



## COMMENTS TO: RUBINO FRANCESCO, AMIEL STEPHANIE, “IS THE GUT THE ‘SWEET SPOT’ FOR THE TREATMENT OF DIABETES?”

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In a paper published in *Diabetes* issue from July 2014 by Rubino and Amiel<sup>1</sup> made a short portrait of Oscar Minkowski, mentioning that, after a contradictory discussion between this young researcher with his master Joseph von Mering regarding the role of pancreas in fat digestion, they decided to carry out a pancreatectomy in a normal dog. They did this together on Friday and because von Mering left Strassbourg that day, it remained for Minkowsky to return the next day to the laboratory to see what happened to the intestinal digestion of fats lacking the pancreatic enzymes. It was a hot summer and, in the lab where the dog's cage was placed, there were flies around and the floor was dirty. The lab assistant replied to his observation: “doctor, I cleaned the dog's cage many times because during the night, the dog urinated continuously”. With his clinical knowledge on polyuria, polyphagia of diabetic patients, Minkowski supposed that the dog had developed diabetes and the confirmation came when he tested the urine of the dog for glucose, which proved to be intensely positive. Minkowski repeated the pancreatectomy two more times, with the same results. After their publication in 1989, it remained that “pancreatic diabetes” was discovered by Oscar Minkowski whose portrait appeared on the cover of July issue of *Diabetes* alongside with his signature.

To be quite frank, we must remember that in 1877<sup>2</sup> the famous French clinician Etienne Lancereaux (1829–1910) published a paper in which for the first time, based on the three clinical autopsy observations, he noted a clear relationship between the pancreas alterations and diabetes. Moreover, in the following years, he presented new cases in which he used the term “pancreatic

diabetes”. Finally, in another two papers published in 1883 and 1888, he succeeded in making a clear description of the two main types of diabetes of which are called type 1 and type 2 diabetes, under the name of “slim” diabetes (or pancreatic diabetes) and “fat” diabetes (or constitutional diabetes).

Here is a quotation of the concluding remarks from his paper<sup>3</sup>;

*“In summary, the diabetes mellitus, as it is understood today, is not an univocal disease, this name standing for different morbid forms, among these, there is one which, due to its sudden onset, intense clinical manifestations, rapid evolution and above all to the characteristic weight loss and pancreatic lesions, represent a different type of which we call **thin diabetes or pancreatic diabetes**. Besides this type of diabetes, there is another, not less distinct. Much more frequent than the former, this type is hereditary in this essence, it manifests initially by a persistent flow of nourishing state and pancreatic lesions are not generally common. Its duration is undetermined forming a syndrome which includes other pathological manifestations, especially chronic articular disease. We named it **“fat diabetes or constitutional diabetes”**”.*

Indeed the incidental experimental confirmation of the relationship between pancreas and diabetes have had the role to activate the research in the field, but later attempts of Minkowski to identify the supposed anti-diabetic hormone, failed. The discovery of this hormone has been achieved later between 1916 and 1921, but not by Banting and Best as the authors say without mentioning the publication of these authors for the simple fact that they did not publish anything before February 1922. In a paper in which they refer to be the only publication which demonstrated the existence of a pancreatic substance called “pancreine”, which

when injected intravenously in a diabetic dog lead to the decrease not only in blood and urinary glucose level but also reduction in blood and urinary ketones and urea levels which concludes that this hormone has anabolic effects on all fuels of the organism. Otherwise, already in 1912, Paulescu mentioned that the pancreas is a mixed organ with double function; one related to the external secretion of enzymes produced by acinar glands which arrives in the digestive tract, helping the digestion of carbohydrates, lipids and proteins in order to be absorbed then into the circulation and another deals with internal secretion, producing a hormone which stimulates the utilization of carbohydrates, lipids and proteins in the human body. Starting on this background, Paulescu conceived his experimental protocol with the aim of demonstrating that indeed his hypothesis has been punctually confirmed by the above mentioned anabolic effect of "**Pancreine**". It is interesting to know that the term "insulin" has been proposed by the Belgian physiologist Jean de Mayer in 1909, suggesting that when the anti-diabetic hormone will be discovered, that it will bear the name "insulin". Indeed in May 1922, Macleod used this term in a Physiology Congress in Washington D.C, when the discovery of insulin was announced, however without mentioning the two publications of Paulescu in 1921<sup>3,4</sup>.

It is interesting to know that one month before the discovery of insulin

announcement by MacLeod, in Bucharest, on 10th April 1922, Paulescu applied for a patent under the number 6255, entitled; "**Pancreine and the process of its production**".

"I give this name to the active principle discovered by me in the extract of the pancreas. Paulescu **Recherches sur le role du pancreas dans l'assimilation nutritive**. Archives Internationales de Physiologie, tom 17, Fascicule I: 86–109, 31 Aout 1921.

*This substance has remarkable properties- which, when injected into the blood of an animal rendered diabetic by extirpation of the pancreas produces:*

- a. a diminution or even a transient suppression of hyperglycaemia and glycosuria;
  - b. a diminution in blood and urinary urea;
  - c. a diminution in blood and urinary acetone;
- in order to isolate Pancreine as much as possible from others proteins, I proceed in the following manner:*

*Observing antiseptis carefully, I take a certain portion of the fresh pancreas from a recently sacrificed animal.*

*The gland is well minced in a Broyeur Latapie machine and sterilised in an oven.*

*To this minced pancreas is added ten times its weight in distilled water, after which I shook it many times and introduced it into a cooler.*

*After several hours, 6–24, the minced pancreas is filtered through a sterile double gauze compress in order to remove the very voluminous solid parts.*

*The filtrate which is cloudy is more or less rose in colour and to it is added pure hydrochloric acid – 10 pp 1000 – which brings on an abundant protein precipitate.*

*The grey precipitate is separated with a sterile gauze filter and, as the liquid is acid it is neutralised using caustic soda.*

*Thus a new and abundant protein precipitate is produced.*

*The new precipitate is separated using a Berselius paper and sterilised.*

*The filtered liquid is clear and transparent and still gives a protein reaction.*

*Finally, the volume of this liquid is reduced by evaporation at a temperature which must not exceed 50° C.*

*In order that pancreine be used in the treatment of human diabetes, it must be prepared in large quantities – which requires a lot of capital.*

*In addition, it is absolutely necessary that strict measures for antiseptis be observed in making this preparation.*

*At the same time, all the physico-chemical requirements of the process must be carefully observed especially that the liquid temperature does not exceed 50° C.*

*If these diverse steps are not very rigorously followed, the medicine may become either a focus of infection thus bringing about a disaster or it loses its physiologic action.*

*In order to ensure the fulfilment of this fundamental condition of preparation – as well as to maintain the scientific standard of the product – thought it necessary to demand a patent.*

#### Claim

*I claim the invention of the organic pancreatic product, which, when injected into the blood, produces a diminution or even a transient suppression of the symptoms of diabetes.*

In conclusion: the first paper published by Banting and Best is dated February 1922<sup>7</sup> and their patent application has been made in 1923.

The historical achievements are normally based on the date of publication, and the scientific value of this. The both these criteria are in favor of N.C. Paulescu., and we hope that on centenary anniversary of insulin's discovery, will be necessary to celebrate in 2021 in Bucharest, the discovery of insulin and in 2022 in Toronto, the application in therapy of this discovery.

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