and important contributions to isolating the parathyroid hormone (1925, "Parathormone"); the placental estrogen-like Emmenin (1930, the first orally active estrogen), precursor to Premarin (1939-1940), launched in Canada in 1941; the ovarian and gonadotropic hormones and the adrenocorticotropic hormone (ACTH, another great achievement). Between 1922-27, he added 40 articles to his credit.

Collip was asked to join the Toronto group, I assume, because the trio of Banting, Macleod and Best, in spite of all their efforts could not get any further than their precursors had (November 1921). Bliss considers this interpretation "a legend", but in this case it is almost miraculous how Banting and Best suddenly have a degree of creative effervescence that nobody had seen from them, just prior to Collip's "official arrival" on 12 December.

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[78] Bliss, (fn 3), p. 237.

The actual date of Collip's involvement is not clear, Bliss assumes it was 12 December.[79] According to him he was "at work" on that day. He certainly must have had relevant discussions with all three researchers and most certainly with Macleod before starting on his new mission. One should assume that it must have taken several days before getting his laboratory ready for such a challenging task.

It is impossible to establish for sure how much Collip was influenced by Macleod's suggestions in various respects, but when he started his work, his plan appears to have been well established, strategically well oriented and innovative. Everything else is pure speculation.

Collip was given the assignment to purify the pancreatic extract and render it suitable for medical use. In addition to his many publications, he also had an impressive amount of experience in medical research, including physiology, biochemistry and successful extractions from various organ tissues[80]. He quickly went to work and the quality of the work at Professor Macleod's facility rapidly improved. Collip used from the very beginning whole beef pancreas, undigested, and used rabbits in lieu of dogs, cheaper and easier to get. The extraction method was also from the very beginning significantly innovated.

He conducted his own experiments and prepared from the very beginning his own method of extracting insulin (according to him[81]) quite different from Banting's extracts. Collip used vacuum in lieu of heat, reducing the total volume to one fifth of the original volume, filtered the suspension and obtained a clear fluid and a residual of solid particles, both being very potent. The article describing Collip's method (Collip 1923 L, Bliss), "The Original method as used for the first clinical case", Journal of Biological Chemistry, 55: xl-xIi is mentioned by Bliss in Sources, (p. 289). But this is not mentioned on p. 261, note 42 where he cites "the five articles he

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79 Bliss, (fn 3), p. 99.

80 Li, J. B. Collip, (fn 70), p.17, "In this work, he prepared extracts of many mammalian tissues: heart, lung, spleen, liver, brain, cord, pancreas, skeletal muscle, testes, small intestine, pituitary, thymus, thyroid and parathyroid."

81 Here we enter a controversial terrain, who did what first, who suggested it first etc. It is a fact that Collip had discussions with Macleod, Banting and Best prior to 12 December 1921. There seems to be little doubt that it was Collip who introduced the Toronto group to the new Shaffer-Hartman method of determining the glucose level in blood. He had used it at Wood's Hole during the summer (Alison Li [our note 70], p. 23). It is also well known that he had considerable experience in producing tissue extracts for laboratory experiments (fn 70). It is equally obvious to me that his modification of "Banting's method" was a rather radical change. The first genuine advances and breakthroughs came only with Collip. With his experience in the field of making tissue extracts and coming back from USA, acquainted with the latest advances in this field it seems to me that he had precious little need of guidance from the "Toronto group", apart possibly from Banting's demonstration of what sheer will power can do.

was able to locate" and as such it is simply ignored by him (but also by Alison Li and this is rather strange). The difference in method is obvious[82] (full text in our note 82).

Even healthy rabbits were used in his experiments and this was a contribution of immense practical significance, being cheaper and also allowing testing of the potency of a batch of extract.[83]

Unlike his colleagues, he checked the effect on healthy animals (as Paulescu had done before), checked very carefully its effects on urea in blood and urine, on acetonuria and acetonemia [84] (as Paulescu had done) all the while concentrating on the purification of the pancreatic extract. He got his blood samples without resorting to anesthetics, from fine, superficial ear veins. His intellectual and empirical resources were impressive indeed.

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[82] Collip 1923, "The Original method as used for the first clinical case", Journal of Biological Chemistry, 55: xl-xIim mentioned by Bliss on page 289, but nowhere discussed. We reproduce the essential paragraph: The original method was as follows: "To a small volume of 95 per cent ethyl alcohol, freshly minced pancreas was added in equal amount. The mixture was allowed to stand for a few hours with occasional shaking. It was then strained through cheesecloth and the liquid portion at once filtered. The filtrate was treated with 2 volumes of 95 per cent ethyl alcohol. It was found by this treatment that the major part was removed while the active principle remained in alcoholic solution. After allowing some hours for the protein precipitation to be effected the mixture was filtered and the filtrate concentrated to small bulk by distillation in vacuum at a low temperature (18° to 30° C.). The lipoid substances were then removed by twice extracting with sulfuric ether in a separating funnel and the watery solution was returned to the vacuum still where it was further concentrated till it was of a pasty consistency, 80 per cent ethyl alcohol was then added and the mixture centrifuged. After centrifuging, four distinct layers were manifested in the tube. The uppermost was perfectly clear and consisted of alcohol holding all the active principle in solution. Below this, in order, were a flocculent layer of protein, a second clear watery layer saturated with salt, and a lowermost layer consisting of crystals of salt. The alcohol layer was removed by means of a pipette and was at once delivered into several volumes of 95 per cent alcohol, or better, of absolute alcohol. It was found that this final treatment with alcohol of high grade caused the precipitation of the active principle along with adherent substances. Some hours after this final precipitation the precipitate was caught in a Buccaneer funnel, dissolved in distilled water, and then concentrated to the desired degree by use of the vacuum. It was then passed through a Berkfeld filter, sterility tests were made, and the final product was delivered to the clinic. The essential points relating to the extract prepared as outlined above are: 1) It contains only a minimum of protein. 2) It is practically salt-free and can readily be made isotonic. 3) It is lipoid free. 4) It is almost free from alcohol-soluble constituents. 5) It can be administered subcutaneously without fear of any local reaction. Note – this method was developed by the writer while he was attached to the Department of Pathological Chemistry, University of Toronto".

[83] Bliss, The Discovery, (fn 3), p.100.

[84] Bliss, The Discovery, (fn 3), p.103.

On 22 December, he discovered a markedly increased liver, full of glycogen, a proof that the insulin in the extract he was using was enabling the glucose to be accumulated in the liver in form of glycogen, something that does not otherwise take place in a diabetic. However, Collip did for understandable reasons not study the role and mode of action of glycogen as Paulescu had done.

Even more impressive is how he, not a medical doctor, in a moment of sudden insight and history-making intuition was able to understand, diagnose and successfully treat with sugar rabbits in insulin shock. One morning he found several rabbits dead or having convulsions. He took a blood sample, quickly prepared a solution of sugar, injected it intravenously and the symptoms quickly disappeared. He had just discovered a new medical entity that will be called hypoglycemic reaction or insulin shock, confirmed after the fact by the test that showed practically no sugar in blood. This was a "tour de force" indeed (in the first week in January 1922). This is in our view in no way diminished by the fact that Bliss mentions (p. 109) that F.C. Mann and T.B. Magath had reported (1921) similar effects, but following hepatectomy (a different chapter).

It was most likely the evening of 16 January[85] when according to Bliss he had his moment of "inspiration", but unlike Banting's it was based on informed, scientific, logical thinking. A later date, as suggested by A. Lee (see our note 71) is most unlikely. He realized that at a concentration of about 90% alcohol most impurities were eliminated. Then he discovered that by raising only slightly this concentration, the "internal secretion" would "precipitate" and could be isolated in almost pure form and then could be injected into diabetic rabbits with positive results and no appreciable side effects.

It was actually quite a complicated and demanding job. He further benefited from having brought with him from the USA the most refined laboratory investigation methods, including the Shaffer-Hartmann[86] micro-method for glucose measurements already mentioned and more refined extraction techniques.

Tensions and even ugly conflicts involving Banting were the rule in this laboratory but eventually peace was restored at the faculty of Physiology in Toronto,

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85 Bliss, The Discovery, (fn 3), p.117 gives the date of 16 January after midnight. Alison Li, (fn 70), p.184, based on a letter to Tory on 25 January gives the date of 19 January. But it is more likely that Li's interpretation is incorrect. The quoted text: "last Thursday Jan.19th I finally unearthed a method of isolating the internal secretion of the pancreas" would rather indicate the date when he actually extracted the insulin and was ready to experiment with it. It is hard to conceive that in only three days (20, 21 and 22 January 1922) he could conceive the method, utilize it for extracting a purified insulin, submit this extract to tests on animals and have the courage to inject it into Leonard. Only God could have done this.

86 Li A, "J.B. Collip", (fn 71).

but in our view, Banting could no longer ethically claim any laurels from Collip's eventual victory.

Victory surely came on 23 January when Dr. Walter Campbell injected into the same Leonard Thompson 20 cc of Collip's extract. Leonard went on to survive into adulthood and the victor's laurels deservedly came to Toronto. According to L.G. Stevenson "This was the first clearly successful clinical test of the internal secretion of the pancreas on a human diabetic"[87]. In February, six more patients were treated.

Macleod proudly announced this great moment (23 January 1922) to the world at the meeting of the Association of American Physicians in Washington, DC on 3 May 1922. It was received with great enthusiasm and a standing ovation almost unique in the history of this Association. Diabetes was finally conquered! (So it appeared).

C) **Toronto 1921-1922; The Paulescu Factor**

That Paulescu's work became known in Toronto cannot be disputed. Best's notes published by Bliss and dated sometime during November 1921 remove any doubt. That Banting and Best at least initially were incapable to properly understand the significance of Paulescu's findings is obvious.

We have mentioned that Banting and Best misrepresented, actually falsified Paulescu's findings ("Compte Rendu" of April 1921) in their first publication *The Internal Secretion of the Pancreas", by F.G. Banting and C.H. Best, published in Journal of Laboratory and Clinical Medicine in St. Louis, February 1922*. Pavel and Martin reacted (around 1970) and Bliss acknowledged this impropriety (The Discovery of Insulin 1982 and subsequent editions).

In his Nobel Lecture on 15 September 1925, Banting only mentions Paulescu once "en passant": "Paulescu also briefly reports favorable results". After all Macleod had already acknowledged Paulescu's merits in his address to the Nobel Assembly on 26 May 1925[88] and Banting could not do otherwise. In all other articles published by Banting's, including "The History of Insulin" Paulescu is not even mentioned.

John J. R. Macleod, acknowledged Paulescu's work even more emphatically in his "Carbohydrate Metabolism and Insulin", London, New York, Toronto, 1926, properly listed in Bliss' "Sources", p. 294, but otherwise not discussed in his book. It is here that Macleod states unequivocally:

"While this work was in progress in Toronto a paper by Paulescu came to our

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87 Stevenson L. G., Sir Frederick Banting, 1947, 75-108, The Ryerson Press.

88 "Special reference must also be made to the more recent work of Paulescu who prepared extracts having very decided effects on the sugar and the urea of the blood of diabetic animals."

notice and after it was completed, one by Gley. Paulescu's researches were communicated at a meeting of the Réunion Roumaine de Biologie in the spring of 1921 in which he describes the effects produced by intravenous injection of sterile pancreatic extracts on the percentage of sugar, of acetone bodies and of urea in blood and urine of depancreatized dogs. Typical observations are shown in Tables 1-5. *There can be no doubt that all three substances became markedly reduced in amount, in both blood and urine, as result of the injection*. The results were the same whether the injection was made into a branch of the portal vein or into the jugular vein. The effects were noticeable in one hour following the injection, attained their maximum in two hours, and passed off in 12 hours. They varied with the amount of gland present in the injected extract. Paulescu also observed that the blood sugar as well as the blood urea in a normal dog become lowered by the injections" (emphasis ours).

There is no doubt that Macleod understood and accepted Paulescu's important findings. How can we explain Macleod's silence prior to 1925?

Bliss (p. 208) comes with following explanation, while referring to Macleod's silence in general: "Probably it was just an oversight; perhaps, as commonly happens even with the best-informed professors, Macleod had not yet read Paulescu". Perhaps Bliss is right, but I can hardly believe that such an important article so closely related to their (Banting, Best and Macleod) work could have gone unnoticed by Macleod or him not being informed about it. By the way, Bliss does not give Macleod's text about Paulescu's work, and the above is his only reference to this chapter (Macleod on Paulescu).

From everything, we know about Macleod, he was a correct, honorable researcher. Actually one will be hard pressed (I would say likely impossible) to find in Macleod' work any dishonest misrepresentations.

Macleod will admit in 1926 that Paulescu's work "came up to our attention" in November 1921. Surely, he must have informed Banting and Best to seriously consider this matter. Most likely, this must have come up during their conversations

But how many times did Banting and Best disregard, or postpone by many months Macleod's important advice. Certainly, the two young researchers would not easily give up on their "great idea" of the trypsin's malefic role.

Accordingly, is there any wonder that when they present to Macleod their first paper for publication, including serious distortions, actually falsifications of Paulescu's work, Macleod refuses to have his name added? It is not difficult to accept that a scientist of Macleod's reputation simply could not add his name to a text he knew was flawed by falsification of another scientist's work.

So here, we have Macleod, leading a team already afflicted with increasing

mutiny and almost impossible to control. While pondering this incendiary situation he must have realized that any attempt to set straight the record would have only aggravated this and particularly Banting, who was already showing signs of paranoia.

It is not difficult to assume that Macleod would expect that Paulescu would reply and set straight the record himself, with much less damage to his "team". Little did he know that in Romania for Paulescu it would be most difficult, for financial reasons to keep abreast with publications in the English-speaking world. He would only find out after the Nobel prizes would be announced.

Banting never retracted and Best would only add insult to injury in 1972.

But most revealing is the fact that in November 1921, Banting and Best used whole-undigested canine pancreas and shortly thereafter they committed the ultimate sin: using undigested beef pancreas. So far, no satisfactory explanation for this change has been revealed.

D) How to discredit a Rival

Paulescu's essential contributions during the years 1920-1921 were unfortunately corrupted and misrepresented in the English medical literature by Frederick Grant Banting and Charles Herbert Best with serious consequences for Paulescu's reputation as will be demonstrated.

It should be stated at the very outset that both Banting and Best deserve our respect for their hard work, dedication and for having initiated the chain of events that will eventually be crowned with success thanks to Collip. Banting will become a respected, fatherly figure vainly trying to find a cure for cancer, while Best (and Collip) would make further important discoveries in medical science. But the way they treated Paulescu in 1921-1922, a highly respected scientist, highly esteemed among many others by Harvey Cushing, Lancereaux and others cannot be allowed to go unchallenged.

More specifically this has to do with the way they misrepresented his work:

1) Some may be familiar with the misreading by Best of Paulescu's text where the French "non plus" becomes "no bon". In other words, Best and Banting claim that in Paulescu's research injections of pancreatic extract into peripheral veins had no effect on the level of glucose in blood and urine, exactly the opposite of what Paulescu had demonstrated and stated. Ion Pavel (1969) uncovered this misrepresentation. Michael Bliss quite rightly comments in his important book The Discovery of Insulin: "It is such an odd error, with apparently such devastating

consequences for Paulesco's reputation."[89] May I say that the word "odd" is most inappropriate when we deal with such shocking behavior. That they erred, one could understand and forgive, but that they never apologized or tried to correct their error is inadmissible. Certainly even an ignorant like Banting must have realized this. As to Best, even after I. Pavel informed him of the problem, he only expressed his regrets in a letter of reply dated 15 October 1969, "I regret very much that there was an error etc."[90] This is very easy to say, but certainly it was not sufficient, as he never mentioned this in public. Any scientist with a sense of dignity and respect for others would have repeated this in some form in public, but not Charles H. Best. A second reply was even insulting, by pretending that after all he and Banting were the only discoverers of insulin.

Naturally, not everybody shared this opinion. Besides Pavel, Ian Murray and Eric Martin[91] took a dim view of Best and Banting's behavior. Martin, as quoted by I. Pavel, wrote[92]: "Thus, probably due to their poor knowledge of French the merit of the Romanian author is reduced to naught".

2) Likewise the claim that "his experiments [also] show that second injections do not produce such marked effect as the first", is completely false. The same errors are repeated in the publication "The Internal Secretion of the Pancreas" where we can read: "Paulesco has recently demonstrated the reducing effect of whole gland extract upon the amounts of sugar, urea and ketone bodies in the blood and urine of diabetic animals. He states that injections into peripheral veins produce no effect and his experiments show that *second injections do not produce such marked effect as the first."*[93]

The first assertion was shown above as proven untrue by various authors. As to the second part, this also has been exposed as being without any foundation among others by I. Pavel and Ian Murray. We have not been able to find any such

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89 Bliss, The Discovery, (fn 3) p.16.

90 I. Pavel, (fn 69), p.109: " Dear Doctor Pavel: In answer to your letter of the 8th of October, I am very pleased to learn that you plan to celebrate the 50th Anniversary of Professor Paulescu's publication of his paper on the secretion of the pancreas. I regret very much that there was an error in our translation of Paulescu's article. I cannot recollect, after this length of time, exactly what happened. As it was almost fifty years ago 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 honor Professor Paulescu will be rewarded with great success. With every good wish and kind regards, Sincerely yours, Charles H. Best".

91 Eric Martin, "Problèmes de priorité dans la découverte de l'insuline", Schweizerische Medizinische Wochenschrift, 101, p.164-167,1971.

92 Pavel, The Priority, (fn 69), p.109.

93 F. G. Banting and C. H. Best, "The Internal Secretion of the Pancreas," Journal of Laboratory and Clinical Medicine, 5 February 1922, 7 (fn 5), pp. 251-266.

statement by Paulescu in his presentation ("Compte Rendu") of April 1921, read and criticized by Best and by Banting. On the contrary, Paulescu in his 4th experiment (23-26 February 1921) had conclusively shown a markedly increased effect of a second injection of a double amount of pancreatic extract.

But what is puzzling is the fact that other equally serious errors by Banting and Best, to my knowledge, have not drawn any criticism so far.

3) I refer to the fact that Paulescu in his four presentations read by Best and Banting, quite clearly and repeatedly states that he injected his extract in the *jugular veins (in experiments I and II the term superficial jugular veins is used)*. Now the jugular vein (naturally the superficial one) was then and still is today, when it comes to injections, a peripheral *vein* (please consult any textbook of Anatomy of that era and today)[94]. Here Best's poor knowledge of French cannot be invoked as an excuse.

The pertinent text in French of Paulescu's first presentation is: *"Si, chez un animal, diabétique par ablation du pancréas, on injecte dans une veine jugulaire, un extrait pancréatique*." In translation: "If one injects a pancreatic extract *in a jugular vein* of an animal rendered diabetic by removal of the pancreas". Then, *"Les mêmes effets s'observent aussi lorsqu'on injecte l'extrait pancréatique, non plus dans une veine périphérique, mais dans une branche de la veine Porte*" (emphasis ours). In translation: "The same effects are *also* observed when the pancreatic extract is injected not only in a peripheral vein, but into a branch of the portal vein". The jugular vein is again mentioned in the other three presentations. Likewise, it is mentioned in eleven out of his twelve "Experiments" and the term "superficial jugular" in the first two in *"Recherches sur le rôle du pancréas dans l'assimilation nutritive"*. By the way, I. Kleiner refers to the jugular vein as "superficial jugular" in all his experiments. But this is how Best interprets this text: "extract was given shortly after pancreatectomy - no record of volume of urine or volume of extract. States that injections *into jugular (*accordingly peripheral, an*),* portal, or mesenteric

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[94] Peripheral veins: Wikipedia, Intravenous Therapy, Peripheral IV lines. http://www.answers.com/topic/intravenous-theray: "This is the most common intravenous access method in both hospitals and paramedic services. A peripheral IV line consists of a short catheter (a few centimeters long) inserted through the skin into a peripheral vein. *A peripheral vein is any vein that is not in the chest or abdomen*. Arm and hand veins are typically used although leg and foot veins are also. According to HEARTCENTERONLINE: The peripheral veins are located in areas of the body such as the feet, legs, lower abdomen, arms, neck and head. According to >MedicineNet.com< the jugular veins are a) external or b) internal. But at the time of Banting the distinction was clear: peripheral and central (inside thoracic or abdominal cavity).

veins work but *into "peripheral veins" no bon*, C. H. B. "[95](emphasis ours).

This is no longer a lack of knowledge of French, but sheer ignorance of anatomy, perhaps even malice or worse. Reading Best's interpretation it is even grotesque. Obviously, Best with no medical training whatsoever did not know this little detail of anatomy but he did not hesitate to criticize a researcher already respected for his many accomplishments. I might even be inclined to forgive him for his faulty translation from French and his ignorance of anatomy. But what about Banting and all those learned professors who when reading the quoted text forgot a very elementary fact of anatomy, for which a first year medical student would have flunked his examination. Some authors never studied anatomy and might be forgiven. This error about the jugular vein automatically refutes Best's and Banting's ridiculous interpretation of "non plus". It is hard to believe that such an error about such a simple, self-explanatory detail could have gone unnoticed all these years, as this seems to be the case here, at least to my knowledge.

4) Even more inexcusably erroneous misrepresentations are contained in Best's notes. Referring back to the above quoted comment by Best "*no record of volume of urine or volume of extract*", Best fails to pay any attention to the prominent footnote on the very first page of this first presentation.[96] This prominent footnote refers the reader for further details to the more comprehensive study *"Research on the function of the pancreas in nutritional assimilation*".[97] Here one can find an impressive amount of information and details including the amounts of injected extracts, the amounts of urine excreted, temperatures, conditions of the experimental animals, autopsy results, etc. Perhaps one could excuse Best as he was not even a medical student but it is difficult to find any excuse for Banting. It was Banting's duty as the senior man to check his student-collaborator's findings, particularly when these were critical of a man of science with an established reputation. This certainly helps explain why Paulescu has disappeared, and not only in the Anglo-Saxon medical world, after such unacceptable misrepresentations.

