

The Discovery of Diabetes Mellitus and its Three Hormones: Insulin, Proinsulin and Preproinsulin

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Received date: December 15, 2023; **Accepted date:** December 26, 2023; **Published date:** January 09, 2024

Citation: Hans E Weber, (2024), The Discovery of Diabetes Mellitus and its Three Hormones: Insulin, Proinsulin and Preproinsulin, *J. Clinical Research and Clinical Trials*, 9(2); DOI: [10.31579/2693-4779/176](https://doi.org/10.31579/2693-4779/176)

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Abstract

As the discoverer of Preproinsulin, I became interested in the other landmark insulin-related discoveries. It is a story of great science. Many Nobel prizes were given but, unfortunately, it is also a story of intrigue, deception and politics. In this article, I want to outline my own personal perspectives, opinions, and thoughts about how these discoveries came about.

Keywords: diabetes mellitus; three hormones; insulin; proinsulin; preproinsulin; medicine

Summary

As the discoverer of Preproinsulin [1], I became interested in the other landmark insulin-related discoveries. It is a story of great science. Many Nobel prizes were given but, unfortunately, it is also a story of intrigue, deception and politics. In this article, I want to outline my own personal perspectives, opinions, and thoughts about how these discoveries came about.

1. The discovery of Diabetes mellitus and Insulin

Much of what I want to say concerning the discovery of Diabetes mellitus and Insulin has been expertly summarized by Alberto de Leiva-Hidalgo and Alejandra de Leiva-Perez in the “Nobel Prize of Physiology or Medicine, 1923: Controversies On the discovery of the antidiabetic Hormone” [2]. The term Diabetes comes from the Greeks. Apollonius of Memphis, around 300BC, coined the term Diabetes meaning siphon or passing through. Mellitus is a Latin word meaning sweet.

Modern history of insulin-related discovery begins with Paul Langerhans, a German medical student, who wrote his doctor's thesis at Charité Berlin in 1869 under Virchow and Cohnheim [3]. In his dissertation “Beiträge zur mikroskopischen Anatomie der Bauchspeicheldrüse” (pancreas), he describes how he found small irregularly formed polygonal cells (Zellen mit rundem Kern ohne Kernkörperchen, meist zu zweien oder in kleinen Gruppen zusammenliegend). He made no reference to what these numerous spots (Gruppen) in the pancreas of rabbits were good for. He contacted tuberculosis and died at age 40 in Fenchal, Madeira.

Oskar Minkowski (German), was born in 1858 in Lithuania, and wrote his doctorate thesis under Bernhard Naunyn in Königsberg. When Naunyn was promoted to full professor in Straßburg, Minkowski followed him. There, he discovered that Diabetes mellitus is closely linked to the pancreas. He removed a canine pancreas, and found that the dog constantly urinated and that the urine contained high amounts of sugar. He published his discoveries in 1889 and 1893. A letter written in 1926, where he himself describes the rather odd circumstances of how this discovery came about, was later found in Buenos Aires, where Minkowski's widow lived. Minkowski, who came from a prominent Jewish family, died in 1931 in Fürstenberg, Germany.

Soon, the hypothesis was proposed that a substance is being produced by the pancreas that prevents diabetes. Speculation was that the islets in the pancreas were the source of this substance. In 1893 the French histologist G.E. Laguesse called these spots “îlots de Langerhans” [4]. Thus, the ground was laid to experiment further to develop the substance in purer form and use it to combat diabetes. It was not an easy task. In 1900, Marcel Eugene Emile Gley (1857-1930), practicing in France, was the first to demonstrate the presence of the “antidiabetic principle” in extracts from “sclerosed pancreas”. He showed that a pancreatic extract, when given parenterally, can reduce symptoms of diabetes.

In 1906 Georg Zülzer, chief of Internal Medicine at a Berlin hospital, also experimented on diabetic dogs using pancreatic extracts and gave this extract which was called ‘Acomatol’ to a dying patient via injection. He continued his studies and worked with Hoffmann La-Roche on a purer form of this

extract. He obtained patents in Germany and the United States. Unfortunately, WWI broke out and he was enlisted. After 1918, it is unclear as to why he failed to further pursue his research. Malaria, myocarditis, envy by his colleagues in Berlin, as well as his Jewish heritage, may have played a role. He emigrated to the United States in 1934. Other researchers followed, mainly Americans, but none was able to reach satisfactory results, unable to keep a diabetic patient alive for a longer period.

