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Editorial
To Be Worthy of the Nobel Prize or to Get the Nobel Prize? That is the Shakespearean question

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Shortly after the inspired initiative of rewarding research work through the award of the Nobel Prize, this shining distinction became an emblem of scientific excellence. In the medical field, the intention of this prize's initiator was to reward a discovery capable of furthering both the knowledge of physiology and biology in general, as well as of the pathogenesis of disease, giving perspective on the development of new therapeutic approaches, as a consequence of the respective discovery. Most, though not all, of the Nobel Prizes awarded in the field of medicine have so far fulfilled these conditions.

Nicolae Constantin Paulescu
Nov 08, 1869 – July 19, 1931

In 1921, Paulescu published in two of the most widely circulated international journals a coherent set of experimental data, through which he demonstrated that the pancreas secretes a hormone, which he called 'Pancrein', for which he specified all the metabolic, physiological and pharmaco-dynamic properties that are currently known. (Paulescu 1921, 1921).

But few people are aware, and this is something even we were able to find out fairly late, that in order to formulate his laborious program of experiments, Paulescu looked at diabetes in a paradigm different from that which interpreted this disease as being strictly a dysfunction of carbohydrate metabolism. On the basis of careful observation of the clinical and biochemical effects that pancreatectomy had on dogs, Paulescu understood that diabetes constitutes much more than a dysfunction of carbohydrate metabolism, since the dysfunctions he investigated reflected the failure of the entire energy metabolism (proteins, carbohydrates and lipids). As a consequence, his research program, characterized by an extremely meticulous conception and a similarly meticulous execution, brought forth the experimental proof attesting to the veracity of this new concept. It is only in this way that insulin was discovered, confirmed one by one the influence the hormone he discovered had on the entire energy metabolism.

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***For the *change of paradigm* and later on, for the *discovery of insulin*, which was in turn conditioned by this paradigm change, Paulescu ought to have received not one, but two Nobel Prizes. However, following Paulescu's latter accomplishment (the discovery of insulin), the Nobel Prize was awarded – in a context that nowadays seems very difficult to understand fully – to Federick Grant Banting and James Richard MacLeod, two arch-enemies who nurtured a deep-seated animosity for each other and did not share in the joy that worthy laureates of the Nobel Prize usually feel. As it turned out, this was to be only one more unfortunate incidents in the sometimes troubled history of the Nobel Prizes. Nevertheless, this later proved ominous not only for the officials who awarded the prize (the Nobel Committee, which would later be defeated and proved wrong by a concerted media campaign) but also for the winners of the prize (Banting and MacLeod), and at the same time obviously painful to the person to whom it should have been deservedly awarded (Paulescu), the prototype of the honest, dedicated and modest researcher.

One hundred years after the paradigm of Diabetes Mellitus was changed and described as a disease of the entire energy metabolism (Paulescu in 1912) and after 90 years that have passed since the confirmation of this paradigm through the discovery of insulin (again Paulescu, in 1921), when we reconstitute the events that followed, we find that besides the natural consequence of this discovery – the purification of the pancreatic extract done by Collip at the beginning of 1922 (Collip 1923) and the subsequent saving of millions of lives – one may say that on a theoretical level progress in the field of diabetes research experienced a delay of at least 70 years. And this can be explained by the superficial thinking of the people who unjustly pretended to be the authors of Paulescu's discovery of insulin and who never realized that this discovery was preceded and conditioned by the change of the paradigm of the disease. This is why the respective group continued to conceive diabetes in the old paradigm in which they shrouded their chaotic experiments, not only those of 1921, but also the subsequent ones, in which the only indicator of the disease and of diabetes was the lowering of the level of glucose in the blood and urine.