I also find that M. Bliss, otherwise always trying to be objective, in our opinion is erring when discussing this chapter. He only mentions (p. 87) and criticizes Banting's and Best's misrepresentations with regard to the "non plus" being "no bon", and a second injection not being as effective as the first one. These unacceptable falsifications had been inserted in their first published article of

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[95] Photocopy of a handwritten index card initialed by Best (it bears the initials C.H.B.) from the F. G. Banting Papers, Digital Collections of the Fisher Library, University of Toronto, Toronto, Canada.

[96] N. C. Paulescu, "Action de l'extrait pancréatique injecté dans le sang chez un animal diabétique", C. R. Soc.Biol. (Paris), 23 July 1921, 85 (27), pp. 555-558.

[97] N. C. Paulescu, "Recherches sur le rôle du pancréas dans l'assimilation nutritive," Arch. Int. Physiol., 31 August 1921, 17 (1): pp. 85- 103. Received for publication 22 June 1921.

February 1922. Furthermore, they had already been exposed by Pavel and Martin and accordingly Bliss simply could not afford to ignore them. But he fails to criticize all other distortions by Best and Banting of Paulescu's work, as exposed above. One might be able to excuse and forgive one or even two distortions, but when all of them are listed together as I have done, they together, in my opinion form quite a substantial and unpardonable "corpus delicti".

What makes this chapter even more difficult to understand are the revelations by Macleod in 1926 in his important article "Carbohydrate Metabolism and Insulin" already mentioned in section C of this chapter but not in Bliss' work. The pertinent paragraph includes the most important statement: "*There can be no doubt that all three substances became markedly reduced in amount, in both blood and urine, as result of the injection*".

It becomes obvious that Macleod, as a true scientist, unlike Banting and Best, understood Paulescu's paper very well and accepted his findings. This admission by Macleod raises lots of questions and we are even more at a loss to understand what was going on in Toronto in the fall of 1921 and the following months. How can one explain Banting's and Best's irresponsible statements and falsifications of Paulescu's work? Again, how can we understand why Bliss publishes the incompetent interpretations of a novice like Best but does not quote or at least summarize the more significant text by Macleod, except for a much too vague reference on page 208. It would certainly be enormously helpful if one could clarify this anomalous situation (Best and Banting versus Macleod). One might speculate that this might have been one of the reasons why Macleod refused to have his name listed as author in "The Internal Secretion of the Pancreas", by F.G. Banting and C.H. Best, published in Journal of Laboratory and Clinical Medicine in St. Louis, February 1922. I shall welcome any better explanation (Bliss believes that Macleod just wanted to be fair).[98]

Again, one cannot overlook the fact that Collip and Macleod were on very friendly terms and certainly, there could have been many discussions between these two scientists. It is more than likely that Macleod informed Collip about the true significance of Paulescu's results that he perfectly understood (unlike Banting and Best). This might have induced Collip to research himself the effects of insulin on the metabolism of fats and proteins. But this would certainly in no way diminish Collip's enormous contributions.

As to Banting a very sad, even shocking fact is that the previously noted aberrations of judgement or conduct were not isolated cases. They could fill many pages.

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[98] Bliss (fn 3), p. 94, " The article does not omit the misreading of Paulesco's work […]. figures given in the text and the charts sometimes disagree […]. The description of the last experiment is particularly bad".

In his Nobel Lecture on 15 September 1925, Banting only mentions Paulescu once "en passant": "Paulescu also briefly reports favorable results". In the article "The History of Insulin", Paulescu is not even mentioned. By contrast, John Macleod, in his Nobel Lecture of 26 May 1925 acknowledges Paulescu's work. [99]

It is not to Banting's honor that he never admitted his mistakes. It is also difficult to believe that he never found out about Paulescu's real results and conclusions. Again as the senior man he should have checked Best's assertions.

The posture of the University of Toronto group towards Paulescu was perhaps best exemplified when Banting received a letter from Paulescu written on 5 February 1923, and he did not deign it with a reply. Neither did Macleod reply to the request of Maurice Arthus, Professor of Physiology in Lausanne[100], dated 3 November 1923, for copies of the papers of 1922, instead sending him a totally unrelated book. Perhaps by taking the slights towards Paulescu one at a time it is possible to excuse them, as Bliss did, but this is difficult when considering them all together. Compounding this is the fact that they never tried to rectify their mistakes, and Best in 1969 did not do so in public.

One final thought: Certainly after Collip's trail blazing work in 1922, the other workers' contributions were rendered to a secondary level. But one must wonder what the consequences would have been if someone had submitted Paulescu's name in 1923 for the Nobel Prize. It would seem almost certain that John Sjöquist, from the Nobel Prize Committee would have discovered Banting's misrepresentation of Paulescu's work. We can only speculate what the consequences would have been. A similar thought is expressed by Prof. Ian Murray: "It is certain that if he (Paulescu) had known of the false quotation that compromised his work he would have responded actively and the matter would have taken a quite different course."[101] Even more so, if we consider the fact that there was more than one misrepresentation as we have shown above.

It is sad when one compares the boorish way Banting treated Paulescu with the courteous, civilized, almost adulatory regard shown by Harvey Williams Cushing as we have already described in a previous chapter in this essay. We have mentioned that Cushing even invited Paulescu to the USA. He was a brilliant scientist and a true gentleman with high regards for his fellow scientists in true Hippocratic tradition. And he too was a very busy man.

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[99] "Special reference must also be made to the more recent work of Paulescu who prepared extracts having very decided effects on the sugar and the urea of the blood of diabetic animals."

[100] Pavel, (fn 69), "The Priority of N.C. Paulescu", pp.110-111. Text of letter is included.

[101] Ian Murray, "Paulesco and the isolation of insulin," J. Hist. Med. Allied Sci., 1971, 26 (2), pp. 150-157. Text included in Pavel (fn 69), p. 25.

BANTING: FURTHER CRITICISM

The errors concerning Paulescu have not been the only criticisms made regarding Banting's publications and conduct and in an almost kafkaesque manner the medical literature is full with hundreds of similar misleading quotations and opinions. It is almost as if the entire medical profession (and this includes the historians too!) forgets that in 1899 N.P.S. Shepovalnikow, working with and under the great Ivan Petrovich Pavlov at the University of St. Petersburg described a new enzyme in the intestine that would convert the inoffensive trypsinogen present in the pancreas in an active proteolytic ferment, already mentioned in our text. This will be called *enterokinase* by W.H. Thompson in 1902. Others ascribe the paternity of the word enterokinase to Pavlov himself. In order to complete this most intriguing story, on 6 February 1909 Barbara Ayrton, from The Physiological Laboratory, University College, London published[102] a most important article describing the properties of trypsinogen after conversion into trypsin and those of enterokinase, to the English speaking medical world. She mentions that the former is converted by the latter into trypsin, either by the action of enterokinase in the intestine, but also at times spontaneously inside the pancreas by calcium containing substances, or by heating. The year of the discovery was 1899 and Pavlov received the Nobel Prize in 1904. Pavlov became an instant international celebrity, received many honors in the West and as such his achievements inevitably were known to western scientists through translations of individual accounts, or through Ayrton's article, etc. A complete translation of his works was first published in English in 1927. As such, it is difficult to accept that in North America there were scientists unaware of his work. We have seen that Ffrangon Roberts in 1922, without mentioning their names, described the conversion of trypsinogen into trypsin as "*the best established fact in physiology"*. It would be quite reasonable to assume that Kleiner, Paulescu and Collip were aware of this fact of elementary Physiology as they went straight to whole, undigested pancreas in order to obtain their extracts.

This explains how, based on a total amnesia by the medical profession (including again the historians), false statements abound in books, articles, movies etc. and Nobel Prizes were awarded, but unfortunately distinguished careers were also ruined. This says a lot!

Banting was definitely not a true scientist. His methods were too sloppy and his research had little direction. Bliss' revelations are more than embarrassing. For example, Banting often forgot in which order certain experiments had been done

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[102] "The Activation of Pancreine Juice", Quart Journ of Experimental Physiology 1909:2: 201-217.

(Bliss, p. 59). In one instance, he enters in his scrapbook notes on a dog that actually had already died earlier (p. 61).

Further Bliss tells us about the dogs that died because of his unsure handling of the scalpel (pp. 89-90). Also, he had the tendency to minimize, even forget his own failures (pp. 94-95). On 9 December, a dog, moribund with infection was narcotized in order to have the blood pressure and sugar checked and recorded!

It is hard to believe that they only once checked the temperature (on 26 October according to Bliss, p. 89). Again, they checked only once their extract to be given to Leonard Thomson. If I were asked to name Macleod's greatest error, it would be the day when he interceded with Prof. Graham to make it possible for Banting's extract to be used for the first time on a human being in Toronto. An extract produced in great haste, for the glorification of two unscrupulous young men when everybody knew that Collip was further advanced in his research. This was the lowest point from a deontological perspective. We all know how Banting thanked Macleod who had risked his prestige for Banting.

But even worse, there was often quite a difference between his laboratory notes and his publications. For example, there is quite a discrepancy between his handwritten notes and the data published in the Bulletin of the Academy of Medicine. In his important *"Pancreatic Extracts*" in the Journal of Laboratory and Clinical Medicine, VII, 8 (May 1922): 3-11, Bliss finds 18 errors when compared to the original notes (p.123).

Even stranger is the experiment on 17 August with whole pancreas and using chloroform to which we have already alluded. The results surpassed the experiments with degenerated liver, but in an incomprehensible manner, they arrived at the conclusion "that the whole gland extract is much weaker than that from the degenerated gland" (Bliss pp. 76-77).

The heaviest criticism came from Dr. Ffrangon Roberts (we have referred to him above) in his appraisal of Banting's work, published in the *British Medical Journal of 16 December 1922* and discussed by M. Bliss in the same work *"The Discovery of Insulin",* so often quoted by us, on pages 203-208. Robert's criticism, well documented and revealing a multitude of errors in Banting's papers is devastating.

Banting, according to Roberts, based his work on the hypothesis that "*it was necessary to protect the internal secretion of the pancreas from the powerful external secretion, the proteolytic enzyme trypsin by ligating the pancreatic ducts to cause the trypsin-producing cells to atrophy".* He was ignorant *"of the best established facts in physiology, that the proteolytic enzyme exists in the pancreas in an inactive form – trypsinogen – which is activated normally with another ferment, enterokinase, secreted by the small intestine".*

Roberts continues with the analysis of the glaring, "*factual disparity between the charts and text in the first paper, as well as the apparent abnormal condition of some of the dogs"*. The most startling example was the experiment they conducted on 17-18 August 1922, (already mentioned in our text), using whole gland pancreas "*which proved to have more positive and more lasting effect than those made from degenerated pancreas."* But unbelievably they obstinately claim the opposite in order to prove "their theory". Then incomplete data about the blood glucose after pancreatectomy, but prior to injecting the extract, undermines any conclusion.

Again, their experiments with exhausting the pancreas of its external secretion were meaningless[103], as they could not prove that the pancreas was indeed exhausted, by checking the three pancreatic enzymes. Roberts was perfectly right, Banting had actually proven nothing new and his own theory was irremediably flawed.

The list of errors continues, and as such Roberts concludes:

"Having therefore failed to establish their main thesis, but encouraged by a complete misreading of their results (I challenge any unbiased person to read the paper carefully and come to other conclusion), Banting and Best then proceed to investigate further methods of preparing a hormone free from the destructive action of ferments. They tried fetal pancreas...no comparison has been made between fetal and normal adult pancreases."

And in conclusion*:*

"The production of insulin originated in a wrongly conceived, wrongly conducted and wrongly interpreted series of experiments. Through gross misreading of these experiments interest in the pancreatic carbohydrate function has been revived, with the result that apparently beneficial results have been obtained in certain cases of human diabetes... Whatever success the remedy will have will be found to be due to the fact that the hormone has been obtained free from anaphylaxis [104]producing and other toxic substances. The experiments of Banting and Best show conclusively that trypsin ...has nothing whatever to do with it".

Reading the article by Banting and Best "*The internal secretion of the pancreas"* (J. Lab Clin. Med. Feb. 1922) we've found it ourselves shocking! It contains one grave fallacy, repeating the misrepresentation of Paulescu's conclusions with regard to injecting into peripheral veins. In "Conclusions" there are also two important falsehoods: a) their own I.V. injections of macerated pancreas "invariably"

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[103] In order to eliminate the digestive effect of the trypsin, p. 204.

[104] Although Collip is not mentioned by name, it is obvious who earned the merit (F.I.D).

reduced the percentage of blood sugar, thus intimating that it also was superior to whole gland extract (and, unbelievably, completely disregarding all their failures and the many dead dogs), and b) the pancreatic juice destroyed the active principle in the extract. Ironically, the article appeared only weeks after Collip's epoch making success with whole pancreas extract, when he completely ignored the presence of trypsinogen. But unbelievingly, Banting believed for the rest of his life that he had received the Nobel Prize because he had discovered the significance of the elimination of the dangerous trypsin!

According again to Bliss the Venerable Sir H.H. Dale responded in the next number of *British Medical Journal,* but did not counter Robert's criticism, but rather mentioned that the important fact was that insulin had been isolated and was in use. Naturally, he was England's medical Ambassador to Toronto, sent to negotiate the production of insulin in England and it was prudent not to offend Toronto! As a result, young Roberts refrains from continuing his offensive and contradicting his idol (Dale).

Very significant is the fact that to this date nobody has contradicted Robert's devastating criticism.[105]

No less devastating was the critique by Dr. Joseph H. Pratt's major article in 1954 "*A reappraisal of researches leading to the discovery of Insulin*"[106]. He expresses good reasons to doubt that the dog "Marjorie" (the survival test dog) was really diabetic, and is surprised to see that Banting's dogs did not show toxic effects like those registered by Zülzer, Scott, Kleiner, etc. and as he himself noticed when duplicating Banting's experiments.

Very revealing are Pratt's comments challenging Best. Pratt concluded that Collip's contribution was essential in furnishing the clinicians "with the first insulin ever to be used successfully in the treatment of diabetes," and argued powerfully that all four members of the team deserved recognition. (Best helped Feasby draft a reply to Pratt aimed at correcting the "errors of fact and several omissions and misinterpretations" in Pratt's article, p. 262).

We might add ourselves that Banting had actually proven *nothing new when compared to Kleiner or Paulescu.* That Banting had never heard of Israel Kleiner's work and shamelessly dismissed Paulescu's work cannot be easily overlooked.

We have criticized Banting and Best for the ignominious way they misrepresented Paulescu's work, but at the same time we want to praise Banting's rather benign demeanor later in his life (he still hated Macleod, but was nice and encouraging towards young students).

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[105] See Bliss (fn 3) p. 206.

[106] Pratt J. H., "A reappraisal of researches leading to the discovery of Insulin", J. Hist. Med., 1954, 9, pp. 281-289, also included in Bliss' work (pp. 207-208).

As to Best, he contributed important scientific achievements in later years. Still we are puzzled as to the reasons why Best regretted his previous errors in a letter to Ion Pavel, dated 15 October 1969, but refused to say so in public?[107] It is also a bit strange that he claimed in his book, and in a second letter to Pavel, that he and Banting were the true discoverers of insulin[108] completely disregarding Collip's epochal achievements.

Returning to Banting, we must also refer to some instances of aberrant behavior. His relationship with Professor Macleod quickly deteriorated, in particular after the first presentation of their work in New Haven (30 December 1921). Banting's own performance in public on this occasion was rather embarrassing and so Macleod took over during the question period. This saved Banting from further embarrassment, but Macleod erred in Banting's eyes by using the word "we". In lieu of being thankful for his help, Banting never forgave Macleod.

He never considered for a moment how lucky he was. He was able to work at the University of Toronto, at that time one of the best research institutions with significant opportunities for research and particularly with experiments on animals. He was also able to take advantage of starting his work at a time when science had made great advances in laboratory testing, such as the determination of blood sugar and the purification of tissue extracts, etc., as discussed above. Naturally, he was not aware of this. He also enjoyed the advantage of being guided by a respected scientist in the person of Macleod.

He never appreciated Macleod's guidance, without which he never would have made any progress. He resented the fact that Macleod had not collaborated in the "manual work" (how infantile!) after having taught them how to perform pancreatectomies, etc. Further, as the experiments started to bring encouraging results, Banting's ego grew to the point of paranoia. He became a declared enemy of Macleod until his death.

There were however other problems, again originating with Banting who started again to think and act irrationally[109] as he was sensing that Collip was making important progress. He instructed Best to make a "new" extract in a hurry.[110] The next step was to insist that he be given the first chance to have his extract used on a

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[107] Pavel, The Priority, (fn 69) p.109.

[108] Charles Herbert Best and N. B. Taylor, "The Antidiabetic Hormone: Insulin" in The Physiological Basis of Medical Practice, William & Wilkins Company, 4th ed., 1945, p. 575.

[109] Li, J.B. Collip (fn. 71), p. 29, "Banting was turning his and Best's work on purification into a competition with Collip's work."

[110] Bliss, The Discovery, (fn.3), and p.101: December 12-16 using whole pancreas extract "experimenting with dialysis (use of semi-permeable membrane), washing with Toluene after alcohol evaporation, etc." First test December 15, good result but this was followed by failure after failure.

human being. He applied for a temporary appointment in the department of medicine so he could test the pancreatic extract at the hospital, but was turned down. This only added to his sense of injustice. Unfortunately, Macleod interceded with the head of the clinic to allow use of their preparation[111] (naturally Banting was not thankful) and so on 11 January 1922 Leonard Thompson became the first human to receive insulin in Canada, "7 and half cc in each buttock" (possibly intramuscularly?). The result was a failure; "Banting and Best's extract had failed."[112]

In our opinion, it was even worse. It was not proper for a medical doctor to insist on using his extract on a patient when he was perfectly aware of the fact that Collip was further advanced with his own extract. It violated the Hippocratic Oath and ran contrary to the most elementary rules of deontology. Although the glucose levels in his blood showed some decrease, the patient had serious reactions, including sterile abscesses and no further treatments were allowed.

The tension between Banting and Collip eventually led to a physical assault by the former as alluded to earlier (in a room according to Best or a hallway according to Time Magazine, 17 March 1941). Philippe Decourt describes the disarray at Toronto in 1921-1922 as a true «den of vipers » [113] (the English equivalent of « un vrai panier de crabes »).

Eventually peace was restored but in our view, Banting could no longer ethically claim any part of Collip's eventual victory. Victory surely came on 23 January when Dr. Walter Campbell gave to the same Leonard Thompson 20 cc of Collip's extract. Leonard went on to survive into adulthood and the victor's laurels deservedly came to Toronto. According to L.G. Stevenson "This was the first clearly successful clinical test of the internal secretion of the pancreas on a human diabetic"[114]. In February six more patients were treated.

One wonders how much Banting's ego must have been inflated after Macleod in a most gracious attempt to restore peace and normalcy in his Department suggested in January 1922 that henceforth all publications should have the names of all collaborators in alphabetical order. Thus Banting's name appeared first in all publications, even when Banting had made no contribution whatsoever. One example was "Insulin in the Treatment of Diabetes Mellitus", in the Journal of Metabolic Research, November 1922, pp. 547- 604, where the first author listed is Banting.

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[111] Louis Rosenfeld Insulin: Discovery and Controversy, Clinical Chemistry. 2002; 48: pp. 2270-2288.

[112] Bliss, The Discovery, (fn 3), p.113.

[113] Philipe Decourt, "un vrai panier de crabes", in English "a vipers nest". («La véritable Histoire de la Découverte de l'Insuline", introduction, Arch. Int. Claude Bernard, 1976).

[114] Stevenson L. G., Sir Frederick Banting, 1947, pp.75-108, The Ryerson Press.

Certainly, for someone with already manifest signs of paranoia, this was the worst possible treatment.

If we consider the falsification of Paulescu's text, the horrendous, base falsehoods he was spreading about Macleod, his atrocious, base physical attack on Collip, his plebeian speech and behavior, his intellectual dishonesty, crowned by a supreme ignorance and pathological self- aggrandizing – how many universities would have put up with such behavior? Banting would be a forgotten name without Macleod. His thanks to Macleod for his immense help: a despicable hate (he considered himself now God) and a base, unworthy behavior.

It is almost embarrassing to mention that Banting in his Nobel Lecture, "Diabetes and Insulin" delivered at Stockholm, 15 September 1925 had the audacity to present his failed experiment on Leonard Thompson on 11 January 1922 as a success!

CRITICISM OF PAULESCU

We are not going to repeat the unfounded, misleading and outright ridiculous criticisms by Banting and Best already mentioned above.

Yes, there are good reasons to criticize Paulescu, and for reasons in no way connected with his scientific work. In 2003, reprehensible anti-Semitic publications of the 1920s were revealed at the occasion of a projected unveiling of a plaque honoring Paulescu and E. Lancereaux on 27 August, at the Hôtel-Dieu Hospital in Paris. Due to the revelations by Nicolas Weill of the Paris publication Le Monde, and the intervention of the Simon Wiesenthal Institute in Los Angeles the ceremony had to be cancelled.

Without criticizing this intervention, I personally believe in separating scientific or artistic achievements from political errors of judgement (although not from deeds). I agree with the courageous words of Dr. Nicolae Cajal, the leader of the Jewish Community in Romania in 2003, that such dissociation is necessary in the realm of sciences and arts.[115] Obviously not everybody will agree with this.

It appears certain that, prior to 2003, this unfortunate intrusion into the political domain that he did not understand had no bearing whatsoever on the reception or rejection of his scientific work. His works were practically unknown abroad and forgotten in his own country, except for few people like Dr. Cajal whose father had been a student and great admirer of Paulescu. In a personal communication M. Bliss, at present the best-informed expert in this field shared his opinion that Paulescu's political activities were unknown in Toronto or in Stockholm in the 1920s. As such, they had no bearing on how the Nobel Prize Committee and the scientific community regarded, or rather ignored Paulescu, his work and his persona.

One has to consider however the equally important fact, that, with the above-mentioned exception, Paulescu's life was exemplary in every respect. He was fully dedicated as a doctor to patients of all nationalities or races. In his private life, he was considered a saint. His case belongs to the competence of psychologists, the only ones who could perhaps explain how such a high level of morality could possibly coexist with such a primitive bigotry and such a base racism.