Nicolas C. Paulescu was able to produce a more purified extract a few years later and named it 'Pancreina'. He succeeded with this and demonstrated that only subcutaneous and intravenous routes were effective. He obtained a patent in Romania in 1922.

Occurring exactly 100 years ago, in 1923, before the Nobel Prize was awarded to Banting and MacLeod, the following story—from the accounts of Leiva-Hidalgo and Leiva-Perez—is worth recounting: August Krogh, a Danish researcher, was awarded the Nobel Prize in 1920 for developing the "Krogh Principle". He probably had a significant influence on who should be awarded the Nobel Prize in 1923. His wife was diagnosed with diabetes in 1921. While Krogh was in the United States in 1922, he was informed by Dr. Joslin in Boston, about the Toronto team. He wrote to MacLeod, asking him about the possibility of producing insulin in Denmark. That endeavor led to a successful cooperation. Whether there was foul play or not by deciding to give the award to Banting and MacLeod is unclear, but doubts clearly exist. Krogh had made a deal with MacLeod in December of 1922. He was friends with Göran Liljestrand in Copenhagen (Liljestrand was Executive Secretary of the Nobel Committee since 1918).

Protests came in immediately by Zülzer, E.L. Scott (Chicago), J.R. Murlin (New York) and N.C. Paulescu. None of them were shortlisted. Minkowski and Gley did not protest as far as we know. But even Best, Banting's student, protested. In 1972, the Nobel Committee finally responded. There is a rule that nothing can be changed unless 50 years have passed. This resulted in changing the language to "the credit for having produced the pancreatic hormone in a practical available form" from "for the discovery of insulin".

Then who discovered insulin? In 1909 'insuline' was proposed by Belgian scientist Jean de Meyer and the name insulin was given by E.A. Sharper Schafer in 1916. In my opinion, the discovery of the actual hormone insulin is difficult to decide. Clearly, it was not Langerhans. Minkowski came closest. He laid the groundwork with his canine experiments by demonstrating that when the pancreas is removed the dog will die from uncontrolled diabetes. All others before Banting et al were great pioneers who all raced to purify the pancreatic extract and all deserve to be recognized. Gley was the first in this group.

Why all were not shortlisted for the Nobel Prize remains a mystery. Had too many years passed since their experiments? (Not in the case of Gley and Paulescu). Or were they just ignored? Or were they wrongly not considered because of their Jewish heritage (Minkowski, Zülzer), or outspoken anti-Semitism (Paulescu)? Were they just outfoxed by Krogh? We may never know.

The discovery of Proinsulin

The discovery of proinsulin is typically attributed to Donald Steiner, in 1967. As far as this author is aware of, there has never been a challenge in this regard. I want to raise some doubts, since I learned myself of the irregularities Steiner has used in connection with my discovery of preproinsulin and his failure to attribute proper credit.

Neither in his two articles published by him in 1967 nor in his Banting lecture given in 1976 [5] does Steiner state he discovered proinsulin. He mentions in his two articles published in 1967 [6,7], the work of Wang and Carpenter [8]. These researchers had already published a paper in 1965 in which they used the word proinsulin in their title. Apparently, somebody before Steiner knew something about proinsulin. Steiner only proposes a "probable precursor of insulin" and makes that somewhat awkward statement that Wang and Carpenter concluded that „proinsulin „ makes out less than 10% of the total insulin. But isn't insulin the most important molecule in the body anyway?

In his Banting lecture given in 1976, Steiner states that his studies on the biosynthesis of insulin began about 10 years prior, which would have been 1966. However, Wang and Carpenter spoke of 'proinsulin' already in 1965. Steiner omits their work in his references. One has to ask oneself: did he discover proinsulin? No doubt, he kept a busy laboratory and advanced insulin research with the help of brilliant collaborators, but, in my opinion, he cannot lay claim to discovery of that peptide. In his *Science* article from 1967 [7], he writes in the abstract the following sentence. "The name 'Proinsulin' is suggested for this protein". He also states in the same article, somewhat opaquely, that "it might be less cumbersome, therefore, to designate this material 'proinsulin'." I will later come back to these sentences.

The discovery of Preproinsulin

Steiner tried to claim that his laboratory discovered preproinsulin in an article in PNAS in 1976 [9] after I had discovered a larger precursor than proinsulin already in 1973. There he mentions me in reference but in his Banting lecture he omits me completely, whereas he quotes Lomedico and Permutt in his references. Both, I believe, worked with him after we had presented work in 1975 showing the translation of mRNA for insulin [10,11].