The restriction of the perspective of the pathogenic character of diabetes to the study of blood sugar (an illustration of the concept of *glucocentricity in diabetes*) continued to dominate the diabetological thinking long after 1921. One can hardly understand why the remnant side of this manner of thinking continues to manifest its reverberations even nowadays, when diabetes mellitus is defined quite often, even in important treaties, as being characterized by hyperglycemia. In fact, blood sugar testing is still the unique criterion of diagnosing diabetes, one that we have been continually trying to modify and complete, so far without success (CIT 1996).

The Nobel Prize for medicine awarded in 1923 to Banting and MacLeod mistakenly conferred on the Canadian group the credibility that, in a manner that was at once obviously inevitable and deliberate, has hitherto hindered an accurate understanding of the research carried out by other scientists before them. The effect was devastating. Since the most valuable and advanced research

dealing with the endocrine function of the pancreas published at the time belonged solely to Paulescu, the interest to obstruct its results was vital for the rival group. The proof of this is the fact that after Banting and Best's quoting of Paulescu's papers in February 1922, in none of their subsequent papers was Paulescu's name cited among the sources, with the likely intention of not suggesting to anyone the idea of consulting his papers. This was how a thick and heavy curtain fell over Paulescu's masterly work, while during the two world wars – a period that Paulescu spent in Europe, far from them – the beneficiaries enjoyed the economic force which they later held on tight to, and thus Banting and Best, the false gods of diabetology (the foremost figures of Canadian historiography until the '70s) were able to stand on the polished wooden pedestal built overnight. Unfortunately, before the wood of the pedestal crumbled, in a haste that was itself foreboding, the American Diabetes Association prepared another platform for Banting, calling for the establishment of a 'Banting Memorial Lecture', which would be held annually at the congresses of this prestigious association. We do not believe that such a controversial figure, who was more famous for his capricious behavior rather than his scientific achievement in his own time, should have become the emblem of North-American Diabetology. In 1971 Prof. I. Pavel wrote to the president of the American Diabetes Association, saying that the use of Banting's name as an emblem of the North American Diabetology does not honor in the least the prestigious association he was leading. The answer received from North America stated that it would be unrealistic for anyone to believe that the changing the title of the Memorial Banting Lecture was still possible. It is thus obvious that the deadweight called Banting will continue to hang heavy on the neck of the North American Diabetology. To think that '*Banting Memorial Lecture*' is equivalent to '*Claude Bernard Lecture,*' an honor conferred every year by the European Association of Diabetes and to mention the two names one near the other (Grant Banting and Claude Bernard) as an expression of the essence of Diabetology can only be considered as misguided.

In spite of all this, one of the farces that history played on the Canadian group is the fact that the discovery of insulin was dated in time in the year of 1921, a year when the only researcher who published data on the pancreatic endocrine secretion, and this data that is still valid even nowadays, was Nicolae Paulescu. His two publications from that fateful year appeared in extremely reputable international journals. The most important among these publications, *Archive Internationale de Physiologie,* is dated 31st August 1921, a journal that gathered among its editorial committee the most prestigious personalities of the time, some of them laureates of the Nobel Prize themselves, such as Ivan Pavlov, Maurice Arthus, Willem Einthoven, Charles Richet, Jules Bordet, Ernest Wertheim et al. It is worth mentioning that from the numerous researchers who at the beginning of the 20th century were devoted to the study of the endocrine secretion, be they European (for instance Zulzer, Eugen Gley or Oskar Minkowski) or North American (E.L. Scott, R. Murlin or I. Kleiner) all of them, bar none, had to abandon their research of the pancreatic endocrine secretion because of the

difficulties they encountered when they attempted to purify the pancreatic extract and to characterize it in a convincing manner. This was probably the most difficult problem to solve, one that required a long and painstaking effort, and the fact that in the end the person who managed to unravel the mysteries of the pancreatic endocrine secretion was Paulescu was explained by his unabated perseverance during two decades of steady work. In the end, this work bore the fruits that the scientific community had expected, despite the fact that there was a certain period when the results of his work were unduly claimed by others.