When we consider Paulescu's scientific work, the most serious criticism comes from M. Bliss, some of which will be discussed in more detail in our last chapter, with regard to the experiments published in 1923 (Bliss: 1923A[116] and

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[115] "ISRO-Press Newsletter Excerpts, Newsletter # 287," on the Internet, 31 August 2003, <http://www.romanianjewish.org/en/index_isro_arhiva_15.html>.

[116] N.C. Paulescu, (1923A Bliss) "Quelques Réactions chimiques et Physiques Apliquées à l'extrait aquaeux du pancréas pour se débarasser des substances protéiniques en excès" Archives internationales de Physiologie, (21 May 1923): pp.71-85.

1923B[117]), in other words after insulin was already in use in Toronto, after Paulescu had published his main work in 1921 and after Paulescu obviously became quite isolated and unaware of the great advances in North-America. On 24 March 1923, Paulescu conducted an experiment (1923A in Bliss' work) where the glucose dropped after an hour to 0.000, in other words total aglycemia, but Bliss distorts Paulescu's interpretation of this finding.

As to the "Plasmine" in blood, idea conceived in 1916, published by Paulescu only in 1920 (it was impossible under German occupation) as a "personal hypothesis"[118], and criticized by Bliss, who somehow fails to consider the much more important fact as stated by Sir George Alberti in 2001, that soon afterwards, in 1921, "He (Paulescu) was the first to describe the actions of what was later called insulin and demonstrated clearly that it was a hormone with actions on all aspects of metabolism."[119]

Paulescu also has been unjustly criticized because, using more primitive and less reliable methods, his numeric data did not match those of the more advanced methods used in the West. However, by using the old Pflüger method, he was nevertheless able to show relevant changes in glucose levels, and this is what was essential. The fact remains that in spite of using more primitive methods Paulescu's conclusions from his 12 experiments (1920-1921) published 7 months before Banting's paper were correct, more comprehensive and were confirmed later independently by James Bertram Collip and by other researchers.

We have already mentioned the way Bliss treats Best's totally unfounded accusations (p. 87). When he discusses Best's misinterpretation of Paulescu's "compte rendu" on page 87, in the third paragraph he rightly points to Best's errors (he had to; they had been exposed by Pavel and others). But in the preceding paragraph he renders Best's equally misleading, and at times false statements (re amounts of urine excreted, etc.) as discussed above, but this time without one word of dissent and thus intimating that Best was right.

Perhaps one could also criticize Paulescu's habit of publishing his results by choosing "one among many other similar experiments". In other words, one could say that he did not publish his failures. Acting in this manner, he is perhaps less convincing. One should however keep in mind the already mentioned fact that his research papers were destroyed by their keeper in the 1950s because of an impending house search by the communist authorities. If we also include the surgical

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[117] N.C. Paulescu (1923B Bliss), "Divers Procédés pour introduire l'Extrait Pancréatique dans l'Organisme d'un Animal Diabétique", Archives Internationales de Physiologie, 21(1923): pp. 215-38.

[118] Bliss, The Discovery, (fn 3) p. 267, endnote 79 referring to Paulesco1920, pp.301-305.

[119] Sir George Alberti, "Lessons from the History of Insulin," Diabetes Voice, December 2001, 46 (4), also available on Internet.

experiments during the years 1911-1916 while he was mainly focussed on the glycogen storage problem, the number of Paulescu's experiments could be very high, possibly approaching 100.

There is however, one instance when Bliss' critique is well founded and I am unable to find any easy explanation for Paulescu's statements. Referring to Paulescu's "Traitement du Diabète" published in 1924 by which time thousands of physicians had seen hypoglycemic reactions, Bliss very correctly observes that he is still denying that hypoglycemia causes any abnormalities (p. 268, note 79). Actually, the fact that he was unaware of hypoglycemic reactions would not be as calamitous if Paulescu had not stated clearly: "We have to add that our dogs have supported quite well hypoglycemia and aglycemia, and that except for the fever caused by diastases, we have observed neither convulsions nor other signs of intoxication". This would appear to defy any reasonable explanation and would rival the aberration in Toronto in 1921 when they were unaware of the well-established fact that Trypsinogen's conversion into Trypsin only occurs in the intestine! (see footnote 168).

Nevertheless, we should keep in mind that Paulescu as a scientist was very correct, scrupulous and above any reproach. If he did not notice any convulsions or other obvious abnormal behaviour in his experimental animals, we have to believe him. Again, the fact that some results obtained with his outdated Pflüger method were abnormally low should also be accepted as a true statement. But nowhere does he state that aglycemia or even hypoglycemia (a term introduced by him) should be considered the ultimate goal in the treatment of diabetes as Bliss quite unjustly claims. Nowhere does Paulescu make any comments about the clinical significance of these findings. He simply states that these unexpected results will be the subject of his next study.

Again one should consider the possibility, even the likelihood that these erroneous findings were not of his own making, but rather the results of the imperfection of the old and unreliable method he was using in determining the levels of blood sugar. It is known that the Pflüger method was not very precise in the high and low ranges. As such it is quite possible that Paulescu having been the first to apply this method in cases with low glucose content, *where this method likely was simply inoperable* was confronted with these unusual and puzzling findings. Again he quite clearly and correctly states that he intended to pursue this matter and he refuses to draw any clinical or physiological conclusions. Certainly Paulescu handles this subject with absolute objectivity and with utmost scientific honesty. Most likely he is an honest victim of the imperfect and primitive laboratory method that was the only one at his disposal. I personally cannot see any other plausible

explanation for this odd event in this chapter in the history of diabetes. But I also wish to repeat that Bliss was perfectly right in drawing attention to this oddity, although his misrepresentation of this case is questionable.

On the other hand, some Romanians continue to praise Paulescu as the "true discoverer" of insulin. They claim that both, the credit for the discovery and the Nobel Prize were stolen from him by Banting, which is not quite true. Banting is guilty of many other sins, and Paulescu has been vilified in many other ways, but nobody has stolen the Nobel Prize from him as we have discussed in detail.

If we may return to the criticism of Paulescu's laboratory data, specifically the glucose levels in blood, working with such primitive methods because of financial problems, among the many respectable scientists that have critically discussed Paulescu's work, including the members of the Report of the International Diabetes Federation in 1970-71, to my knowledge only three have disregarded and criticized Paulescu's findings and conclusions: Best, Banting and Bliss.

THE DISCOVERY OF INSULIN AND THE NOBEL PRIZE

As is well known the Nobel Prize for Medicine in 1923 was granted to Frederick Grant Banting and John James Richard Macleod from the University in Toronto for the discovery of insulin. It would have been more appropriate to say "for the introduction of insulin as an effective drug in the treatment of diabetes" since Scott, Kleiner and Paulescu had already discovered the glucose lowering properties of insulin, among others.

The Nobel Prize was inaugurated in 1901 according to the provisions in Alfred Nobel's will of 27 November 1895. He was the inventor of dynamite, an arm of destruction that had made him rich, and he wanted to make amends and do something to benefit humanity. With his Nobel Prize he apparently, to his great honor, has fully succeeded. Some critical remarks will follow at the end of this chapter.

As such, the Nobel Foundation was created with the mission to annually distribute prizes for Physiology and Medicine, Chemistry, Physics, Literature and the promotion of Peace. In 1968, Economic Sciences were added, financed by the Bank of Sweden. In each of the six categories, there is a Nobel Committee of 5 members, elected for three years, in order to select among the applications and make their recommendations. The Nobel Assembly at the Karolinska Institutet in Stockholm was entrusted with the prize in Physiology and Medicine.

Accordingly every year in September the Committee sends invitations to qualified persons or institutions (there are seven categories that qualify) asking them to submit nominations that would remain confidential for 50 years. These nominations must be received before 1 February. The Nobel Committee for Medicine then examines the applications and makes its recommendations. These are submitted to the fifty members of the Nobel Assembly of the Prize for Medicine that following a secret vote proclaims only the names of the winners.

The Nobel Prize in Medicine in 1923

The Prize for Medicine in 1923 was bestowed on F. G. Banting and J. J. R. Macleod for the "discovery of insulin". This prize selection was unique in many respects. It was the first time that the prize was granted for a discovery made only one year earlier. Also, it was only the third instance when the prize was bestowed in the year of its first submission.

In order to understand these peculiar aspects we have to study the role played by August Krogh of Denmark, the Nobel Prize laureate of 1920 for his work on the "regulating mechanism of capillaries", a good friend of Prof. Göran Liljestrand, the Secretary of the Nobel Committee for Medicine. In the fall of 1922, he was invited to the USA. At a banquet, his wife was seated besides the renowned American

diabetologist Eliot P. Joslin who informed her that insulin was in use in Toronto. She had been diagnosed the previous year as being a diabetic. Accordingly, they changed their itinerary and went to Toronto where they were guests of J. J. Macleod (23-25 November 1922). The only other member of the group they met was Banting as all the others were out of town. Krogh received without delay the patent to manufacture insulin in Denmark from Macleod. Immediately on his return home, 12 December, Krogh started working on production of insulin and on 13 March 1923, the first Danish patient received treatment.

According to Jan Lindsted, professor at Karolinska Institutet and longstanding member of the Nobel Committee, Banting was nominated by G. W. Crile of Cleveland, F. G. Benedict of Boston and by August Krogh. Macleod was nominated by G. N. Stuart of Cleveland and August Krogh. Nobody had nominated Best, Collip or Paulescu. The initial Committee review reduced the number of nominations to 57 serious candidates. By April 1923, the number had been reduced to 9. The written evaluation of Banting's and Macleod's work was made by two Committee members, namely John Sjöquist (Chemistry and Pharmacolgy) and Hans Christian Jacobaeus (Internal Medicine). Krogh's great influence is demonstrated by the correspondence between Krogh and Liljestrand.

The recommendations of the Nobel Committee were presented to the Nobel Assembly but on 11 October, they were returned to the Committee as an objection was registered. The reason was that August Krogh had based his arguments on his visit to Toronto, and this was considered unacceptable. However, on 25 October 1923, the 19 professors from the Karolinska Institutet, by secret vote, bestowed the Nobel Prize for Medicine 1923 on Banting and Macleod. This choice by the Committee has been criticized on many occasions.

Some additional information that sheds some light on these events can be found in the Nobel Archives. From the group of researchers working on isolating the insulin in 1923, no one other than Macleod and Banting was nominated. Collip and Best were eventually nominated, but not until 1928 and 1950 respectively. Paulescu was never nominated. Thus, according to the statutes of the Nobel Foundation, none of these candidates could have received the prize. This also is the case with Von Mering who had been nominated in 1902 and 1906 and Minkowski who was nominated in 1902, 1906, 1912, 1914, 1924 and 1925.

John Sjöquist mentioned Paulescu's name among others in his allocution announcing the choice of Banting and Macleod. Linsten believes that the former had never read Paulescu, I. Pavel thinks[120] likewise and we tend to agree.

Protests were made to the Nobel Foundation almost immediately,[121] but in accordance with their statutes they were included in their archive without any

[120] I. Pavel, (fn 69), ibidem, p. 223.

comment or reply. In Toronto Macleod and Banting were received with honors, the University of Toronto in a special session granted them the title of "Doctors in Sciences", followed by a glittering banquet including 400 guests in the Great Hall of the Hart House.

Banting and Macleod shared their monetary prizes with Best and Collip, respectively. In contrast, Paulescu received no money, no awards, nothing of even symbolic value for the rest of his life. He was simply forgotten. A major reason for this is *this simple fact that nobody in Romania or France had thought to nominate him.* Add to this the falsifications of his work by Banting and Best and it becomes easy to understand why he simply disappeared in the Anglo-Saxon medical world.

The question is how can one explain such terrible injustice? Even if Banting had properly quoted and credited Paulescu, without having been nominated for the Nobel Prize his receiving this great honor would have been out of question. This is the truth in a nutshell, as explained above and once the Nobel Prize has been conferred, no further Nobel Prizes can be given for same discovery. It would appear that many Romanians believed that this honor would come "automatically" if I may use such a word.

Otherwise, I venture to say that if Paulescu had been able to recruit some of his friends in France or Switzerland where he was well known and appreciated he might have had a good chance. It is hard to know what hurt Paulescu more, not getting the Nobel Prize, or having Banting and Macleod declared as discoverers of Insulin.

We have already expressed our opinion that in our view the true discoverers of Insulin were Paulescu and Collip. Paulescu was the first to demonstrate the global effect of Insulin on all intermediary metabolisms, and Collip was the first to purify a pancreatic extract sufficiently to be well supported by a human patient. Compared to this Banting's own scientific merits, and this is what we are discussing now, were quite modest to say the least.

Furthermore in Banting's case, may I speculate what his fate would have been in the hypothetical case that Paulescu would have been nominated in time for this honor. In this case, undoubtedly, his works (like Banting's) would have been studied carefully by impartial and competent scientists and Banting's falsifications would have been uncovered. In this hypothetical situation, the best fate that could have befallen Banting would have been a deferral of the prize for this discovery by at least one year, thus giving Banting a chance to apologize and regain his lost honor. A similar scenario would have occurred had Paulescu informed the Committee before October 1923. The same thought was expressed by Ian Murray in 1971: "it is certain

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[121] Nobel Archive, " miscellaneous correspondence", G. Zülzer writing to G. Liljestrand, 22 December 1923 and 18 August 1924; N. Paulescu writing to the Nobel Committee, 5 November 1923.

that if he had known of the false quotation that compromised his work he would have responded actively and the matter would have taken a quite different course".[122]

The idea of the Nobel Prize itself is worth considering. While in theory it is laudable, in reality it is often not as simple as some well-meaning people, like Alfred Noble, had foreseen. Not always can the merits of various competitors be established correctly. Accordingly, such a noble distinction can often create deplorable conflicts that can not always be resolved satisfactorily and justly.

Even more, the Nobel Prize can become a fata morgana, directing scientists away from the main purpose of Science, becoming a goal in itself, for which they are ready to cast caution, but also deontology to the side. At times, it can even become an obsession with tragic, but at times even comic results.

It is hard to decide as to whether to abolish the Nobel Prize or modify it if possible. In any event, I should like to quote from Sir George Alberti

> "My own view is that Paulescu's observations were fundamental to our understanding of insulin (…). The real problem was the Nobel Prize. The difficulties could and would have been resolved much more rapidly if the Nobel Prize had not existed. I personally believe that such prizes and awards do more harm than good and should be abolished. Many a scientist has gone to their grave feeling deeply aggrieved because they were not awarded a Nobel Prize (it is actually rather comforting to be a bit stupid and not be in the frame at all!). What really matters is the benefit to mankind" [123].
>
> "Romania is justly proud of the contribution made by their hero, Paulescu. Some 80 years later the rest of the world should acknowledge the key role that he played and honor the role of not just Paulescu, Banting and Best, but also the many others who helped in the delivery of the life-saving hormone, insulin, to man".

Banting's Nobel Lecture, 15 September 1925

To mention this speech in Stockholm by Banting is more than embarrassing, it is painful. Rather than comment on this in detail, I shall give only few excerpts and let the reader pass judgement.

> "The extract at this time was sufficiently purified to be tested on *three cases* of diabetes mellitus in the wards of the Toronto General Hospital. There was a marked reduction in blood sugar and the urine was rendered sugar-free. However, the high protein content rendered the continuous use undesirable, due to formation of sterile abscesses.
>
> *At this stage* in the investigation, *February 1922*, Professor Macleod

[122] Ian Murray, "Paulesco and the isolation of insulin": Journal of the History of Medicine and Allied Sciences, 1971, XXVI, 2. See Pavel (fn 69), p. 25.

[123] Sir Alberti, (119), Diabetes Voice, vol. 46, December, no: 4/2001.

> abandoned his work on anoxaemia and turned his whole laboratory staff on the investigation of the physiological properties of what is now known as insulin. Dr. Collip took up the biochemical purification of the active principle (….)".

Here he must refer to his failed attempt on 11 January 1922, as he was not allowed to do any more at this stage (January 1922). In fact Macleod added additional staff in *December* and Collip's intervention began on *12 December* and his history making injection was on *23 January* (and ignored by Banting) – all many weeks earlier than in Banting's chronology of events. In a previous paragraph he stated:

> "On *April 14th,* 1921, (…) our first step was to tie the pancreatic ducts in a number of dogs. At the end of seven weeks, these dogs were chloroformed. The pancreas of each dog was removed and *all were found* to be shrivelled, fibrotic, and about one-third the original size".

And one last pearl:

> "The beneficial results obtained from this first type of extract substantiated the view *that trypsin destroyed* the antidiabetic principle and suggested the idea that by getting rid of the trypsin, an active extract might be obtained". (Please note that the date of this speech was 15 September 1925!)

I doubt that the walls of the venerable Great Hall of the Karolinska Institutet in Stockholm have ever echoed such irresponsible, fallacious statements, "verging on scientific fraud", to use Bliss' own words when criticizing Best. No further comments.

THE NOBEL PRIZE AND ITS AFTERMATH

The Toronto Team

We have already described the devastating effect the forbidden Nobel Price 1923 has had on Paulescu. As to the four protagonists in Toronto, we shall try to summarize their careers and how these were subsequently affected.

John James Rickard Macleod continued his distinguished career as a scientist, even adding more laurels. In 1923, he proved that in a certain fish species ("teleosti") the acinar tissue of the pancreas was anatomically separated from the insulin producing Langerhans cells thus adding a decisive proof as to the role of these cells in producing the "inner secretion", in other words insulin. In 1923, together with John R. Murlin and Kimball, he discovered the existence of another hormone in the pancreas, antagonistic to insulin: Glukagon.

On 26 May 1925, he gave his "Nobel Speech" ("The Physiology of Insulin and its Sources in the Animal Body"). He belatedly acknowledged Paulescu's published texts and contributions. He also received many well-deserved honors and titles. Perhaps what we should most admire in him was his tremendous strength of character while dealing with an unprincipled bulldog like Banting. Bliss rightly uses the word "superman". Only a superman could have steered the ship of the Department of Physiology in the presence of such a boorish and ignorant character as Banting was at that time. The suddenly proclaimed media hero Banting continued to vilify him in a most undignified way. Wounded by such despicable maneuvers Macleod left Toronto a bitter man, but not before cleaning all Toronto dusts off his shoes before entering the railcar. History proved him right. In 1922, he wrote "A History of the Researches leading to the Discovery of Insulin". It was discovered at his death in 1948 but was kept secret because of the intervention of the University of Toronto in order to keep Banting's glory untainted. It eventually got published by Lloyd Stevenson in the Bulletin of the History of Medicine 1979 ("J.J.R Macleod and the discovery of Insulin"). This fact is mentioned in Bliss' work, but without any details.

Charles Herbert Best (1899-1978) received his M.D. in 1925 and also received many honors. He contributed to the discovery of histaminase (anti-allergic) while in London, England. After Macleod's retirement in 1929 he became the head of the Department of Physiology at the University of Toronto and made important contributions to the isolation of choline and the discovery of the properties of heparin. Following Banting's death in 1941 he became the director of the "Banting and Best" Department of Research. We have mentioned that in a letter of 15 October 1969 addressed to Ion Pavel in Romania he expressed his regrets about his misreading and falsification of Paulescu's publication. He never did so in public, although his letter became known and was very evasive when replying to a second

letter from Pavel.

James Bertram Collip (1892-1965) continued his impressive scientific career and also received many well-deserved honors. In 1923, he discovered a new hormone "glucokynin". His most productive years were 1928-1939 as professor of Biochemistry at McGill University in Montreal. Among his important contributions were the isolation of the parathyroid hormone (1925) and the discovery of the feminine hormones oestriol and premarin, as well as pituitrin, emmenin and the very important hormone ACTH.

It is no exaggeration to say that he became "a legend in Canadian Medicine". We have already mentioned that in our opinion his very important contribution towards the isolation of insulin and its introduction in Medical Therapy for diabetes was Collip's and Canada's greatest gift to humanity. (The great Canadian born physician Osler did his work in the USA).

As to *Frederick G. Banting* (1891-1941) few people in science have been so undeservedly glorified. We will not repeat here our already formulated serious criticisms. Fortunately, he mellowed with age and to his honor became befriended with Collip and took great interest in students and their education. He was unable to make any other discoveries. He received all imaginable honors and was even made Knight Commander of the British Empire. In the world of science, he is perhaps the best-known Canadian. He died in 1941 in a tragic accident when his plane crashed in Newfoundland while trying to go to London, England where he was to apply his genius towards the war effort. Recently I visited the Banting Museum in London, Ontario. I was surprised to learn of his talent as a painter and admired his paintings. He was befriended with A.Y. Jackson, the great Canadian painter. On display was the cover of a book written by Jackson about Banting's paintings. The man was really talented and I was very impressed.

PAULESCU REDISCOVERED

A Few voices in the Desert

Even before the Nobel Prize announcement, some positive reactions to Paulescu's history-making results had already surfaced. We have mentioned Ernest Lyman Scott (1877-1966) who on 5 November 1921 congratulated Paulescu. In 1912, he himself had obtained positive, but not conclusive results. He expressed his interest in acquiring a patent from Paulescu and cooperating with the production of insulin ("Pancreine")[124]. Paulescu's assistant Trifu suggested that Paulescu accept the offer, but Paulescu decided otherwise.

Raymond Murlin (1874-1960) from the University of Rochester was so influenced by Paulescu's paper that he resolved to resume his own work in this field. In his article published in The Journal of Biological Chemistry, May 1923, vol. LVI, p. 253 he stated: "The direct stimulant for beginning again this work was represented by the favorable results obtained by Paulescu (…) The method of extraction used by Paulescu seems to us to have many advantages".[125]

Following the announcement of the Nobel Prize in 1923 there were vigorous protests from both Paulescu and Zülzer. We also have mentioned that some scientists protested in favor of Paulescu shortly after the announcement of the Nobel Prize, while other scientists would do the same thing, even more energetically, on the occasion of the 50th anniversary of the discovery of insulin.

Among the first group were Casimir Funk, Alfredo Sorelli, Juan Lewis, Ed. Sharpey-Schaffer and P. Trendelenburg.

Casimir Funk (1884-1967), in "Histoire et conséquences pratiques de la découverte des vitamines", Vigot Frères Edit. Paris 1924, p. 73, states: "In 1920 and 1921, Dr. Paulescu of Romania and Dr. Banting and Best from the University of Toronto, have proven in a decisive manner that the pancreas and particularly Langerhans' islands, contain an anti-diabetic substance that has been called since insulin."[126] It is interesting to note that Funk was familiar with Paulescu's Textbook of Physiology II, 1920. He is well known for having coined the term "vitamins" and his pioneering work on their importance to health and relationship with hormones. He later postulated the existence of other essential nutrients, which became known as vitamins B1, B2, C, and D. In 1936 he determined the molecular structure of thiamin, though he was not the first to isolate it. He was the first to isolate nicotinic acid (also called niacin or vitamin B3).

Alfredo Sordelli, also quoted by Pavel (p. 112), in his work Insulina, Los Instituto Bacteriologico del D.N. de H. y de Fisiologia de la F.C.M. I vol., Buenos

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[124] Paulescu, Traitement du Diabète, 5 March, in "la Presse Medicale", No.19, 1924.
[125] Ionescu-Tîrgoviste (fn 7), "The Re-Discovery of Insulin", p. 13.
[126] I. Pavel, (nf 69), p.111.

Aires, 1924, p. 7, 21 states: "The results (of Paulescu) are the same as the results of Banting in discovering the insulin".

E. Sharpey-Schäffer in 1926 published his book "The Endocrine Organs", Chapter XLIX: The Internal Secretion of the Pancreas, Insulin. Longman, Green & Co. Ltd, London, p. 343, quoted also by Pavel (p. 113). After describing Paulescu's method of extraction and his results, he concludes: "In the same year that Paulesco published his first experiments, investigations on the subject were commenced by J. C. Banting and C.H. Best and have led to important practical results". Sharpey-Schaffer had been among the first to indicate the relationship between Langerhans islands and insulin (1917).

Even more unequivocal is this statement by *Paul Trendelenburg* in 1934[127]:

"It was Paulesco who achieved full success ("zu vollem Erfolge"), using parenteral administration of his extracts to depancreatized dogs, that reduced the blood sugar even within an hour"; this was followed shortly by his "Beschreibung der Darstellung des Insulins" (1921). The blood sugar reductions were proportional to the quantity of the extract. The ketonic bodies in blood and urine were reduced. Paulesco induced hypoglycemia even in normal dogs. He proposed the term pancréine for the active ingredient.[128]

After this Paulescu disappeared into total oblivion until 1968.

The Rediscovery

Paulescu's impressive contributions were suddenly resurrected in 1968 in a dramatic fashion by *Ian Murray*[129] (1899-1974) following his retirement as professor of Physiology at the Anderson College of Medicine, Glasgow. He was a founding member of the International Diabetic Federation, etc. Murray was almost immediately joined by the distinguished Romanian diabetologist Ion Pavel. This chapter is a most fascinating page in the history of medical sciences. The recently retired Scottish diabetologist decided to write an essay on the 50th anniversary of the discovery of insulin and to his great surprise discovered that the hypoglycemic effect of pancreas extracts had been proven in convincing fashion prior to Banting, in Romania[130]. After painstaking work to clarify this matter, he wrote to "Professor of

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127 Die Hormone, Ihre Physiologie und Pharmakologie, 2. Band, Julius Springer Verlag, Berlin, 1934, p. 298 (again quoted by Pavel, ibidem, p.113).

128 Actually: "Recherches sur le rôle du pancréas dans l'assimilation nutritive".

129 All quotations from Murray's and Paulescu's correspondence are based on I. Pavel's work (fn 69).

130 Similar experiences by Arthur Colwell, Chicago, "Diabetes 1968, vol. 17, no: 10, pp. 599-610; also Dr. Witte, Secretary of the International Federation of Diabetes who upon discovering Paulescu's contributions, invited a Romanian delegate to the Meeting of IDF in Buenos Aires.

Physiology, Faculty of Medicine, Bucharest". The addressee Prof. Grigore Benetato didn't respond, perhaps wanting to avoid potential problems with the communist Romanian authorities. Murray obtained the name and address of Prof. I. Pavel (1897-1992) in Bucharest, a former student of Paulescu, from Prof. J.G.L. Jackson, who according to C. Ionescu–Tîrgoviste was likely the only Romanian diabetologist known in the West. As such, Murray wrote a second letter (17 November 1968) addressed to Pavel.

It so happened that at that time Prof. I. Pavel was also interested in reviving discussions about Paulescu's merits. This is how the collaboration between these two scientists that was to illuminate this obscured page in medical history began.

Evidently quite enthusiastic, Pavel gathered informative material, including Paulescu's work on the Pituitary gland and Cushing's appreciative comments and sent it on loan to Murray.

On 28 August 1969, Murray submitted "The Search for Insulin" that was published in the Scot. Med. J., 14: 286, 1969, and a copy of his letter to the British Medical Journal. Pavel's subsequent letter (10 October 1969) is characteristic: "How can I express my joy" and he also points out Banting and Best's erroneous translation of Paulescu's text. Very interestingly, in same letter Pavel mentions that Dr. Witte (Secretary of the International Federation of Diabetes**),** probably after reading Murray's article, had invited Romania to send a delegate to the IDF meeting in Buenos Aires (19 September 1969).

We have already commented on Pavel's letter to Best (8 October 1969) and the latter's ambiguous and evasive reply dated 15 October 1969 (and his misleading statement in "The Physiological Basis of Medical Practice"). It is not often mentioned the fact that Pavel, not satisfied with Best's answer, sent him a second letter at the end of 1971. Best's second reply on 10 January 1972 is one of the most cynical documents in the historiography of Medicine and we are reproducing its full content in the footnote.[131] It should go into history as a masterpiece of

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[131] Dear Dr. Pavel, I apologize most sincerely for the long delay in answering your letter. I have been lecturing in England and on the Continent and I have only recently returned to Toronto. I have talked about the history of Insulin many times during 1971. On some occasions, this has been, by invitation, a review of the Toronto work, on others, accomplishments of those like Paulesco and Kleiner have been outlined in detail. Some of these lectures will be published. As I think you will agree, it was important that we purify our Insulin containing extracts and to give them over long periods to depancreatized dogs. Fifty years ago, at this time we had over 100 successful experiments and the way was prepared for the clinical administration of the material. It will be fifty years ago tomorrow that the first Insulin was given to a patient. As you know, Dr. J.B. Collip, utilizing the information we had obtained over nine months, purified our extract and it was used in the treatment of patients here in January and February 1922. Difficulties developed in the process and I had to return to the preparation of insulin. A greatly modified process functioned well. I have had several talks with Professor Frank Young

Machiavellian cynicism and falsification of History.

A most significant comment by Murray is to be found in his letter of 4 April 1970 when he wrote: "but I know that any criticism of the Toronto workers will be regarded as almost sacrilegious in certain quarters". Here Murray reveals the sad reality of a society that refuses to accept the true facts, and where Pavlov's and Shepalnikov's 1899 discovery of the innocent role of trypsinogen cannot even be mentioned.

Very significant is Murray's remark revealing the relationship between Best and Young: "Young worked with Best in Toronto and is a friend of his" (letter to Pavel of 10 February 1972)[132].

As such the incredibly distorted Report of the IDF of 1971 that we shall discuss in the following chapter should come to nobody's surprise.

We should also mention the other men of stature in the field of diabetes who expressed favorable opinions with regard to Paulescu's important contributions.

Prof. Arne Tiselius, head of the Nobel Institute, wrote on 29 December 1969 in response to a letter by Prof. S.M. Milcu and Prof. I. Pavel:

> "In my opinion Paulesco was equally worth the award. As far as I know Paulesco was not formally proposed, but naturally the Nobel Committee could have waited another year." And further: "I can only express the hope that in an eventual celebration of the 50th anniversary of the discovery of insulin due regard is paid to the pioneering work of Paulescu".[133]

One should keep in mind that he was expressing his personal views and was not writing on behalf of the Nobel Institute.

Equally important is the article by *Eric Martin*, of Geneva, former Vice-President of the IDF. This is what Martin had to say: "Sans contestation possible, Paulesco apporte le premier la demonstration exemplaire de l'effet antidiabétique, anticétogene d'un extrait pancréatique," (Without any doubt Paulesco was the first to prove in exemplary fashion the anti-diabetic, anti-ketonic effect of a pancreatic extract). He includes here Best's first letter in response to Pavel. He rather benignly concludes: "Ainsi, probablement par meconnaissance du français, le mérite de l'auteur roumain est reduit a zéro,"[134] (and so, probably because of his lack of understanding of French, the merit of the Romanian author is reduced to zero).

Finally, we should consider the views of *Rolf Luft*, President of the IDF, published in Laksrtidningen (Stockholm): "According to my opinion the works of

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recently and I am preparing some material on the Toronto work, which will be published in due course. With…."

132 C.I-Tîrgoviste et all, (fn 13), p. 267.

133 Pavel, (fn 69) pp. 119-120.

134 Ibidem, pp.121-129.

Paulesco are of higher class than the works of the two Canadian scientists". When referring to Banting and Best he states quite clearly: "This report about Paulesco's work is not correct." Further, he quite justly mentions that Banting and Best ignored many of the facts established previously by Paulescu. He also mentions the arrogant claim by Best in 1946 ("The Physiological Basis of Medical Practice"), already mentioned in this essay, where Banting and Best "were the first to obtain a preparation containing the anti-diabetic hormone". He concludes "According to my opinion the prize should - without any doubt - have been shared between Paulescu, Banting and Best."[135]

Another voice that should not be overlooked is that of *J.S. Bajaj*[136] of New Delhi, at the All India Institute of Medical Sciences. In spite of a few incorrect dates given in his text he gives us a few interesting insights. For instance, he makes note of the fact that Best together with Banting mistranslated Paulescu's text. Also, he is aware of Best's insincere letter to Pavel evading the responsibility for having falsified Paulescu's text in 1921 and of Macleod's admission in 1926 that "a paper by Paulesco came to their attention" and he correctly renders Paulescu's text. Like others Bajaj is unable to explain how Banting and Best were not aware of the correct significance and interpretation of Paulescu's findings

Another accolade comes from *Dorothy Hodgkin* (Nobel Prize winner 1964). In her presidential address "Discoveries and their uses" (British Association for the Advancement of Science), September 1978: "Successful extracts were obtained almost simultaneously in different circumstances, in Romania by Paulescu and by Banting and Best in Toronto. Paulescu, an experienced medical scientist was returning to an old interest after interruption by the war; his results were not immediately recognized".[137]

The list could go on: Rodrigues Minon (President of the Spanish Diabetes Society), Prof. H. Bour (France), Prof. I, Magyar (Faculty of Medicine of Budapesta), Prof. R. Korec (Czechoslovakia), Prof. Iulio Castro Franco (Peru), Phillippe Decourt (France), Dr. Bernard Knight (England), Prof. Barbero and Prof. Bruni (Turin, Italy etc.).

One opinion Pavel chose not to mention was a response from F. N. Allan[138]:

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[135] Ibidem, pp. 130-137.

[136] J.S. Bajaj – S.S. Ajgaonkar, Insulin and Metabolism, Diab. Ass. India, Bombay, vol. 1, 1972, pp. 44-45.

[137] Pavel, (fn 69) ibidem, pp. 284-285.

[138] F. N. Allan, "Diabetes before and after insulin", Medical History, 1972 July; 16 (3): 266–273, (Presented at the annual Symposium of the New England Diabetes Association 13 November 1971).

> "Last year, I received a letter from Professor I. Pavel of Bucharest, Romania, accompanied by documents supporting a claim that Dr. N. Paulesco of that city had discovered insulin before the Toronto project was begun. Paulesco's report, submitted to the International Archives of Physiology in June 1921 and published on 31 August 1921, did indeed show that he had made a pancreatic extract that lowered the blood sugar of diabetic and normal dogs. Another paper by Paulesco quoted by Banting and Best was published in Comptes Rendus de la Société de Biologie, 23 July 1921. The documents sent to me included copies of correspondence between Professor Pavel and Professor Tiselius, President of the Nobel Institute. (...) In reply, I agreed that Paulesco had earned a place of honor in the history of research in pancreatic physiology. I said further that this need not minimize the credit to a number of others who prepared active pancreatic extracts even earlier".

But the horrendous falsifications in the IDF report, as we shall soon demonstrate, closed the book on Paulescu for a second time, condemning him again to oblivion.

Recent Developments

In his own country, he was again a forgotten man, until the communist era came to an end. There is now a vigorous attempt to reestablish the historical truth, to unmask all calumnies of the past and to restore Paulescu's great merits for all his accomplishments in the fields of Medicine and Physiology. In 1990, Nicolae Paulescu was elected post mortem member of the Romanian Academy and in 1996, a commemorative plaque was unveiled at the Paulescu Memorial House. The year 2001 was declared "The Year Paulescu" and in the great hall of the Romanian Academy, a ceremonial session was held in his honor. The Center for Diabetes studies in Bucharest was renamed "The N.C. Paulescu Institute for Diabetes and nutritional and metabolic diseases".

Impressive attempts to reestablish the prestige of Paulescu in the world of Science are being undertaken by such great names in Romanian Medicine as Prof. Nicolae Hâncu in Cluj-Napoca and Prof. C. Ionescu-Tîrgovişte in Bucharest.

The great merits of Paulescu are being recognized by many great leaders in the field of Diabetes from outside Romania. Suffice to mention the renowned *Dr. Jean Pirart* from Brussels who wrote in 1983 a paper in French entitled "The History of Diabetes and of Insulin. Some Landmarks", 1983. We reproduce from C.I - T's work (13), pp. 283-284 under the subtitle "The proof was made by Paulescu in Bucharest (1921)":

> "It was during the difficult years of war 1914-1918 that a Romanian physician trained in Paris, started in Bucharest the work of isolating insulin. Following a

> series of remarkably conducted experiments, Paulescu demonstrated with the highest clarity that the intravenous injection of an aqueous pancreatic extract from dogs, obtained by mincing these pancreases at low temperatures, leads to a decrease of the blood sugar levels in dogs rendered diabetic by ablation of the pancreas, and induces hypoglycemia in normal dogs. Only the pancreas extract (and none from other organs) does lower glycemia, glycosuria, the blood and urine acetonemia or the nitrogen compounds. For the first time in the history of medicine, the phenomenon of insulin hypoglycemia was presented. (….) Paulescu published the whole results of his studies in a precise, detailed and convincing paper, written in an excellent French and published in the 'Revue Internationale de Physiologie' which is edited in Liège by Léon Fredericq and Paul Heger".

A more recent assessment of the Paulescu's work that we have been able to find comes from the already quoted Rolf Luft in a letter to Henry Bruce Macleod Best, son of C.H. Best. In his speech to The Academy of Medicine, Toronto, The Vaughan Estate, on April 24, 1996 and published on the Internet, H.B.M. Best states: "At the 1991 Meetings of the International Diabetes Federation in Washington, D.C., I had a talk with Professor Rolf Luft of Stockholm's Karolinska Institutet. Afterwards, Dr. Luft wrote to me, naturally not wishing to fault the Nobel Committee: 'I can only say that, with reservations, I think it might have been fair to give the Prize to Banting, Best and Paulesco'".

Considering the date of this recorded correspondence, this is a very important testimony.

Equally important (and surprising) is Bliss' comment in 1993: "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 endocrinologic circles. The Paulesco case was based on the realization that, in fact, Banting and Best had not produced results more impressive than Paulesco's" (see our footnote 170).

We should also add the name of the respected Prof. G. Alberti (our footnote 119) who wrote these wise words in 2001:

> "Meanwhile, Paulescu, having trained with Lancereaux in Paris, was carrying out painstaking experiments. He demonstrated clearly that in animal, pancreatic extracts – containing what he called pancréine – could not only lower blood glucose rapidly, but also clear ketones and increase liver glycogen. He was the first to describe the actions of what was later called insulin and demonstrated clearly that it was a hormone with actions on all aspects of metabolism. His experiments were rudely terminated when Bucharest was occupied in 1916. He

was unable to publish his results or continue his experiments until well after the end of the 1st World War. His work was finally published in August 1921".

THE REPORT OF THE INTERNATIONAL DIABETES FEDERATION

Essential to understanding the lack of recognition accorded to Paulescu is the Report of the International Diabetes Federation published in 1971.[139] In the late 1960s there was a renewed interest in Paulescu's role in the discovery of insulin, in particular by Ian Murray (Glasgow)[140], Eric Martin (Geneva) and Ion Pavel (Bucharest). As a result, following an intervention by Prof. I. Pavel, Rachmiel Levine, Federation President at that time, at the VIIth Congress of the International Diabetes Foundation held in 1970 in Buenos Aires appointed a Special Committee to study this problem and submit a report. This Committee included R.E. Haist (Canada), W.J.H. Butterfield (United Kingdom), Rolf Luft (Sweden) and P. Ranbert (France), and was chaired by F.G. Young (United Kingdom). This committee was entrusted with providing a factual summary of all research related to the discovery of insulin. Unfortunately, instead of helping to clarify the situation, the Committee produced a final report that was deeply flawed.

One of the reasons for this was the objective imposed by the Committee to have "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."

In other words from the outset the Committee was instructed to give sanctuary to Banting, Best and Macleod at the expense of other researchers. This placed the Committee in a position similar to Galileo Galilei[141]: free to put forward any theory provided it fits into a pre-determined result.

A related problem was the actual composition of the Committee. Haist had been a co-worker of Best and succeeded him as Head of the Department of Physiology at the University of Toronto. Also Young, the chair of the committee was a personal friend of Best[142] who at that time was still alive and sacrosanct. It was

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139 International Diabetes Federation, "Report of the Special Committee set up to present a written summary of work leading up to the discovery of insulin," News Bulletin of the International Diabetes Federation, 1971, 16 (2), pp. 29-40. Reprinted in "The Priority of C. Paulescu in the Discovery of Insulin," ed. I. Pavel, (Bucharest: Editura Academiei Republicii Socialiste România, 1976), pp.150-166.

140 Ian Murray: 1) The Search for Insulin, Scot., Med. J., 1969, 14, 286; 2) Insulin: Credit for its Isolation, Brit. Med. J., Sept. 1969, p. 651. 3) No Man an Island, Brit. Med. J., April 1971, p. 119; 4) Paulesco and the Isolation of Insulin, J. Hist. Med. All. Sci., 1971, XXVI, 2, 150; last article was reproduced by I. Pavel in his often quoted work.

141 As we know, Galileo was allowed to present any scientific discovery, as long as the sun was rotating around the earth.

142 Ionescu-Tîrgovişte et all (fn.13), p. 267, quoting from letter of Murray to Pavel, (10 February 1972). "Young worked with Best in Toronto and is a friend of his"

clear that the position of the researchers from the University of Toronto would be adequately defended, but the lack of a representative from Romania was a flagrant omission.

An additional flaw was the exclusion of Collip from the names mentioned as part of the research group at the University of Toronto. From the outset there was no chance that the contribution of Collip would be properly acknowledged.

The Report itself was completed in May 1971. It begins with a history of diabetes research and quickly commits a major error. It mentions that G. Zülzer's intravenous injection of his extract in 1908 caused serious side effects and forced Zülzer to abandon his research. But it fails to mention Zülzer's experiment on *21 June 1906*, when he injected *subcutaneously* 8 cc of his extract into a moribund diabetic patient with remarkable clinical success[143]. The Committee thus incorrectly assigned the honor of the first human injection via the subcutaneous route to the Toronto group (minus Collip). Furthermore, they err when suggesting that Zülzer's success in reducing hyperglycemia was a result of the fever his extract was causing. They appear completely unaware of Paulescu's experiment XII that had convincingly proven that fever per se did not affect the level of glucose in blood. Apparently, they had not read Paulescu's work with the necessary attention it commanded.

It is not surprising that the Committee gives 11 January 1922, the date of Banting's failure, as the date of reference. The date of Collip's real breakthrough, 23 January 1922, is not even mentioned.

The Committee states: "The year 1971 marks the fiftieth anniversary of the announcement of the result of the first investigations by Frederick Banting and Charles Best." By using the word "announcement" the Committee cleverly names the insignificant and unconvincing oral presentation by Banting on 30 December and occults the major discoveries by Paulescu in the same year. Furthermore Macleod is not mentioned and neither he nor Collip will be mentioned later, when the research will eventually be on the right track and bring positive results. Even more disturbing, in 1921 only Paulescu published his results, there was nothing published by Banting and Best. The years 1920-1921, I believe that one can rightly re-state, belonged to Paulescu. Also, Banting and Best had done nothing in 1921 that had not been done before (by Paulescu, Kleiner and others).

The Committee's report also absurdly states that Banting and Best's extract *"always* reduced the amount of glucose in the blood and urine and that there was usually a *distinct improvement* in the clinical condition of the treated animals"[144]

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[143] Bliss, The Discovery (fn 3), p. 29.

[144] Pavel, The Priority (fn 69) p.156.

(emphasis ours). This is in flagrant contradiction to Bliss' embarrassing revelations.[145]

Then much credit is given for the famous dog "Marjorie" that survived without a pancreas over 70 days on fetal pancreas extract.[146] But as Bliss has pointed out there is practically no written data about this dog. Similarly, J.H. Pratt in his "A reappraisal of researches leading to the discovery of Insulin" had grave doubts that this dog was indeed diabetic, based on the given D: N ratio.[147] Furthermore, the Committee states that Banting was using 95% aqueous alcohol when in fact it was 50%. It was Collip who later used 95%.

We also find the following statement quite strange: "What they did (Banting and Best) 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"* (emphasis ours, p. 162). In reality, it was Collip who produced the first suitable extracts for man. Again and again, Collip's work and achievements are attributed to Banting.

The failed human experiment on 11 January, actually a less than glorious event scientifically and even less so deontologically, is portrayed by the Committee as the dawn of a new era. Banting's insistence on using his inferior extract in the first experiment on a patient is in my opinion the most sad and disgraceful deed in his undistinguished "scientific" career. Collip is only mentioned later in connection with the commercial production of insulin, as all the glory had to be reserved solely for Banting. Completely ignored are Collip's great contributions in establishing the physiological properties of Insulin in all body metabolisms, the glycogen storage in the liver, introducing to Medicine the new syndrome of hypoglycemia or Insulin Shock, etc. Not to mention the supreme achievement of purifying the insulin in a form that could be used for treating human patients. The Committee, I must say shamefully ignores all these great achievements that brought glory and honor to Toronto.