When the celebration of the discovery of insulin takes place by relating this groundbreaking discovery to the year of 1921, the names Banting and Best should automatically come in second, because their first publication on this theme, of slightly lesser value than Paulescu's material, appeared 8 months later, in February 1922. As it happened, the month of February coincided with the date when the pancreatic extract was introduced in therapeutic practice, further complicating the tiebreaker that ought to have been used to differentiate between the two distinct stages: the discovery of insulin and its use in medical practice. But this stage unquestionably belongs to Collip, who by refining the method of extracting the unknown active 'principle' from the aforementioned extract, was able to deliver small quantities of the product, which was used in the treatment of diabetes until the end of 1922, when the method was taken over by a company called Eli Lilly in Indianapolis. This company imagined a new method, applicable on an industrial scale. To make matters worse, with the strong support of the University in Toronto, Banting also claimed to be responsible for the short but laborious and efficient activity of Collip. In any case, if the Canadians wish to celebrate an achievement that they can in all righteousness claim, then this is *the introduction of insulin in the therapy of diabetes*, which, since it occurred in practice in *1922*, will have to be celebrated every time one year after the celebration of the discovery of insulin, and the names of James Bertram Collip and maybe Richard MacLeod, the man who selected Collip to solve this small, yet crucial step towards achieving the therapeutic use of insulin should be remembered as pivotal. Approaching the pathogenic character beyond the paradigm operated by Paulescu at the beginning of the previous century, that of diabetes being a disorder of the entire metabolism of the human body, we may infer the two missing links that we would need to consider in order to take a real step forwards: the first link is the development of a non-invasive method to assess the β-cellular mass, which will permit the validation of an idea resulted from clinical intuition, the idea according to which diabetes starts the moment when a β-pancreatic cell that undergoes the process of apoptosis can no longer be replaced by a new one, while the existing β cells, whose number becomes lower and lower, will not be able to completely take over the task imposed by the 'lipid intoxication' – common in obesity, metabolic syndrome and type 2 diabetes. We consider that the intracellular β-pancreatic substructure that restricts this adaptation is the Endoplasmic Reticulum, as results from our data that identify the 'primary cause' of diabetes in the incapacity of the β pancreatic cell to thoroughly use the proinsulin and the

proamilin, whose concentration in the β cell and in the systemic circulation will induce significant pathogenic modifications. In turn, this dysfunction will disable the secreting vesicles in the pancreatic β cells to mature in due time. All of the insulin-secreting dysfunctions that occur in the 'pre-hyperglycemic' stage of diabetes may be attributed to these secreting vesicles' incapacity of reaching maturity. This is where the second link comes into play, namely that of (b) understanding of the manner in which the surplus fat overflow is produced not only by the *hyperplasia* or *hypertrophy* of the already existing adipocytes, but also by an *ectopical* stacking up of lipids in the liver, myocardium, skeletal muscle, pancreas or other organs. The ever-growing gap between an immense mass of adipose cells that require an increased secretion of insulin and the β-cell mass, which gradually becomes smaller and smaller has become the subject of intense debate, one that we hope will be fully understood in the decades to come.

The duty of our generation is to indicate the direction which the science of diabetes ought to follow from now on. Our successors' duty is to discover the realms of science that the last generation has not managed to touch upon, the as of yet unknown fields that are at present inquired by the new generation within the intricate framework of the human genome. Genome White Association Studies has already identified 41 loci associated with type 2 diabetes. At the moment, all we have is a mere number and a few tiny stars shedding a pale light in the clear sky at the beginning of spring. What molecules influence the function of which genes and what role they play in the complicated machinery of the human body are questions that still await clear answers. A breakthrough in this direction has already been achieved (P + CIT 11). We are at present attempting to further this breakthrough, so that the already existing 'instruments of bio-informatics' may help us understand what happens in the utterly fascinating pancreatic β cell.