Again incredibly the Committee claims that Banting, Best & Macleod (yes, Macleod did exist after all!) "provided the information on which Collip could without delay base methods for "the large-scale production" of an insulin-containing extract from normal pancreases suitable for continual subcutaneous administration to animals and to man" (p. 164). We have demonstrated already that such claims (crediting Banting and Best) belong to the realm of legends. Furthermore, the distinguished members of this Committee did not realize that the "large-scale production" would come only later thanks to the Eli Lilly Company.

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[145] Bliss, The Discovery (fn 3), p. 95.
[146] Pavel, The Priority (fn 69) p. 156.
[147] Bliss, The Discovery (fn 3), p. 267, endnote 79.

What the Committee does not understand or refuses to acknowledge is the fact that Banting and Best were unable to cross the barrier that had stopped their predecessors like Zülzer, Murlin, Scott and Paulescu. They will have to wait for Collip in order to cross this barrier. Or that Paulescu had been able to discover much more about the physiological properties of insulin than Banting and Best had. Not to mention the many exaggerations and distortions of the true facts when they try to aggrandize Banting's achievements. To give more examples would be too embarrassing and to again mention Banting's totally wrong conception about the danger of trypsin would be just too painful.

When the Committee turns its attention to Paulescu they stress his merits,[148] including his observations and studies on urea and the ketone bodies, but strangely it states that by so doing he wasted precious time which could have been dedicated to the purification of the pancreatic extract. Such a statement is odd indeed. They omit to mention that Collip had conducted similar experiments, which he as a true scientist had considered essential. Again, they forget that Banting had been completely sidetracked studying degenerated pancreas, fetal pancreas, and "exhausting" the pancreas with secretin. He also had to be stopped by Macleod (October 1921) from going into pancreas transplants. This was a waste of precious time indeed.

It is hard to imagine that a group of learned scientists could think and write in such an infantile manner when they try to dabble in History!

How does Bliss treat this chapter of history? On page 16 of his book, so often quoted by us (fn. 3) we can read:

> "*The report, published in 1971, was a careful, tightly written summary of historical knowledge about the discovery. Its conclusions, difficult to simplify because of the subtlety of the argument, were to the effect that Paulescu might indeed have discovered insulin as a therapy for diabetes had not the North Americans been able to move so swiftly and successfully to develop the results of Banting and Best's research. Pancreine probably contained insulin – so did the pancreatic extracts prepared by several earlier researchers, especially a German named Zülzer – but it was the Canadians who made insulin suitable for the treatment of diabetes".*

This is all he has to say. It is an odd assessment indeed, but perhaps the fact that he did not want to offend the members of the committee, many still alive, might be a reasonable explanation.

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[148] Pavel, The Priority, (fn. 69) pp.163-64.

KLEINER AND PAULESCU

Michael Bliss considers the work done by Israel S. Kleiner to be superior to that of Paulescu. Kleiner was certainly a great scientist and a wise and honest man. He did not protest when he did not receive the Nobel Prize and, as always, behaved with dignity. As such, I can only salute Bliss for praising his work. But I suspect that this is also due to the low opinion Bliss has of Paulescu, to which he is fully entitled, but that in my opinion has no justification.

There is no doubt that Kleiner's article was an important advance in the history of the discovery and extraction of insulin.[149] It was the most advanced research on this subject prior to Paulescu. On a superficial comparison with Paulescu's work it was more convincing, but only in reference to the data on the hypoglycemic effect. His measurements of blood glucose levels were in keeping with the modern laboratory methods of his time, while Paulescu's data had to be interpreted considering the old and less reliable Pflüger method, the only method he could afford.

Kleiner was using the Myers and Bailey modification of Lewis and Benedict's method to measure the blood glucose level, certainly superior to the Pflüger method. According to Bliss "*without exception in sixteen experiments the pancreatic extract caused a decline in the blood sugar of diabetic dogs*."[150] While Kleiner more modestly admits: "*the reduction of glycemia - occurred to a marked degree in 10 out of sixteen experiments, and to some extent in fifteen out of sixteen*".[151] The marked reductions were 0.20 to 0.09, while the "moderate reductions" were 0.07 to 0.02. "*Only one of all the sixteen pancreas experiments had practically a negative result, while only one of the controls showed anything resembling a positive effect*". Kleiner also conducted six experiments with other tissue-extracts: sub-maxillary gland (4), spleen (1), and muscle tissue (1), out of which three show reductions as low as 0.02, 0.02 and 0.06 (*spleen*, experiment LP83, following which the dog died the following day). These results are certainly difficult to accept.

There is no doubt that Kleiner has added more convincing proof as to the existence of an inner secretion in the pancreas that reduces the hyperglycemia in diabetic animals, that can be separated, but not sufficiently purified.

But on the other hand, he did not perform total pancreatectomies in all his experiments. *He often left a small amount of pancreas during his operations*. In one case (LP73), where the glucose had been reduced by 0.17, the autopsy revealed that

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[149] I.S. Kleiner, "The Action of Intravenous Injections of Pancreas Emulsions in Experimental Diabetes", 20 September 1919, pp. 153-169.

[150] Bliss, "The Discovery" (fn 3) p. 41.

[151] Kleiner, ibidem, p.166.

25 per cent of the pancreas had not been removed. He used fresh dog's pancreas, simple water extractions, with subsequent dilution with saline, given slowly intravenously. He also checked the temperature in all cases, as Paulescu will do later, but that Banting did not. He also checked the hemoglobin and also performed a few autopsies (Paulescu performed autopsies on all his experimental animals).

Paulescu's glucose readings were very significant but not as convincing to the uninformed for reasons explained above (Pflüger's method). His autopsies (in all cases) revealed no residual pancreas. Let's not forget that he was a superb experimental surgeon and his method for removal of the pancreas was by far the more rigorous in comparison to his rivals. As an experimental surgeon he had even introduced a new method in brain surgery (28 hypophysectomies), adopted by Cushing in animal experiments as we have mentioned above, as well as the first end-to-end anastomosis of the ureter!

But Paulescu's work shows its definite superiority in devising and executing a rational and well-conceived plan of investigating the complexity of the effects of insulin on all aspects of the body's metabolism. Besides checking insulin's glucose reducing effect in normal dogs, and the same effect in diabetic dogs, he judicially and convincingly proved the role of insulin in the *protein and lipid metabolisms as well*. He also proved that artificially induced fever did not interfere with the action of insulin and did conclusive research on the conversion of glucose into glycogen in the liver. As such, he was ahead of all other researchers until Collip confirmed some of Paulescu's findings and succeeded in sufficiently purifying the pancreatic extract for use in human patients in January 1922.

I fully agree with Bliss' observation that Kleiner's work was a "beautiful piece of scientific writing" (p. 41), but I take with a grain of salt his ruling that: "Of all publications before the work at Toronto, it was the most convincing". His data on glycemia were certainly expressed more correctly, based on modern techniques and he proved the existence of something in the pancreas that lowered the glucose in diabetics.

But what Bliss does not fully appreciate is that Kleiner's notions of "decrease of the permeability of the kidney by a toxic action " (p. 167), or "decreased permeability to sugar of the capillary endothelia and perhaps of other cells as well" (ibidem) have no place in modern Physiology. The same is true for "the pancreas emulsion had restored the permeability" (p. 169); or "The author has presented evidence that the diabetic blood sugar is in a combined or poorly diffusible state" (ibidem); or "The enzymes present in the pancreas emulsions may be able to break up this combination setting free crystalloid glucose" (ibidem). As to "The fact that these pancreas emulsions lower blood sugar in experimental diabetes without causing marked toxic effects indicates a possible therapeutic application to human beings" (ibidem), this would be very nice indeed, had Kleiner not frequently left a

chunk of pancreatic tissue behind; and in Summary: *"There was no compensating increase in urinary sugar, but rather a decrease, which may be partly due to a temporary toxic renal effect"*. It is hard to accept that after all these unfounded speculations Bliss declares on several occasions that Kleiner's work was superior to Paulescu's epochal findings and interpretations thereof!

Because instead of speculating like Kleiner about "*impaired permeability of the kidney to sugar by a toxic action*" (p. 167) and the diabetic blood sugar being in a combined poorly diffusible state etc. - Paulescu sticks like a true scientist to the facts that could be proven. In addition, he covered a much larger territory. As such, Paulescu was the first to prove that this was a hormone that affected all intermediate metabolisms in the human body and Collip later confirmed some of these findings.

In view of these achievements, Bliss' criticism that Paulescu "did not set his work and its implications in the context of past and current knowledge", according to the very correct Anglo-Saxon custom, appears quite irrelevant. However, in his Textbook of Physiology, vol. II, Paulescu gives a very comprehensive account of "past and present knowledge".

It is true that Paulescu had also expressed nebulous theories about insulin combining to form "plasmine", but this was in 1916-1918, published only in 1920 because of the war. Furthermore, through his research in 1920-1921 he helped to clarify this matter more than anyone else.

I agree with Bliss that Kleiner's "follow-up discussion was a beautiful piece of scientific writing" but the truth is that all his beautifully expressed suppositions were dubious at the date of publication and soon were outdated, whereas Paulescu's contributions after 80 years are more in tune with modern science then when initially published.

Surely, Bliss must accept the fact that the value of discoveries in medicine rests not on the stylistic beauty of the text, but on the veracity of the presented facts or theories. Kleiner's interpretations represented the prevalent confusion on this subject at that time while Paulescu's discoveries opened new vistas and remain relevant even today. Kleiner was representing the views of the past and his contemporary era, while Paulescu showed the way to the future, when the terms "diabetes lipidus" and "diabetes proteinus" will become exciting new fields of research.

In view of the above, Bliss' comments when discussing Kleiner on pages 40 and 41, such as "Of all publications before the work at Toronto, it was the most convincing" or "his follow-up discussion was a beautiful piece of scientific writing" become meaningless metaphors - unless his aim was to lower Paulescu's standing in this field of science.

With all due respect for Kleiner as a man and for his achievements in science, as I have expressed on many occasions, Paulescu went one huge step further.

MYTHOLOGY IN SCIENCES

Quite often when describing great discoveries a certain amount of embellishment and exaggeration is to be expected. Every civilization, every country, every nation needs its heroes, to serve as examples, to be emulated, to serve as beacons of light to encourage and inspire new generations and be a source of pride for the living. We should all encourage this. What is nobler in life than to admire, honor and celebrate true greatness?

But everything has a limit, beyond which it becomes grotesque. Such is the case with the cult built around Banting by the mass-media and uninformed people, but mostly by well meaning people misled by the mystique created around this man.

I hope I shall be allowed to repeat my praise of what was admirable about Banting:

> "Banting on the other hand was a more complex person. He was an honest man of his word, loyal, straightforward and had character, and we want to stress this at the outset. For example, he spontaneously split the money from his Nobel Prize with Best. He and Best first reciprocally injected themselves with the extract they were going to inject into Leonard, their foolish human experiment. Also, he initially refused to have his name on the patent for their discovery, in the true Hippocratic spirit. Later on, he had to give in, in order to protect the rights of everybody, including the public. He excelled with his unflinching dedication to a great cause, and his tremendous willpower proved unstoppable".

But when it comes to intellectual probity and deontological honesty, the picture is altogether different.

The beginning of his career as a "scientist" is rather embarrassing. Everybody knows of his "*great idea*" inspired by the article by Moses Barron *"The relation of the islets of Langerhans to diabetes with special reference to cases of pancreatic lithiasis"* in Surg. Gynec. Obstet. 1920; 31: 437-448 and his note jotted down on a piece of paper: "*Diabetus (sic). Ligate pancreatic ducts of dog. Keep dogs alive till the acini degenerate leaving Islets. Try to isolate the internal secretion of these to relieve glycosurea (sic)".* This is presented as his own illuminating intuition based on Barron' findings in the dissection room. In reality it is the essence of Barron's detailed presentation of previous attempts involving ligature of the pancreatic canal, in the very same article, a fact never mentioned by Banting. In other words, Banting appropriates methods conceived by others, thus creating the false impression that it was his original idea! Even if his desire to isolate the "internal secretion" could not

have been realistic at the time of Ssobolew (1902), and is not specifically mentioned by Barron, Banting was aware of Scott's attempts to isolate this internal secretion.

I cannot escape my conclusion that even this small piece of paper by Banting and the many following referrences to it, while it certainly makes a nice story, *is actually nothing more than an unacceptable falsification of history and a shameful attempt to glorify himself*. Very sadly, this is how Banting launched his career as a scientist!

The further facts of this case are as follows. While doing routine autopsies, Moses Barron[152] had come across a rare case involving the formation of a pancreatic stone in a patient who also had diabetes. The case was particularly unusual in that the stone had completely obstructed the Wirsung canal, the only pancreatic duct present in this case (the Santorini duct was absent). Although all the acinar cells had disappeared through degeneration, many of the islet cells had apparently survived. Many of these cells appeared intact, but he found areas with atrophic and degenerated islets surrounded by a "dense connective-tissue stroma, (...) with extensive infiltration of leucocytes", which he regarded as relatively recent in origin and caused by "a local infection" (p. 445). As this patient was also diabetic, Barron likely rightly concluded: "It is fair to assume that the diabetes very likely made its appearance at the time when the islets began to suffer" as pancreatic lithiasis is usually without diabetes. His final conclusion was: "Simple obstruction of the ducts *per se,* does not result in glycosuria, but only in the later stages, when an interstitial pancreatitis is superimposed and diabetes ensues" (p. 446).

According to Bliss, this article by Barron was not "brilliant". I myself was rather impressed. Not only does he give quite a detailed history of lithiasis of the pancreatic duct, but he also gives a very informative history of experiments with ligature of the pancreatic canal.

What has been often overlooked is the fact that Barron, in reviewing the literature (pp. 437-441) pointed out the similarity of these observations to those that occur when the pancreatic ducts were blocked experimentally by ligation. He mentions that others have experimented with ligation of the pancreatic ducts, including Arnozan and Vaillard 36 years earlier on rabbits, and in particular Leonida W. Ssobolew in 1902[153], discussed at length by Barron and read by Banting.

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[152] Moses Barron, M.D.., Minneapolis, Minnesota, From the Department of Pathology, University of Minnesota, Minneapolis, Minnesota.

[153] "Zur normalen und pathologischen Morphologie der inneren Secretion der Bauchspeicheldrüse. Archiv für pathologische Anatomie und Physiologie und für Klinische Medizin" 1902;168:91-128.

Ssobolev used rabbits, cats and dogs. He found a gradual atrophy and sclerosis of the organ with relatively intact islets and no glycosuria. He published most of his work in Germany and was considered the real discoverer of insulin in Communist Russia. He painstakingly conducted experiments that proved that by tying the ducts in dogs, cats or rabbits, the acinar tissue of the pancreas atrophied over a period of several weeks, but not the Langerhans' islands and the animals did not become diabetic – this is not until 30-120 days later when one can find *sclerosis of the islets accompanied by glycosuria.* It is true that Ssobolew did not go any further as at that time there were no known methods to measure blood sugar or to extract the active substance from the pancreas.

It is thanks to Barron that Banting found out that intensive work had been done involving ligature of the Wirsung pancreatic duct that resulted in degeneration and disappearance of the acinar tissue while the Langerhans' cells remained intact for many weeks. We find out that besides Schultze, Mankowski (1901), Sauerbeck (1904) and Ssobolew, Kamimura in 1917 also experimented on 100 rabbits and described the changes in the pancreas after 1, 2, 3, 5, 10 and 15 weeks respectively. Banting discovered through Barron about MacCallum's interesting experiments as well as those of Mering and Minkowski in 1889 and Opie in 1900.

Barron had also provided the important information that leaving even a small portion of pancreatic tissue following ligature prevented glycosuria, temporarily at least. This represents in essence what Banting read in the night of 31 October 1920.

Surprisingly Bliss maintains (p. 51): "the survey in the Barron article actually said very little", which is more than surprising!

The more accepted version by public and authors alike, is that Banting, *inspired* by what he had read, actually *conceived the idea* of extracting the insulin from degenerated pancreas, after applying his genial new method of ligating the pancreatic canal. This is the "official version of this episode where he simply appropriated the facts as rendered by Barron.

In the Nobel speech by Banting in *1925,* Barron is only vaguely evoked:

> "On October 30th, 1920, I was attracted by an article by Moses Baron, in which he pointed out the similarity between the degenerative changes in the acinar cells of the pancreas following experimental ligation of the duct, and the changes following blockage of the duct with gall-stones. Having read this article, *the idea presented itself* that by ligating the duct and allowing time for the degeneration of the acinar cells, a means might be provided for obtaining an extract of the islet cells free from the *destroying influence of trypsin* and other pancreatic enzymes."

Here Barron's name is mentioned, as by then Banting was immortal and could afford to be generous, especially if we consider the fact that only very few people read the actual texts of speeches in this august assembly.

There is a slight difference when compared to the notes written on 31 October 1920 and kept in the Banting Archive in Toronto. Bliss points out that the word “extract” does not appear here. I personally can see no essential difference between the terms “isolate” and “extract”. Interestingly Barron’s extensive review of experiments with ligating the pancreatic ducts was never mentioned. We know that Banting gave several versions of this moment of inspiration and Banting’s understanding of diabetes was the presence of glucose in urine, not in blood.

Furthermore, going through Banting’s publications in 1921-1922 Barron’s name does not appear as far as we could ascertain. But he must have mentioned the name in an “address” at the end of 1922 or early in 1923 as Barron writes to him on 14 February 1923 and thanks him for this courtesy. Naturally, by then Macleod had announced to the world the great breakthrough by Collip on January 23 1922 and Banting’s glory was assured.

Banting read Barron’s article and also vaguely knew that essential procedures (obtaining a pancreatic extract) were now possible as he quoted Ernest Lyman Scott (1911) as already mentioned.

He certainly knew that it was possible to check the level of sugar in urine, although not in blood! He had no idea that Kleiner and Paulescu had extracted insulin from whole beef pancreas. Nor that in 1898 Pavlov and Shepovalnikow had proven that the trypsinogen in the pancreas was inoffensive and that this only became a proteolytic enzyme in the intestine under the influence of enterokinase. It must also be acknowledged that for reasons difficult to understand it seems that few others in Toronto or elsewhere were better informed. It is certain that Paulescu, F. Roberts (1922) and Collip and likely Kleiner were aware of this most important fact of modern Physiology.

It is certain that Banting found out from Barron’s article that experiments involving the ligature of the pancreatic ducts had been done also by Vassale (1891), Zunz (1905), Dewitt (1912), G. E. Laguesse (1906), Tchassonikow (1906), Lydia Dewitt (1906), Aldo Massaglia and Zanini (1912). It is doubtful that he understood their significance. But in his mind, he was convinced that he was the only person with such divine intuition and perhaps it is a good thing that he was so ignorant, otherwise he would have never gone to Macleod with his "great idea".

Obviously, since Ssobolew’s experiments, the methods for detection of sugar in blood and for obtaining extracts from various organs had improved tremendously and what had been impossible then might be possible now. This was Banting’s great luck. As such, his worldwide fame was largely the work of “Lady Luck” and certainly not of his own knowledge or genius.

The irony of his convoluted theories and experimentation is this simple fact, stressed also by other authors: the ligature of the pancreatic ducts had little, if anything to do with the extraction and purification of the internal secretion of the

pancreas. This will only come with the realization that eliminating the trypsin (actually trypsinogen) from the liver was entirely unnecessary, as Kleiner, Paulescu and later Collip have proven in convincing manner. Eventually Banting did the same thing (November-December 1921), but by then Paulescu became known and accepted in Toronto (certainly by Macleod according to his own testimony) and Collip was in Toronto. That Banting eventually used whole beef liver, but insisted for the rest of his life he received the Nobel Prize for his historic revelation of 31 October 1920 – I leave to psychologists to explain this enigma. I do not hesitate to state that Banting discovered *nothing new and significant*, not then, not before, nor afterwards. In spite of a poorly conceived idea, he had the great luck to end up in one of the best centers for animal experimentation and be guided by a man of unbelievable patience and restraint (Macleod). As a result, *they* were able to achieve results approaching those of other researchers (Paulescu). Even more, with the arrival of a true genius (Collip) the work was carried past the point where all others had been halted and as such they all became immortal.

BLISS, THE "TORONTO TEAM" AND PAULESCU

This chapter was not planned when this essay was conceived. It was clear that M. Bliss had an understandable empathy for Banting, although he subjected him at times to savage critiques. I was content with pointing out some weak points in his criticisms of Paulescu and his ambiguous glorification of Banting in an otherwise excellent book.

I still believe that his book ("The Discovery of Insulin", last edition 2000) is the most important and scholarly written on the subject and for this I can only praise and respect the author. But since reading Paulescu's original works and Bliss' most recent book "Harvey Cushing; A life in Surgery" (2005) it is unavoidable to conclude that Bliss shows a definite, unfounded and regrettable bias against Paulescu.

I also believe that at times Bliss treats even Collip unfairly, who in my opinion was the principal architect of the great achievement in Toronto in 1922. I realize that nobody is perfect and some errors of interpretations are unavoidable and this is by no means a reflection on the author's intellectual integrity. But as this essay is about Paulescu, I feel it is my duty to point out to what I consider unjust critiques by the author. For this reason, my isolated criticisms are now to be considered together and be presented for what I believe they are, namely a regrettable lack of complete objectivity in his otherwise great work that commands our respect. It may likely be that Bliss is not sufficiently familiar with Paulescu's work.

Bliss and Collip

Perhaps we should start first with his treatment of Collip. Much of his treatment of Collip is quite fair. He mentions Collip's paper "The Preparation of the Extracts as used in the first Clinical cases." This is presented together with Best and Banting's paper: "The Preparation of the Earlier Extracts" in May 1922 at the "Royal Society" as "The Preparation of Pancreatic Extracts containing Insulin" (Transactions of the Royal Society of Canada, Section V, 1922, XXX).

Bliss also lists Collip's most important article 1923L on page 285 (Articles, Books, Unpublished Accounts) but does not mention it on page 261 where he mentions "the only five documents by Collip" he was able to locate, nor elsewhere in his text. Strangely enough, the same omission occurs in Alison Li's book (our fn 70).

This article**, "**The Original Method as used for the Isolation of Insulin in semi-pure Form for the Treatment of the First Clinical Cases" was published in the "Journal of Biological Chemistry" in 1923, vol. 55, p. XI, Scientific Proceedings, XVII. It is here that Collip unequivocally states:

"*The method applied in the preparation of the first insulin used in the treatment of clinical cases (emphasis ours) was developed by the writer during December and January last. In the critical first few weeks of clinical trial of insulin the preparation of the extract was carried out exclusively by the writer".*

This should dispel any notion that Collip might have simply brought to a conclusion Banting's original method as claimed by Bliss. We have explained earlier that most likely Collip did not consider Banting's attempt on 11 January a "clinical trial", but rather a badly conceived experiment doomed to failure. Collip's method, entirely different from Banting's method, is given in toto (432 words) in our foot note (82).

Certainly, Banting told a different story, and was believed by the gullible members of the Diabetes Committee in 1970-1971. But comparing the track records of Banting and Collip, we have no doubt whom to believe. Also, we must stress that where Banting's merits are not threatened, Bliss treats Collip quite fairly.

Even more puzzling is the total change in the mythology of Banting during the month of December 1921. Suddenly the notion of the noxious trypsin is forgotten and they use fresh adult dog pancreas on 11 December and Bliss emphasizes the date. Collip only joined them on 12 December according to Bliss, (Alison Li's indicated date was 16 December) thus intimating that Collip was not involved. Bliss uses the term "*Their newly discovered extract of whole pancreas*". But we know that Collip had discussions with Banting and Best during the month of November and Collip had given them the micro-method for sugar determination. It cannot be excluded, as a matter of fact it is most likely, that he gave them other advice and information as well.

We have already mentioned that Macleod admitted in 1926 in his important article "Carbohydrate Metabolism and Insulin" the fact that in "the fall of 1921" they became aware of Paulescu's publications, which Macleod correctly condenses[154],

[154] Macleod, "Carbohydrate Metabolism and Insulin" London, New York, Toronto, Longmans, Green and Co.; 1926, pp. 27-411926, properly listed in Bliss' "Sources", p. 294, but otherwise not discussed in his book. And here Macleod states unequivocally (same text already quoted by us in a previous chapter) "While this work was in progress in Toronto a paper by Paulescu came to our notice and after it was complete, one by Gley. Paulescu's researches were communicated at a meeting of the Réunion Roumaine de Biologie in the spring of 1921 in which he describes the effects produced by intravenous injection of sterile pancreatic extracts on the percentage of sugar, of acetone bodies and of urea in blood and urine of depancreatized dogs. Typical observations are shown in Tables 1-5. There can be no doubt that all three substances became markedly reduced in amount, in both blood and urine, as a result of the injection. The results were the same whether the injection was made into a branch of the portal vein or into the jugular vein. The effects were noticeable in one hour following the injection,

unlike Best. It is quite likely that Paulescu's findings, properly explained by Macleod, or the subsequent arrival of Collip, or both, could explain Banting's sudden conversion of faith – no longer avoiding at all costs the dangerous Trypsin (that resurfaces in their article of February 1922 and even in his Nobel Speech in 1926!). But this certainly is not a "breakthrough" originating in his brain. Furthermore, they (Banting, Best, and Bliss) completely ignore or knowingly fail to inform the reader that this "new discovery" had been made and used earlier many times by Kleiner and Paulescu.

The "important breakthrough" of 6 December (the use of alcohol in obtaining the pancreatic extract) had actually come from Macleod. Actually, nothing "new" on this page (Bliss, p. 97) can be ascertained, nevertheless Bliss gives all credit to Banting and Best. As Bliss fails to clarify this matter, as well as many other "major advances" that were contrary to Banting's dogma, we could assume that some of these "breakthroughs" possibly came from either Collip or Macleod.

It remains to be answered: how much did Collip know of Paulescu's work? It is certain that Macleod knew of, understood, and accepted Paulescu's publications of 1921 as we have discussed above, and furthermore he and Collip were befriended. It is difficult to imagine that Macleod never discussed this with Collip. One might reasonably assume that Collip's experiments could have been influenced by Paulescu through Macleod. Certainly, this is only mere speculation on our side but it is plausible, even likely. But even if such were the case, this in no way would diminish Collip's immense merits for his crucial contributions.

More strange revelations follow on page 101(Bliss). Again, there is no attempt to explain how Banting reversed his quasi-religious belief in the dogma that the trypsin had to be eliminated at all costs. Bliss does not explain this strange change of mind nor does he mention *here* that Collip had successfully used whole ox pancreas. Nor that Kleiner and Paulescu had successfully experimented with extracts from whole canine pancreas (but Paulescu also used successfully beef pancreas in his "9th experiment"[155] as well as in his experiments of 1922-23). Not to mention the fact that nowhere is it stated that all their "new discoveries" or "breakthroughs" had actually been realized much earlier by Kleiner and Paulescu. As Banting and Best's relationship with Collip deteriorates in mid-December, they run out of new inspirations and out of luck. The timing is suggestive.

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attained their maximum in two hours, and passed off in 12 hours. They varied with the amount of gland present in the injected extract. Paulescu also observed that the blood sugar as well as the blood urea in a normal dog were lowered by the injections" (emphases ours).

[155] F.G. Young, in Medical News Tribune, no. 38, September 1971; "The credit fore insulin should have been shared", quoted by I. Pavel (fn, 69), p. 226; Also Ian Murray, "Paulesco and the isolation of insulin", Journal of the History of Medicine and Allied Sciences (1971, XXVI, 2) Pavel (fn. 69), pp.16-25.

As such it is not surprising to read on page 103 (Bliss): "But they (Banting and Best) must have been a bit chagrined that it was Collip who had achieved so much with their extract". Certainly, Bliss still refuses to admit that Collip's method had very little in common – if anything at all – with Banting's primitive methods as we have demonstrated above.

What is paramount however is the fact that Collip won the race to make insulin available for human use, but the Nobel Prize went to Banting.

Puzzling again is Bliss' assertion (p. 109) that Collip's original discovery of hypoglycemia is actually a bit artificial as *one year* prior, in 1921 F.C. Mann and T.B. Magath had reported similar effects following a hepatectomy. Here Bliss reproaches Collip for being unaware in 1922 of findings published in 1921 about the liver, whereas Collip was experimenting with the pancreas! But how can I express my bewilderment that the Toronto group, including Macleod and Bliss, although not Collip, completely ignored Pavlov's and Shepovalnikow's discovery in 1899 that in the pancreas there is only inactive and innocuous trypsinogen and any attempts to destroy the acinar tissue had absolutely no rational base. These 23 years after the discovery and 19 years since its recognition in form of a Nobel Prize! (We have discussed this in the chapter Banting; Further criticisms).

Why Bliss is trying to diminish Collip's merits in Toronto (he has only words of praise for all other Collip's great achievements) and those of Paulescu, remains a mystery to me.

Paulescu & Cushing according to Bliss

If we start with Bliss' book on Cushing, "Harvey Cushing; A Life in Surgery", it is surprising that Paulescu's name appears only once (p. 208), "They found that the best work was being done in Romania by the physiologist Nicolas Paulesco, who had developed what seemed to be an ideal surgical approach to the pituitary of dogs". This is correct but Bliss feels compelled to add his personal comment: "*Perhaps coincidentally, it involved the same bilateral decompressive methods that Cushing had used on his 1905 patient*". Because this statement is not correct, as a matter of act is contrary to Cushing's true assessment of Paulescu, we regretfully feel obliged to respond.

In his words, Bliss implies that Paulescu's method was just a simple trepanation, cutting out a circular section of the skull to relieve intracranial pressure. In 1905 and 1908, Cushing performed decompressive trepanation in the therapy of refractory brain edema. But what Paulescu actually did, was to sufficiently expose the basis of the cranium in order to allow gentle lifting of the temporal lobe of the brain and thus allowing a visualization of the pituitary gland and active surgical resection of this gland. The difference is enormous.

Bliss does not mention the very informative paper published by Sam L. Teichman and Peter A. Aldea in Journal of the History of Medicine: Vol. 40, January 1985 and titled "Pioneers in Pituitary Physiology: Harvey Cushing and Nicolas Paulescu" emphasizing Paulescu's original publications. We have discussed this article, including many quotations from Cushing, in a previous chapter.[156]

Paulescu published his findings in "The Hypophysis of the Brain; Experimental Research" (1906), and "Research of the Physiology of the Hypophysis of the Brain. Hypophysectomy and its effects" (1907) (see our note 21 A and B) where he reported 24 cases of hypophysectomies using his own method.

Cushing presented his first paper in December 1908 ("Is the pituitary gland essential to the maintenance of life?") to the American Physiological Society, Baltimore, published in 1909. His second paper was, "The Hypophysis cerebri: Clinical aspects of hyperpituitarism and hypopituitarism"[157] (July 1909) and in 1912 his book "The Pituitary Body and its Disorders" was published. We have already demonstrated with ample quotations that Cushing praised Paulescu's work as to both, the surgical method conceived by him and his well founded results. Also, we have mentioned the warm relationship between these two scientists that included a prolonged correspondence, most of which is unfortunately lost. As mentioned earlier Paulescu's whole archive was burnt in the 1950s by his disciple Trifu who had been forewarned that his house would be searched by the communist authorities.

Certainly, Bliss is under no obligation to mention in the 590 pages of his volume the merits of other researchers who are not high in his esteem, but perhaps he should refrain from making unwarranted comments that diminish the value of their work. In any event, we have preferred to quote directly from Cushing and allow him to express his own very favorable opinions of Paulescu's merits.

I wonder whether Bliss has read the detailed and extensive article by Norman M. Dott[158] written in 1923. Dott referred to his experimental procedures as

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[156] In his article "Is the pituitary gland essential to the maintenance of life?" Cushing states: "The only striking series of successful extirpations have been those recently reported by Paulescu". And further: "Hence, in our operations, we have been led to accept Paulescu's method, which possesses (….) unquestioned advantages; for the (….) [technique]…brings into play the principal of cerebral dislocation of importance in many cerebral operations on man, and …[allows]…the hypophysis [to] be brought clearly into view…with little danger of injury to the cerebral substance and without risk of compression symptoms." In 1912 in his book "The Pituitary Body and its Disorders", Philadelphia, J. B. Lipincott, p. 12 Cushing gives full credit to Paulescu for the settlement "beyond peradventure" of the question as to whether or not the pituitary gland is essential to life, etc.

[157] Cushing, JAMA, 53: 248-256, July 1909.

[158] Norman M. Dott (University of Edinburgh), "An Investigation into the Functions of the Pituitary and Thyroid Glands", Part I. Technique of their experimental Surgery and Summary of their Results, Q J Exp. Physiol. 1923; 13; 241-282, p. 241.

"*Paulesco's method*", although he made himself slight modifications to Paulescu's work, and not "Cushing's method", although he was trained under Cushing. A brief look at the picture labeled "view of the field of operation" on page 253 of Dott's article should easily dispel any notion of any resemblance between Cushing's relatively simple trepanation methods of 1905 and Paulescu's surgical method. Also, take note of Dott's remark that, besides Cushing himself, only a few other workers were able to perform this difficult and demanding operation devised by Paulescu (p. 248). We should also mention Dott's important comments (quoted also by Sir E. Sharpey-Schafer, see note 37), where he states "Paulesco, who published the first really satisfactory account of experimental operations on the pituitary body (p. 242)". Further we can read: "*Paulesco in 1908 published his brilliant monograph on the pituitary body, in which is described his method of bi-temporal, intracranial approach in the dog. With slight modifications by Cushing, Paulesco's procedure is the one used to-day in experiments upon mammalian hypophysis."* The main features of Paulescu's findings are given on page 247 (Dott). We repeat them in our footnote.[159]

The details of the "Experimental Operations on the Pituitary", basically Paulescu's method, with only few changes by the author, are given on pages 248-258 of same work. The author states:

> " As regards the operation of Paulescu, this might appear superfluous, but the few workers who have performed it limit themselves to a brief description of its steps. They do not indicate many of the risks and difficulties that have to be met with by the uninitiated in this particular field. Accordingly special emphasis is laid here on the operative dangers which the writer's short experience has impressed upon him".

I am sorry that I have to say that at Harvard Medical School, at Peter Bent Brigham Hospital and other world renowned institutions, unlike the University of Toronto, Paulescu was regarded with due respect.

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[159] "He performed complete extirpation of the hypophysis, which is fatal. He largely removed or entirely destroyed the anterior lobe, which likewise was fatal. He removed the anterior lobe, which likewise was fatal. He removed the anterior lobe partially, and the posterior lobe completely. No obvious symptoms followed. He severed the organ from the base of the brain by section of the infundibulum, which he states was equivalent to total, or almost total hypophysectomy. He separated the gland from its attachments to sella turcica, and no apparent consequences were noted. In explaining the last two effects, he mentions that in dividing the infundibulum stalk the main blood supply to the gland is cut off, while in separating it from the sella turcica only a few small vessels are severed. Paulesco makes no mentions of skeletal changes following these various lesions."

Bliss and Paulescu

To return now to less exciting events, the falsification by Best of Paulescu's results, as shown by Bliss (page 87) has already been discussed in our chapter "*How to discredit a Rival*". We have acknowledged the fact that Bliss chastises Best for the distortions in the 3rd paragraph of the same page (these distortions had already been exposed by I. Pavel and E. Martin after Banting and Best had imprudently included their foolish misrepresentations in their February 1922 article). But the second paragraph does not elicit any negative reaction from Bliss, on the contrary he insinuates that Best was right. These horrendous falsifications of Paulescu's work were unknown to the above named authors (Murray, Martin, and Pavel), actually to all authors in this field and so nobody had challenged them. As such Bliss feels safe to defend Best's ridiculous assertions. How fallacious they were we have tried to demonstrate earlier in our text.

We have to realize that both paragraphs are based on notes jotted down by Best on an index card. In my view, one would expect that Bliss would have shown more prudence when revealing (for the first time) Best's remaining unfounded critiques condensed in this second paragraph of Bliss' work (page 87) now under discussion.

I have already mentioned Macleod's article of 1926 stating clearly that in the fall of 1921 *they* became aware of Paulescu's papers and Macleod renders a correct, truthful résumé of Paulescu's findings, which he obviously accepts. What happened then with Best and Banting that could lead them to such horrendous distortions? I have read this paragraph (p. 87) by Bliss many times and cannot help sensing that Bliss defends Best or argues on his behalf. It is obvious that Paulescu is not his favorite protagonist in this exciting chapter of medical history.

When reading this paragraph please keep in mind the fact that all Best's negative remarks were noted on an index card, in other words not for publication, whereas Bliss is the first to publish them and thus I regret to have to say, is responsible for the way they are presented. As such we can read:

> "Paulesco also 'proves' (sic!) that his extract lowers the blood sugar of a normal animal. Best also thought it germane to note, however, that Paulescu reported normal blood sugars in his dogs as low as 0.44 per cent and obtained hyperglycemic readings in his diabetic dogs no higher than .20 per cent. Both figures, Banting and Best knew, were considerably out of line, and this may have cast a doubt on the Romanian's methods. As well, Paulescu's animals had been under a volatile anesthetic, chloroform, during his experiments, with the extract injected just after the pancreatectomy; Best may well have realized that the anesthetic's effect on blood sugar would throw all experiments with extracts into question. Moreover, Paulescu did not report either the volume of

extract injected or the volume of urine excreted. The index card suggests that Best did not find Paulescu's paper particularly impressive".

Emphases are ours and they (the underlined text) certainly can be attributed to Bliss writing on behalf of Best, and not to Best. Not one word of dissent from Bliss, in contrast to the following paragraph where he chastises the young adventurers for their misreading of Paulescu's "non plus", previously exposed by Martin and Pavel as already discussed. As such, our critique regretfully has to be directed against Bliss.

Perhaps the simplest way to analyze this page in Bliss' work is by reminding our readers that both paragraphs (2 and 3) on page 87 deal with Best's incompetent analysis of Paulescu's text, in fact a falsification. As mentioned above the remarks in the third paragraph had been published and as such they were known to the scientific community and this led to denunciations by E. Martin, I. Pavel and others. As such, Bliss had no other recourse but to condemn them too.

In the case of those elements that had not been published, perhaps Bliss felt safe to condense them in the second paragraph quoted above, without attempting any criticism. Naturally, the juxtaposition of these two apparently different sets of comments can easily convey the impression that Bliss considers them justified. Bliss should have analyzed them more carefully. Had he done so he could have arrived at different conclusions himself.

Going into specifics now, Best's and Bliss' insinuations that Paulescu failed to indicate the amounts of extract given and volume of urine excreted has been proven as unfounded and even fallacious in our chapter "How to discredit a rival". Best was incapable of properly noting the prominent footnote directing him to all these details and even more. As to the effect of chloroform, how many times did our ignorant accusers use chloroform themselves? Just one example: on August 17, on dog 92.[160]

Bliss completely ignores Macleod's competent interpretation of Paulescu's findings, already quoted in our essay, see note 150, stating among other things: "*There can be no doubt that all three substances became markedly reduced in amount, in both blood and urine, as a result of the injection.*"

Besides Macleod, other distinguished scientists have thoroughly investigated Paulescu's work and knew how to interpret his results based on the old Pflüger method. Suffice to mention Sir E. Sharpey-Schafer (The Endocrine Organs, second edition 1926, pp. 343-344), or Ian Murray in several publications 1969-1971, and we can even include the famous Committee of the International Diabetes Federation in 1970, headed by Best's good friend Prof. F.G. Young and "set up to present a written summary of the work leading up to the discovery of insulin". Even this committee,

[160] Bliss (fn 3) p. 76.

including five distinguished researchers in the field of diabetes, dedicated to preserve the good name of Banting and Best and that criticized Paulescu for other reasons, even this committee could find nothing wrong with Paulescu's methodology, his experiments or his results. Their main criticism was that in their opinion Paulescu spent too much time studying the effect of Pancreine on the metabolic functions and "Such exacting and time-consuming measurements may have delayed the completion on the investigations essential for the preparation of the bland pancreatic extract that was needed for the fruitful application of the relief of human suffering of the results of a fundamentally important laboratory investigation".[161]

To my knowledge the only critics of Paulescu's experiments are Best, Banting and Bliss.

It is sad that I. Pavel could not have access to the Banting Archive in Toronto and as such he could not demonstrate how profoundly wrong Best's interpretations on the index card were (as he did with Banting and Best's first published article).

As to the figures given in this paragraph on page 87, I compare Bliss with Ian Murray[162] and imagine that they both look at the same glass. For Murray it is half full, for Bliss half-empty and accordingly useless. Certainly Bliss realized that the Pflüger method was quite old and unreliable (but not useless) and could not compare with the sophisticated new methods in use in Toronto. But Paulescu could not afford to use better methods, for financial reasons. Anyway, the Pflüger method used by Paulescu was perhaps the first method introduced into the medical laboratory and not very reliable in the high and low ranges and you cannot blame a researcher who cannot afford better but more expensive equipment. Bliss stresses his half-empty glass theory by incorrectly claiming that for Paulescu a blood sugar of .044 (very low) was normal. More important is the fact that it does not invalidate Paulescu's absolutely correct conclusions, unlike those of Banting and Best using the most up to date methods but arriving at the most absurd interpretations. Furthermore, he claims that Paulescu's "high" sugar levels never exceeded 2.0 per cent. But here are the figures of Paulescu: 1) low (normal): only #8 shows 0.40. The other "normal readings" are 0.70, 1.04, 0.96, 0.88, 0.54, 1.22, and 0.88. 2). The "high hyperglycemic" values are 1.58, 2.78, 2.00, 1.80, 2.62, 2.70, 2.00, 1.66, 1.80, 2.70, 2.96, and 2.28. To Bliss and the "expert" Best these results are unacceptable (half-empty glass). Analyzing the same data Ian Murray[163] comes to the conclusion: "*Pre-injection blood sugar averaged 190 mg%, while two hours after the injection the average was 81%, a reduction of 57.4%"*. In other words the cup is more than half full, and of significant value!

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[161] IFD in Pavel's rendition (fn 69), pp.163-164.

[162] Ian Murray, "Paulesco and the isolation of Insulin" in Journal of the History of Medicine and Allied Sciences, 1971, XXVI, 2., see Pavel (fn. 69), p. 20.

But more important than all these manipulations with numbers in my opinion is this simple fact, and I hope that Bliss will agree with me, namely that all of Paulescu's conclusions in 1921 were confirmed within six months by Collip and later by many others and were proven correct. I personally tend to have more respect for those who have achieved more with less.

In our chapter on the same subject, we have added two more distortions to those two already detected by I. Pavel and mentioned by Bliss as stated above: their ignorance in not realizing that external jugular veins actually were peripheral and the alleged failure by Paulescu to report the amounts of extracts given or urine eliminated. Both criticisms are without any substance whatsoever.

If we return to the way Bliss presents Macleod's refusal to add his name as a co-author on Banting and Best's first paper "The Internal Secretion of the Pancreas" published in the Journal of Laboratory and Clinical Medicine (February 1922), we have alluded to the fact that Macleod's refusal was, in our opinion possibly based on the fact that he knew that the authors' critique of Paulescu was contrary to the true facts of the case, as he had read and understood Paulescu's text. Certainly, Macleod could not afford to jeopardize his good name in Science by signing such a flawed document.

Might I also add that another reason must have been the fact that Macleod, as a true scientist likely knew by now that Banting's claims as to the noxious effect of the trypsin (actually trypsinogen) were preposterous, had been proven invalid and as such he had no choice but to decline the honor of being the co-author of such a travesty of science. Bliss gives other reasons such as this being a courteous admission that he had not contributed much to this "scientific" work

As to Bliss' critique of Paulescu's claims in 1923 and 1924, Bliss is partially right. But he could have been more merciful, given Paulescu's utter isolation, dependant only on French publications. We have tried to explain how insulin was only introduced in France late in 1923 and as such insulin shock was only belatedly recognized. Paulescu was overtaken in January 1922 by Collip and fell far behind.

But Bliss resorts to unfair tactics on page 267, endnote 79. Here Bliss discusses Paulescu's "*personal theory*" about plasmine. Because of the seriousness of our objections, we shall give all pertinent information. In his endnote Bliss refers to experiment XIII, 1923, where aglycemia (blood sugar: 0.000) is found 2 hours after the injection of his pancreatic extract and published in "Quelques Réactions chimiques et phyiques, appliquées à l'extrait aqueux du pancreas, pour le debarrasser des substances protéiniques en excès". In the introduction, after describing his new method of preparing his pancreatic extract, Paulescu states and we give the original French text with the English translation in the footnote:

"*Mais en injectant dans le sang d'un animal diabétique, l'extrait pancréatique limpide, ainsi preparé, nous avons obtenu un effet inattendu et très*

remarquable. Pareil extrait a non seulement fait diminuer l'hyperglycémie à une proportion moindre qu'à l'état normal, mais il a même produit une véritable AGLYCEMIE, en faisant réduire la glycemie à zero. En d'autres termes, le sang d'un animal diabétique, qui, avant l'injection, contenait 2 ou 3 gr. de glycose, pour 1000 cc., ne renferme plus du tout de glycose après l'injection. Or, l'aglycémie transitoire ne s'observe jamais à l'état normal où le sang contient entre 1 gr. Et 0.3 gr. de glycose, pour 1000 cc. Cet important phénomène nous servira de point d'appui pour établir la théorie du diabète, que nous exposeront prochainement."[164]

In 'Conclusions' he adds also while discussing his extract*: "Il peut même donner lieu à une AGLYCÉMIE totale*" ("it can even cause total aglycemia"), and this is all he wrote. This is the true and complete rendition of Paulescu's text.

Now let's see how Bliss treats this text. On page 267, note 79 he states:

"The clinical tests are described in Paulesco 1923B, the "aglycemia" in Paulesco 1923A. It is remarkable that there has been no discussion of these experiments, except for a passing reference in Murray (1971),[165] in the literature generated about Paulesco's work. The zero blood sugar observation was consistent with Paulesco's hypothesis that the internal secretion of the pancreas acted as a kind of catalyst or cement on the nutrients ingested by the blood, enabling them to combine to form what Paulesco called "plasmine" in the blood. See Paulesco 1920, pp. 301-305. In his model a zero blood-sugar reading meant that the extract was totally effective."

This unfortunately distorts the true facts. Nowhere does Paulescu state that aglycemia meant total efficiency of his extract. Only a writer with preconceived ideas could say such a thing. Please consult Paulescu's actual statements rendered above and draw your own conclusions.

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[164] Nicolae Paulescu, "Quelques Réactions chimiques et phyiques, apliquées a l'extrait aqueux du pancreas, pour le débarrasser des substances protéiniques en excès". Archives internationales de Physiologie, 21 (mai 1923): 71-85. "But while injecting into the blood of an experimentally induced diabetic dog this limpid and thus prepared pancreatic extract, we have arrived to an unexpected and remarkable result. Such an extract has not only reduced the hyperglycemia to a level below normal, but it has also caused a true AGLYCEMIA, reducing the glycemia to zero. In other words, the blood of an experimental animal that contained 2 or 3 gm of glucose per 1000 cc before the experiment contains no glucose at all after the injection. Now, transient aglycemia is never noticed normally, when the blood contains 2 or 3 grams per 1000 cc. This important phenomenon will form the basis for establishing our theory of diabetes that we shall present shortly".

[165] We have already mentioned that it actually was Prof. Young and not Murray: Pavel, The Priority (fn. 69). A letter from F.G. Young to I. Pavel dated 25 May 1971.

Bliss is basically correct with his claim that "In Paulesco 1924, by which time thousands of physicians had seen hypoglycemic reactions, he is still denying that hypoglycemia causes any abnormalities", but regretfully his conclusions are not. We have discussed this in detail in our chapter on "Criticism against Paulescu" and we reproduce the final paragraph:

> "Again one should consider the possibility, even the likelihood that these erroneous findings were not of his own making, but rather the results of the imperfection of the old and unreliable method he was using in determining the levels of blood sugar. It is known that the Pflüger method was not very precise in the high and low ranges. As such it is quite possible that Paulescu having been the first to apply this method in cases with low glucose content, *where this method likely was simply inoperable* was confronted with these unusual and puzzling findings. Again he quite clearly and correctly states that he intended to pursue this matter and he refuses to draw any clinical or physiological conclusions. Certainly Paulescu handles this subject with absolute objectivity and with utmost scientific honesty. Most likely he is an honest victim of an imperfect and primitive laboratory method this being the only one at his disposal. I personally cannot see any other plausible explanation for this odd event in this chapter in the history of diabetes. But I also wish to repeat that Bliss was perfectly right in drawing attention to this oddity, although his misrepresentation of this case is questionable."

As to Paulescu's misconception about "plasmine" from 1916-1920 that was criticized and ridiculed by Bliss, it was not much different from Kleiner's speculations at about the same time (mentioned earlier in our text and not criticized by Bliss), and should not have been connected with later events and the newly acquired knowledge of 1923.

Furthermore, Paulescu clearly presents it as his <u>personal hypothesis</u> "*according to which under the influence of the endocrine pancreas secretion the absorbed elements would form a glyco-lipid-protein complex that he named <u>Plasmine</u>*". According to this hypothesis, without the endocrine pancreatic secretions, the three nutritive components "remain dissociated and can no longer nourish the tissues". Obviously, we know now, this hypothesis is scientifically incorrect although various combinations of carbohydrates, fats and proteins have been discovered in the blood. But neither does this invalidate all other correct conclusions in this remarkable work of the years 1916-1920 and in no way does it undermine all other facts submitted. It is peripheral, not repeated again and presented by the author as a supposition. It is perhaps the most innocent error in the historiography of diabetes.

But where Bliss errs is when he connects Paulescu's finding of "aglycemia" during his experiments in 1923, when Paulescu wisely refrained from any further comments, with the "plasmine" theory conceived sometime between 1916 and 1920, but only published in 1920 because of WW1 and its aftermath. Unfortunately, I have to say that only someone with a bias could make such a connection.

First, he mentions this towards the end of his work (p. 267, note 79), while discussing Paulescu's articles of 1923 and thus creates the incorrect impression that this was still Paulescu's vision in 1923.

Second, Paulescu's faulty concept of "plasmine", published in 1920, is at least an honest error. There is no comparison with the ridiculous and outright dishonest assertions by Banting in his first paper published in February 1922[166] where he claims that he had proven that the pancreatic trypsin was destroying the "internal secretion" of the pancreas. Especially when considering that his own previous experiments had proven the opposite and Collip had already successfully treated a patient using this dangerous trypsin (actually trypsinogen) containing extract. Even more damning is the fact that in the same text Banting falsifies Paulescu's data, which in today's world could have unpleasant repercussions.

Finally may I say that if Paulescu erred in this respect in the years 1916-1920 he more than anybody else has helped to shed light on this complex problem with his brilliant work done in 1920-1921 that has been discussed previously.

> *If Paulescu (and Kleiner) had some fancy notions as to how insulin worked in the human body[167] in 1919 and 1920, Paulescu has more than redeemed himself with his later work by being the first to demonstrate the crucial role of insulin in all aspects of metabolism, even anticipating some of its anabolic effects that were only confirmed many decades later.*

Another part of Bliss' work that is open to criticism is his celebration of Kleiner's theoretical conclusions when compared to Paulescu's work. Kleiner's work was superb and his conclusions were indeed beautifully expressed, but they quickly became outdated. Perhaps when Bliss first published his work on the discovery of Insulin (1982) this was not as obvious. But when in 2000 he published his third edition he ought to have known that most of Kleiner's theoretical conclusions are no longer accepted in modern medicine. In contrast, all of Paulescu's conclusions based on his experiments of 1920-1921 are not only as valid now as they were in 1921, but have even *gained in* significance (see above) and relevance in recent decades. Furthermore, Paulescu, because of his geographic

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166 "The Internal Secretion of the Pancreas", in the Journal of Laboratory and Clinical Medicine, February 1922.

167 Paulescu with his "Plasmine" and Kleiner with his theories re "impaired permeability of the kidney to sugar by a toxic action" (p.167) and the "diabetic blood sugar being in a combined poorly diffusible state" etc.

isolation and having no access to the most recent developments in this field in the West can be at least partially excused for any failings.

Again it is simply not fair to introduce into this discussion ideas of the past that he more than anybody else has helped to clarify. I hope I shall be allowed to repeat the profound observations of Sir Alberti, "*He (Paulescu) was the first to describe the actions of what was later called insulin and demonstrated clearly that it was a hormone with actions on all aspects of metabolism*". Quoting again from same author (Sir George Alberti, see our note 119): "*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*."

These have been the wisest words expressed on this subject. Notwithstanding the above mentioned critical remarks, Bliss' work still remains the most important and informative book written on the subject of the discovery of insulin – although in some respects it has to be read with a certain degree of caution.

Bliss and the Report of the IDF

We have already dedicated a chapter to the Report of the IDF (International Diabetes Federation). We have already stated that the report of this committee had absolutely no merits. It was poorly conceived, incorrectly constituted, with the wrong instructions and that its final conclusions had no justification whatsoever. It was simply a device to enshrine Banting's genial work while taking good care not to upset Best, who was then still alive.

It is interesting to read Bliss' reaction (already quoted in our chapter on the IDF Report. On page 16 (edition 2000) we read:

> "The report, published in 1971, was a careful, tightly written summary of historical knowledge about the discovery. Its conclusions, difficult to simplify because of the subtlety of the argument, were to the effect that Paulesco might indeed have discovered insulin as a therapy for diabetes had not the North Americans been able to move so swiftly and successfully to develop the results of Banting and Best's research. Pancreine probably contained insulin – so did the pancreatic extracts prepared by several earlier researchers, especially a German named Zülzer – but it was the Canadians who made insulin suitable for the treatment of diabetes".

This is an odd comment indeed on a most extravagant report. Where is the subtlety in such a travesty of medical history? As to the statement that Paulescu "might indeed have discovered insulin as a therapy…" this is only a transparent attempt to give an impression of objectivity, by the Committee and by Bliss. I am

sure that Bliss knows very well that this would have been impossible. Suffice to consider the extreme difficulties Collip had when trying to make a second batch of insulin because he had forgotten one minor detail. Consider the advanced techniques they had at their disposal, the superior laboratory methods, vastly superior methods of fractionated precipitation and later on, when work was conducted at Eli Lilly, the isoelectric precipitation method.

Paulescu using more primitive tools, in spite of his superior intellect, could never have done this. He went as far as a human mind, albeit an exceptional mind could have gone, but no further.

Bliss and Banting

At the very beginning I wish to express my bewilderment as to the emphasis on Banting's "oneiric intuition" on the night of 31 October 1920 regarding the significance of having the pancreatic duct(s) ligated in order to obtain an extract unaltered by the malignant trypsin! (Banting gave several versions of this event).

If one reads the whole article by Barron, he must realize that the second half dealt with experimenting with ligation of the pancreatic ducts! Banting simply appropriated this idea without acknowledging it! (He will briefly mention it in his Nobel Prize Lecture on 15 September 1925 when it no longer mattered!).

Furthermore, it was an established fact since 1899 that there was no trypsin in the pancreas, but only the harmless trypsinogen. That Banting was not well versed in physiology is well known. But that Bliss, with one single exception (p. 203, when quoting the critique by Dr. Ffrangon Roberts[168]) fails to mention this most decisive fact when discussing this subject is difficult to explain.

It is hard to believe that the medical literature of that era, and even later on completely ignored this fundamental fact of Physiology. It is almost as if the entire medical profession, (and historians too!) forgot that in 1899 N. P. S. Shepovalnikow, working with the great Ivan Petrovich Pavlov at the University of St. Petersburg, had discovered the new enzyme enterokinase.[169]

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[168] British Medical Journal, 16 December 1922 "Banting was ignorant of the best established facts in physiology, that the proteolytic enzyme exists in the pancreas in an inactive form – trypsinogen – which is activated normally with another ferment, enterokinase, secreted by the small intestine".

[169] As we have discussed already, this enzyme would convert the inoffensive trypsinogen created in the pancreas into an active proteolityc ferment in the intestine. W.H. Thompson will name this enzyme enterokinase in 1902. On 6 February 1909 Barbara Ayrton, from The Physiological Laboratory, University College, London published a most important article on trypsinogen, trypsin and the role of Enterokinase for the English speaking medical world. She mentions how Trypsinogen is converted into trypsin, either by the action of enterokinase in the

As such, because of a total amnesia by the medical profession (including again the historians), false statements abound in books, in articles, in movies etc., Nobel Prizes were awarded but unfortunately distinguished careers were also ruined. This says a lot!

We have mentioned and criticized some of Bliss' unfounded critiques against Paulescu. But the reader can also find on different pages contrasting opinions. One example would be Bliss' speculations about Banting and Best on page 88 (edition 2000). "Had they (B&B) thought about Paulescu carefully, for example, they might have decided to try their extract on normal animals and to measure its impact on ketonuria in diabetic ones, as he had done". Certainly, I cannot find any trace of bias in this statement. Unfortunately, such opinions are rare in his book.

Even more contradictory are his evaluations of Banting's work. The long list of criticisms raised by Bliss against Banting and Best has already been dealt with in a previous chapter. But what is surprising is to see how at times nevertheless he stresses alleged merits or how he justifies Banting's behavior at the expense of others. We shall not repeat Banting's and Best's embarrassing critiques against Paulescu that have already been exposed in a previous chapter. But a real treat is this comment supportive of Banting that is also an indirect criticism of Collip. Bliss states about Banting's reaction to Collip's progress early January 1922: "But they must also have been a bit chagrined that it was Collip who had achieved so much *with their extract* just when their own attempts to make it work at all had resulted in a week of total failure". For Bliss to make such statement is rather odd. He does not include Collip's method in his text (footnote 83 in our text), but to anyone who studies and compares Collip's and Banting's methods, the enormous difference is obvious. Furthermore Bliss himself admits that in the end Banting and Best "borrowed" (without acknowledgment) from Collip quite a few elements in their extract preparations in January 1922, including the extract administered on 10 January of the same year when they copied from Collip the use of a vacuum still and the technique of not evaporating off all the alcohol.[170] Considering the previously established agreements, Bliss should have condemned Banting for such unethical transgressions (not giving the source).

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intestine, but also at times spontaneously inside the pancreas by calcium containing substances, or by heating. The discovery was made in 1899 by Shepovalnikow and Pavlov, who also had other great discoveries to his credit and received the Nobel Prize in 1904.

[170] Bliss (fn 3), p.119, "I presume that Collip and Macleod had little use for Banting's conduct in the past several weeks, particularly Banting's breaking of the spirit of the collaboration by himself and Best making the extract for the first clinical test. And, it appeared, Banting had appropriated some of Collip's improvements in making that extract".

Again, I believe Bliss regretfully errs on pages 114-115 and we shall render the complete text. Here Macleod to his great credit is trying to convince the reporter Roy Greenway not to prematurely publish the unsuccessful treatment of Thompson (11 January 1922) while Collip was progressing well with his experiments. Bliss writes:

> "He probably urged Greenway not to publish anything; Greenway agreed that he would emphasize that the work was preliminary. He did, more or less. The article appeared on January 14, emphasized Macleod's caution. 'We've really no hope to offer any one at all as yet', Macleod was quoted as saying. 'We don't know anything yet that would warrant a hope for cure. But we are working intensively at the thing with a hope that some day we may be able to help on a little bit.' Last summer's experiments had not been new by any means. Hundred of people all over the world had been working on the problem of sugar and the blood. At New Haven we were able to report results that were more definite; that was all. We are working very conservatively striving to awaken no false hopes.
>
> To Fred Banting everything about the article, which barely mentioned Best and himself, was a distortion. To understand why, reread the last paragraph from Banting's point of view. Think about his situation on January 14; think about Macleod's use of 'we'. Banting's near paranoia about Macleod is surely understandable."

I must admit that in Bliss' entire work the above statement is to me the least comprehensible. Banting and Best insisted on being the first to conduct a human experiment although they were not ready. They prepared their extract in a hurry in order to be the first, did not listen to reason, did not conduct enough testing of their new extract and acted like maniacs with no consideration for the consequences on a poor suffering patient. On 11 January their extract was injected into a human being and the result was not only a failure but also resulted in more pain and suffering for their "patient". Poor Macleod was confronted with a failure and very likely had remorse for having given in to these amateurs so ignorant in the field of medical science and deontology. Certainly in the case of a successful outcome all the names of the participants should have been made known to the public and to history, but this certainly was not the case here, on the contrary. Under such embarrassing and almost tragic circumstances to add more names and undermine the good name of the University would have been insane; the less said the better to salvage some honor. While any decent scientist would have gone into hiding our heroes (Banting and Best) claimed immortality for their misdeeds. How can Bliss, or any one for this matter, "understand" and approve Banting's revolting expectations? Perhaps you the readers can, but I cannot.

Bliss and Best

That Bliss could not have much respect for Best is easily understandable and is evidenced in Bliss' article "Rewriting Medical History: Charles Best and the Banting and Best Myth", 1993[171]. Here he also gives a more realistic and accurate appraisal of Paulescu's contributions. This article by Bliss is a well-documented and scathing critique of Best and here he states:

> "From time to time in the 1960s Charles Best would receive 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 endocrinologic 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 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, Zülzer, 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 from 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 collaboration building on the original work of Banting and Best.

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[171] Bliss, Michael, "Rewriting Medical History: Charles Best and the Banting and Best Myth", 1993, The Journal of the History of Medicine and Allied Sciences, Inc. ISSN OO22-5O45 volume 48, pages 253 to 274, pp. 273-274

> Throughout his later life, Charles Best worked very hard and with considerable temporary success, to convince every one of his and Banting's claims to be the sole discoverers of insulin. In the long run he failed."

I personally only wish that Bliss had expressed similar views in the 2000 edition of his "The Discovery of Insulin". It would be too much to go into its sordid details; perhaps it would be wiser to quote only one more sentence from the last page:

> "At times Best's distortions of the historic record seem to amount to a deliberate, unethical exercise in falsification which verges on scientific fraud".

No further comments on this subject in this paper are necessary.

Bliss and Macleod

I can only praise Bliss' insightful analysis of Macleod's role in this unique drama in the history of Medicine. The way Macleod was treated, first by Banting and then by the Canadian mass media, can only be described as disgraceful. Nobody can dispute that without Macleod, the names of Banting and Best would have never appeared in the history of insulin.

The vital contributions and guidance by Macleod are amply demonstrated in Bliss's work. He taught Banting and Best almost everything before Collip's arrival. It would be difficult to deny that when Banting first came to Macleod he was without exaggerating a "tabula rasa". He had read an article, conceived an idea without acknowledging at this time that it had been attempted before. He was unaware that science had progressed to the point that there was a possibility for success where all others had failed in the past.

Insulin as a hormone influencing the sugar metabolism had already been discovered and studied by Kleiner and foremost by Paulescu, but not surprisingly, our young heroes were unaware of this, in part because they were incapable of understanding a scientific paper published in French.

Macleod spent almost one month advising these ignorant young men as Banting's own notes of 9-14 June confirm. The story that he left them alone without supervision almost immediately after their arrival is simply not true.

Macleod taught them how to perform a pancreatectomy, how to obtain an extract of the pancreatic tissue, the use of alcohol for extraction, the use of the evaporation method for removing the excess of alcohol, etc. Before leaving for Scotland Macleod had given them important and precise "parting instructions" according to Bliss, including the use of alcohol after "freezing the pancreas at the lowest possible temperature" for the extraction of the "mysterious" inner secretion of the pancreas. We do not intend to recite all the help the young scientists received

from Macleod but rather to show how ungrateful they were for his patient guidance. Most of the advice he gave is included in Macleod's "History of the Researches leading to the Discovery of Insulin" (1922), hidden by the University of Toronto (in order to protect the sanctity of Banting and Best) and published only in 1978 by Lloyd G. Stevenson, following the death of Best.

Prior to Collip's arrival Macleod certainly was the brain of this scientific undertaking and Bliss deserves our praise for demonstrating this.

Our only criticism of Macleod is that at that time it appears that he was not aware of the role of the enterokinase in converting the trypsinogen into trypsin and that he apparently did not explain in simple, understandable words to Banting and Best the significance of Paulescu's findings, this last opinion being also shared by Bliss.

It is to Bliss' honor that he shows how shamelessly Banting behaved towards Macleod. The most reprehensible case would be his boorish behavior in response to an incorrect interpretation of a brief response given by Macleod to a reporter about an article by Bayliss. Banting, according to Clark Noble, entered Macleod's office, sat in a chair opposite Macleod, put his feet up on the desk and demanded an immediate denial (Bliss, p. 195). The hateful campaign by Banting against Macleod and vividly presented by Bliss is more than disgusting, it is nauseating and shameful.

For presenting a true picture of this great scientist, so often maligned by Banting's fanatic admirers, Bliss deserves our utmost respect.

Perhaps Bliss' wisest words are when he describes the ferocity, I would say the boorish savageness, of Banting's attacks on Macleod that only a superman could have endured; and to quote his concluding words: "*They did not realize that those who understood history would eventually come to honor all of them. Above all we honor their achievements*".

Final Comments

Nobody can dispute the fact that Bliss' work "The Discovery of Insulin" is the most complete and best-documented study on this subject. Years of research were required in order to complete such a task. Also, the author has a rare talent to analyze the myriad events and many researchers involved in these epic events, and above all the ability to pass judgment on human conflict.

Nobody could have done better, but human nature is not perfect. As such, certain lapses and errors of judgment should be expected, but these should not diminish the stature of the author.

The subject of our essay is C. Paulescu and his work, and unfortunately it is here that Bliss commits what we consider a few errors, both factual and of judgment. It isn't surprising that Bliss is not very well acquainted with this researcher from a

distant, little known country. After all Paulescu is the only non-Anglo-Saxon in this drama and furthermore he wrote everything in French and according to French customs.

Some of Bliss' critiques are justified, but some are in our opinion erroneous. As we are presenting Paulescu's role, it was unavoidable to take exception and criticize them. To be a respectable critic is an art only few possess and perhaps we could have done a better job.

Being aware of this possible shortcoming in our work, I nevertheless believe that the criticisms presented in this essay are based on historical veracity, to which we are committed in our attempt to reestablish the merits of Paulescu and his place in the discovery of Insulin.

We regret that in the process of defending Paulescu we were unavoidably committed to also present some inevitable criticism, not of the author, but of certain aspects of his work.

It is by now obvious to us that the Insulin has been discovered thanks to the work of many researchers, beginning with von Mering and Minkowski in 1889. *In our view the most significant contributions were made by Paulescu (1915-1921), with regard to the functions of insulin in the body's metabolisms, among many other contributions to Medical Science; and by Collip (1921-1922) who, besides other very important discoveries, was the first to succeed in sufficiently purifying the insulin for use in humans.*

POSTFACE

I should like to start my concluding remarks by quoting Dick Kleiner who wrote these moving words about his father Israel S. Kleiner:

> "My father had always waived the question when I asked him about his role in researching and discovering insulin. He was a scientist, he said, and the important thing was that the discovery had been made—not who made it. A true scientist wasn't interested in glory or money, he believed, but only in advancing the cause of science and helping humanity."[172]

One can only hope that more scientists will follow the example given by Kleiner.

When trying to analyze the events as they occurred, and trying to compare Bucharest with Toronto, it is obvious that the main difference was that Toronto succeeded in purifying insulin in a form that could safely be administered to human patients, while this cannot be said about Bucharest. The reason for this, in my opinion, is the fact that Toronto had Collip and advanced laboratory techniques, while Paulescu did not. Again, the fact that Toronto's work was a team effort might be relevant.

Before exploring the work of Paulescu I shall try to present what I consider his *main achievements*:

1 The pituitary gland (physiology and surgery).
2 Glycogen metabolism, the liver and insulin.
3 The extraction of insulin (1916) and the discovery of its physiological properties (1916-1921), this is the action of insulin at the global human metabolism level.
4 Surgical techniques: a) End to end ureter anastomosis.
5 b) Resection of pituitary gland
6 c) Technique of complete pancreatectomy.
7 d) Pancreatectomy plus removal of hepatic lobe.
8 Published works:

a) Lancereaux et Paulesco: Traité de Médicine, four published volumes Vol. 1, 1903, (940 pages), Vol. II, 1907 (1052 pages), Vol. III, 1912 (1200 pages) and Vol. IV, 1928.

b) Paulesco: Traité de Physiology médicale. Vol. I, 1919, (448 pages), Vol. II, 1920 (732 pages), Vol. III, 1921 (932 pages).

c) "Recherches sur le rôle du pancreas dans l'assimilation nutritive"
31 August 1921, in "Archives Internationales de Physiologie" (Liège

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[172] Dick Kleiner (on Internet).

et Paris).

9) About 90 scientific papers, many of great significance at that time and some still relevant today.

Obviously this is a personal, subjective assessment that can be disputed.[173]

When trying to judge the merits of the several protagonists in Toronto, my main guide-line was determining who shed new light on various problems and didn't merely confirm previous research, specifically in Bucharest (Paulescu) or at the Rockefeller Institute (Kleiner), without acknowledging this. While some, including myself can argue that Banting had done no more than Paulescu, actually less, nobody could dare say same thing about Collip.

Although I believe that one can reasonably say that prior to January 1922 Paulescu was ahead of Toronto (Banting and Best) the fact is that neither had succeeded in sufficiently purifying insulin for use in humans. As even admitted by Banting and Best on a few occasions it was only with the arrival of Collip that their results were better than those of previous investigators.[174]

As already mentioned Collip states quite clearly that "the preparation of the extract was carried out *exclusively* by the writer."[175] (See the full text in our note 82). He used different techniques, a different approach and in record time (12 December-23 January) he not only purified the insulin so that it could safely be given to Leonard Thompson, but was also able to confirm many of Paulescu's findings regarding the role of insulin in various areas of metabolism, and even more.[176]

In my humble opinion Collip deserves to be considered the main architect of the great success in Toronto.

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[173] Ionescu-Tîrgoviste et al, (fn13), pp.288-289, also adds the following achievements by Paulescu: 1) Surgery and experiments on the thyroid gland, ruling out the then prevailing concept that thyroid was a desintoxication center. He proved it was an endocrine gland producing a substance necessary for the nutrition of the nervous system. 2) Surgery and experiments on the spleen.3) He demonstrated the anatomical structure of the spleen and ruled out any connection to the biliary secretion. 4) Extirpation of adrenal glands that he considered assimilating glands. 5) Treatment of aorta aneurysm by subcutaneous injections of gelatinous solutions (together with Lancereaux). 6) Using chloral hydrate in typhoid fever. 7) Work on pathogenesis and treatment of fever and use of Aspirin. 8) Ruled out the claimed veracity of Ambard's laws.

[174] Alison Li (fn 70), J. B. Collip, p. 33.

[175] Collip James Bertram, J. Biol. Chem., 1923, Baltimore, vol. 55, p. XL-XLI, Scientific Proceedings XVII: "In the critical first weeks of clinical trial of insulin the Preparation of the extract was carried out exclusively by the writer; the method applied in the preparation of the first insulin used in the treatment of clinical cases was developed by the writer during December and January last".

[176] Although he was not a physician he diagnosed and treated a new clinical entity, later known as "Insulin shock", due to hypoglycemia. But foremost, he was able to penetrate the last barrier and develop a pancreatic extract safe for human diabetics.

Again in my judgement the most advanced scientist prior to Collip was Nicolae Paulescu and his achievements were no less remarkable and he displayed a genius equal to that of the younger Collip.

Not only did he achieve more than the others did, but also he did this with less sophisticated means at his disposal. He provides us with a splendid example as to how human ingenuity and perseverance can overcome even the greatest handicaps. He not only published his in some respects superior results 7 months prior to Banting, but very importantly, he covered a much larger field of the body's metabolism. During the years 1920-1921, as already stated, one could rightly state that he was the leading researcher in this field.

Paulescu's main contribution was best expressed by Sir George Alberti (already quoted in our text):

> "*He was the first to describe the actions of what was later called insulin and demonstrated clearly that it was a hormone with actions on all aspects of metabolism. His experiments were rudely terminated when Bucharest was occupied in 1916. He was unable to publish his results or continue his experiments until well after the end of WW1*[177].

To this we should add his work on glycogen formation and storage in the liver during the years 1908-1916 and the encouraging preliminary work on insulin in 1916, which could only be published early in 1919 because of the war and enemy occupation of Romania. We should also keep in mind his important contributions to the study and surgery on the pituitary and thyroid glands and much more. Certainly all these accomplishments attest to his genius in many fields of medicine and physiology.

He was the undisputed leader in the field of diabetes research for a period of time. Things only changed with Collip's considerable advances in 1921-1922 culminating with the history making injection of 23 January 1922. What happened to Paulescu in 1923 and 1924, when he, out of touch with the great advances in this field in the Anglo-Saxon world, was tragically left behind is sad but irrelevant to our discussion.

Frequently in English language publications, Paulescu's results were presented as "inconclusive", much like those of Zülzer, Murlin, Scott and Kleiner. Obviously, this demonstrates how unfamiliar these authors were and still are with Paulescu's work. They completely ignore how conclusive Paulescu's findings were once you take into account how differently the Pflüger readings had to be interpreted (we have quoted the profound observations by Ian Murray in this regard). They completely ignore the immense contribution by Paulescu to the understanding of the complex

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177 Sir George Alberti, (fn 119)

effects of insulin on the various metabolisms of the body that remain valid even today as asserted by Sir George Alberti and already quoted above (this is not the case with I. Kleiner); also his important contributions regarding the complex nature of Glycogenesis. Bliss does not mention one single word in this context. But he is quick to stress Collip's discovering glycogen in the liver[178], although Collip did not attempt to understand its physiological significance as Paulescu did.

This could plausibly be considered in terms of a conspiracy of silence against Paulescu, or at least one that distorts and even occults his contributions.

As to Banting, we must admire his idealism, his faith in a "great idea" (actually a demonstration of his total ignorance in this field), his great efforts during the hot summer months and fall of 1921 and above all the passion and strength of his convictions. He certainly was a visionary and this gave him the power and impetus to push the project forward. Perhaps we should remember here the words of J. Stewart Mill: "a man with a conviction is worth 10 men with ideas". He certainly did not add much to our scientific knowledge, but he played a great role in medical history in great part thanks to the guidance of Macleod. Intellectually and scientifically however his contributions were almost nil in spite of Bliss' assertions that he discovered this or that, or that he realized another "breakthrough", etc. For unknown reasons Bliss refuses to acknowledge when discussing Banting, that other scientists had already made almost all of Banting's discoveries. In my opinion the only "new discovery" by Banting, one without any real significance, is when he went to collect pancreases of unborn calves at the local abattoir!

The great significance placed on Banting's "great idea" of tying and severing the pancreatic is a vast exaggeration to put it mildly. He read Barron's article where as we have demonstrated above, Barron gave a judicious historical review of this problem (tying the pancreatic duct) starting with Arnozen and Vaillard 36 years earlier on rabbits, and in particular by L. W. Ssobolew who had ligated the pancreatic ducts on cats, rabbits and dogs in 1901- 1902. Banting simply appropriated this "idea", claimed it was his inspiration and hoped that what was impossible in 1901-1902 (extraction of the inner secretion of the pancreas for medical treatment), might be possible in 1921. After all, he must have heard that great advances in physiology had been made in the meantime. He was not aware that it was possible to measure blood sugar levels and he had not heard of Kleiner's exciting results. He apparently only learned of Paulescu's even more important results in November, but was unable to understand them. But in an almost unbelievable fashion, he will brag about his "great idea" for the rest of his life. Not to mention that he knew nothing, like many others, about the trypsinogen-trypsin conversion in the intestine. This naturally implied that insulin could and should be

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[178] Michael Bliss, "Who discovered Insulin?", NIPS, Vol. I, Feb.1986.

extracted from the undigested adult pancreas, something he only discovered (we don't know how) after six months of unnecessary meandering (and this is a puzzle indeed!)

Unfortunately, his character when dealing with his rivals also left much to be desired. His "conspiracy of silence" about Paulescu's undeniable merits, and his revolting and unethical distortion of the latter's results lower him to the lowest possible level. Even worse appears to be the fact that he, inebriated with glory, never corrected himself. Best did indirectly apologize in his first letter to Pavel, but never in public. In his second letter, reproduced in our text, he cowardly avoids answering Pavel's questions, but not before claiming that Banting and himself were the true discoverers of insulin!

But one undeniable achievement is the simple important fact that Banting, perhaps because of his ignorance, initiated the sequence of events that culminated with Collip's epochal success. It does not matter whether it was wrongly conceived, wrongly executed and wrongly interpreted, it may have been pure luck, but this is how history was made.

I have already praised Israel Kleiner, both as a man and as a scientist. But our homage goes to all those who have participated in this great and noble endeavor for science, medicine and humanity, even if at times displaying their human imperfection and frailty. Here we include all those researchers, now forgotten, and particularly the scientist Nicolae C. Paulescu, who achieved so much with so little and who was subjected to so much injustice. Suffice to mention the cruel and distasteful falsification of his work by Banting and Best that had such tragic consequences for his reputation. It was enough that he had to struggle with outdated methods. His only advantage was the genius of his mind. He achieved more with the primitive tools at his disposal than any other researcher prior to Collip. No mere mortal could have done more in Romania in 1920-1922.

APPENDIX

The Tools.

While following the heroes of this unfolding struggle it is important to consider the tools at their disposal while conducting their experiments. When Banting first approached Macleod regarding his planned experiments he was intending to only use as a control the level of urinary sugar, as he had been taught at school. He was unaware that detection and measurement of glucose in blood had become possible and was in use.

The chemical identification of glucose in the urine was first achieved in 1815 by the French chemist M. E. Chevreuil[179]. At that point, the term *diabetes mellitus* was coined to distinguish "sugar diabetes" from *diabetes insipidus.*

It is generally accepted that blood sugar testing suitable for clinical use was introduced around 1911 with the Benedict Solution. It is known however that in 1907 Stanley Rossiter Benedict had devised a more cumbersome method for this purpose. An "old Fehling method" is also mentioned and Scott claims that in 1911 he used the dextrose to nitrogen ratio, the Lusk D/N ratio.[180]

In 1915 same Benedict introduced the Lewis-Benedict method. The same year Otto Folin had a new method that he improved in 1919 (Folin-Wu) and again in 1920.

Some sources indicate that it was Dr. Franklin McLean of the University of Chicago who introduced the first reliable method in 1914.

What we know for sure is that Israel S. Kleiner who published his results in 1919 had been using the Myers & Bailey modification of the 1915 Lewis & Benedict method as did Banting and Best in 1921. In November of the same year however they were the beneficiaries of the superior Schaffer-Hartmann method, just brought from USA by Collip. This new method required only 0.2 cc of blood, a tremendous advance.

About Paulescu we only know that he used the old, cumbersome Pflüger method requiring 25 cc for one single blood glucose determination.
The reason was quite simple: he could not afford the newer but more expensive methods. Nevertheless he was able to prove more than his better-funded rivals did. This is the hallmark of the human genius.

Those who labored before 1911 had to rely on urinary glucose, on clinical observation and often on sheer speculation. It is quite possible that in some cases attempts were abandoned because of signs of hyperglycemia being interpreted as

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[179] Note sur le sucre de diabétiques. Ann. Chim. 1815, 95, 319-320

[180] Scott, Aleita Hopping, "Great Scott - Ernest Lyman Scott's work with Insulin in 1911" The Scott Publishing Company, Bogota, New Jersey, Library of Congress, Catalog Number 72-80201, Copyright 1971 by the Scott Publishing Company, Bogota, NJ

signs of toxicity. This we shall never know.

Other Researchers

Eugène Gley in 1891-1892 and again in 1902 obtained a pancreatic extract with marked positive results. He obtained decisive results in causing a diabetic state by ligating the veins giving circulation to the pancreas, thus depriving the organism of the internal secretions of this gland. Very strangely he did not publish his results, but instead he delivered them in a sealed package on 20 February 1905 to the Biology Society of Paris. It was opened at his request only on 22 December 1922. Certainly a bizarre case.

Emmanuel Hédon from Montpellier in 1893 confirmed Mering's and Minkowski's already discussed findings. Later he will perform his *pancreatectomies in two stages* method, also chosen by Macleod for Banting's initial experiments. În 1898, *E. Hédon* proved that a pancreatic extract in glycerine and administered orally had no effect.

Also in 1883, *Caparelli* obtained a pancreatic extract from a dog, in physiological solution. When injected in the peritoneal cavity of a dog it caused a rapid drop (three hours) in the glucose excretion in urine. In some cases he even noticed its complete disappearance.

Again in 1883, *Fernando Ballistini*, in Italy, as well as *Ralfe, Sibley, Wood, Mackenzie* and *White,* in England experimented *on humans*. Ballistini, Sibley and Ralfe reported some "positive results", while the others only registered failures and gave up their reasearch.

Lisser, in Odessa, in 1896, experimented with rectal infusions of pancreatic extracts in physiological solution, claiming a difficult to believe diminution of glycosuria and polyuria.

Spillman, in 1896, tried in two cases an extract obtained by mechanical pressure, with doubtful results.

In 1897, *Thesen and Lauritzen* experimented *on humans* with pancreatic extracts given orally (50-300 gm daily). They realized that given orally their extracts caused nausea and patients refused to cooperate.

Again in 1897, *Hogounena* and *Doyon conducted* rigorous experiments by using pancreatic extracts given orally to depancreatised dogs but without success.

J. Blumenthal, in 1898, while experimenting on animals, but also on *diabetic patients* in terminal stages failed because of toxic side effects. He used pancreatic juice precipitated *in alcohol*. When using the intravenous route the animals died. When given subcutaneously it caused "only necrosis" (in animals *and man).* Certainly not an encouraging success.

The best known researchers after 1898 were *Gutman, R. Lépine, G.E.Laguesse, Karakascheff, Adelheim, Fraenkel, Eugene Lindsay Opie,* and *Cecil MacCallum.*

In 1891, *Lépine* and *Martz* experimented with an extract obtained from the lymph of a normal dog. When injected intravenously into a rabbit it caused a marked reduction of the urinary glucose.
Again in *1898, Ausset* in France and *Bormann* in Russia registered partial successes, while Vanni's and Burzagli's experiments in Italy ended in failure. *Ausset* used fresh extracts of veal on depancreatised *dogs* and on one occasion only, *on man. Bormann* utilized fried pancreas orally, then rectally, in form of infusions, and finally as subcutaneous injections. One of his patients gained 8 pounds in 6 weeks, following daily injections of his extract.

In 1900, one step forward was made by *Eugene Lindsay Opie* (1873–1971) in Baltimore, who noticed post mortem structural changes in Langerhans islands and realized their significance in Diabetes. Interestingly Leonida Ssobolew in Saint Petersburg in 1901 arrived independently at similar conclusions. Opie also noticed that these cells were about 3½ times as numerous in the tail or splenic portion of the organ as elsewhere. He also made the observation that whenever diabetes is caused by a lesion of the pancreas, the lesion always involves the islets; and conversely, whenever that organ is dideased, but diabetes is absent, the islets remain relatively free from involvement (Barron, p. 6).

No significant discoveries were made between 1898 and 1906. This period was marked by the emphasis given to the dietary treatment of diabetes. Only *Lépine* carried on, being convinced of the important role of the pancreas. However he assumed that this substance was discharged in the lymph and not into the blood.

Among many others who failed we can name E. Gley (1905), Dewitt (1906), Rennier and Fraser, in Aberdeen (1907), as well as Sjökuist (1908).

G. E. Laguesse and *Diamare* suggested, in 1893 and 1889, respectively, that this secretion could come from islets of the pancreas, described by Langerhans, already discussed earlier, in 1859. Some authors claim that the existence of an internal secretion of the pancreas was clearly established by the work of Laguesse and Diamare. Laguesse also had found that the pancreas of new born contained comparatively more islet cells than the pancreas of the adult.

Ernest *Henry Starling* introduced the term "hormone" in 1905.

In 1913, at Stanford University, *Edward Albert-Schäfer* uses for this hypothetical hormone, the name *"Insulin"* derived from the latin „insula". Later he will realize that this term had already been used in 1909 by *Jean de Meyer* (1878–1934).

During the years 1913-1922 the prevalent treatment was again dietary, represented by the great personalities of *Dr. Frederick Allen* and *Dr. Elliott P. Joslin*.

Experiments with ligature of Wirsung Canal

D'Arnozan, Charles Louis Xavier, and Louis *Vaillard* in 1884 ligated this canal in rabbits and noticed the atrophy of the pancreas, but no diabetes.
Vassale (1891) and *Schulz* (1900) experimented with similar results on guinea pigs.
Leonida W. Ssobolew, in 1902 in Saint Petersburg, (like Opie one year prior, during autopsies) noticed atrophy of acinary tissue following ligature of pancreatic ducts. By contrast Langerhans cells were not affected, at least for a few weeks.
Sauerbeck (1904), *Zunz* (1905), *Dewitt* (1912), *Laguesse* (1906),
S.G. Tschassownikow (1906) confirm these results in their similar experiments.
Lydia Dewitt (1906), *Aldo Massaglia* şi *Zanini* (1912) also fail to extract insulin after ligation of pancreatic duct.
Ernest Lyman Scott (1911) has already been discussed. He also failed to induce atrophy of acinar tissue. He will however be successful with undiluted alcoholic and also with aequous extracts. Because of resulting pyrexia he is forced to quit.

Experiments on Humans (parenteral).

Poorly documented mentions have been made of early experiments on human beings. We find that that in 1883, Ballistini, in Italy, as well as Ralfe, Sibley, Wood, Mackenzie and White, in England experimented *on humans*. *Ballistini, Sibley* and *Ralfe* raported some positive, unconfirmed results, while the others only registered failures and gave up their reasearch.

Blumenthal in 1898 tried unsuccessfully on animals, but also on *diabetic patients* in terminal stages. He failed because of toxic side effects as did *Ausset*, also in 1898.

The first authenticated experiment using the subcutaneous route was made by *Georg Ludwig Zülzer,* in Berlin on *21 June 1906* with obvious clinical success. It was repeated the next day but it was interrupted because no further extract was available. We have to keep in mind this important fact that prior to 1911 it was not possible to clinically determine the glucose level in blood, but only in urine. The following year he repeated his experiments on five diabetic patients, but this time the reactions were too severe and accordingly no further experiments took place. Again we cannot say whether these reactions were toxic or the result of induced hypoglycemia, then unknown. Remarkable is the fact that in one patient the glycosuria and acidosis disappeared for three days. In two patients a marked clinical improvement was noticed while the other patients showed "serious reactions".

J. Forschbach, at Minkowski's clinic, in Breslau this time, tried Zülzer's method on three patients and three dogs, but with no positive results. As such Forschbach too is forced to stop his experiments.

In 1916, *John R. Murling*, in the USA conducts similar experiments on animals but also *on one patient*. He too is stopped by toxic reactions

We discover on the Internet that in December 1921 *Charles Gardin* in France demonstrated on six persons, out of which four were diabetics – that a pancreatic extract from pigs and administered intravenously lowered the blood sugar. We were unable to find any further details.

Paulescu in 1922 tried his extract on two patients rectally, while Banting, the same year, is doing the same thing but orally. Both claimed some improvement but this is more than doubtful.

On 11 Jauary 1922, pancreatic extract prepared by Banting and Best is administered subcutaneously to poor Leonard, a diabetic adolescent, but with serious reactions to the patient and equally serious damage to *Banting'*s reputation as a physician and scientist.

A new chapter in Medicine in general and in the treatment of diabetes in particular began on *23 January1922,* when *Collip's extract* was administered to the patient Leonard, but this time it was well tolerated and effective. A glorious day in the history of Medicine and the beginning of a new era.

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