Why did he not mention me in his Banting lecture? Was it just plain oversight? Or was it deliberate? He had obtained enough information from me after he had invited me to dinner following my ten-minute talk at the Annual American Diabetes Association meeting in New York in 1975 on the in vitro translation of mRNA for insulin. He heard me proclaim in my lecture that I named this precursor "preproinsulin" I assume he wanted to be the discoverer. It is of interest that he states in his PNAS article from 1976 that "they designate that peptide preproinsulin". No word of the discovery or of the discoverer.

Did he not write a very similar sentence in his science article from 1967, titled "Insulin Biosynthesis: Evidence for a precursor": "the name proinsulin is suggested for this protein" or later in the discussion "therefore, to designate this material 'proinsulin'." Again, no word of discovery or discoverer.

In my opinion, Steiner intentionally failed to give proper attribution about my discovery of preproinsulin. A form of plagiarism, perhaps? He obtained information from me in a private conversation, used this information, copied it as his own and then labeled it as his own discovery. He never came up with the idea to translate mRNA (that is the originality). He never found this precursor doing any of the original experiments. I coined the name preproinsulin after having conducted multiple repeating experiments and then becoming convinced that there was indeed a precursor to proinsulin.

My Discovery of Preproinsulin in 1975

As a medical student in Munich, I became acquainted with a visiting American professor named Robert Shipp, who himself had insulin-

dependent diabetes. He helped me to advance my career in America. After a short fellowship at the Joslin Clinic in Boston, I worked with him in his laboratory in Omaha, Nebraska. After I had received an NIH research fellowship in immunology at UCLA in 1973, I very soon learned the techniques how to translate mRNA *in vitro*. Our chief, John Fahey, came from NIH and brought with him pure T-cell lines. He asked a very young professor and myself to use these cells and see whether they contained minute amounts of immunoglobulins or similar. Was this the hunt for the T-cell receptor?

The young professor and I split the work, each having our own lab. Our paper was accepted in a prestigious journal, except that one of the editors asked the professor to repeat one of his experiments. The professor then came to me and confessed that he had fabricated all of his work. He was demoted, not fired, and I was ruined academically, not to mention emotionally. I was so distraught by his confession that I quit the lab, gave up all research, and avoided any further contact with academia.

Fortunately, early on in the fall of 1973, I had the idea to translate the mRNA for insulin as well. I was young, full of energy and, I guess, was at the right place at the right time. I worked many nights alone and secretly, much to the dismay of the head of the department, who almost dismissed me. However, I continued because I had early success finding a precursor of proinsulin, an unexpected result. Naturally, I became further excited.

Thus, in the fall or winter of 1973 I had discovered a larger precursor. Two abstracts were published, one in 1974 and the second one in 1975 [12,13]. By early 1975, I was so convinced by my work on different animals that there was a definitive precursor, and wondered about the significance of this larger insulin molecule. For months I pondered it but, unfortunately, I did not come up with a good explanation. Too bad, but I was so convinced of my discovery that I named this molecule preproinsulin in the spring of 1975.

I then referred to this molecule as preproinsulin in my ten-minute talk at the Annual American Diabetes Association meeting in New York in 1975, although no record exists, as far as I know.

Over the last few years, I have learned so much more about my discovery of preproinsulin and its significance. Contrary to my thinking in 1975, where I could not come up with any usefulness as to why nature produces an even larger peptide after translation, I am now stunned by how important preproinsulin has become as a research tool. It starts with G. Blobel's work. He discovered the so-called Signal Theory, for which he received the Nobel Prize in 1999 [14]. Ironically, he published his seminal work in the same year preproinsulin was discovered. I only learned about it after he was awarded the prize.

Preproinsulin has been extensively used to understand transcription and translation. Recently, Jean-Yves Boulay from France introduced a new nomenclature proposal for the twenty proteinogenic amino acids using preproinsulin [15]. And most excitingly, lately preproinsulin (PPI) has been implicated as a self-antigen to cause insulin-dependent diabetes [16].

In summary, it is a fascinating story about one of the most important hormones. In the case who discovered proinsulin, I am putting forward a new theory. I tried to reach out to the families of Wang and Carpenter but without success. I am also surprised that these two researchers never challenged Steiner or published any other paper on this subject. My wish is that an independent research committee undertakes the task of finding out who the true discoverer of proinsulin really was.

In the case of my discovery of preproinsulin, I can only say I wish I could find my notes for my talk given in 1975 or that there exists a recording of my talk. The American Diabetes Association apparently lacks one. Steiner and his designated research PhD candidate have passed away. I have been in contact with Lomedico, who presented similar results in 1975, but only spoke of a precursor (Permutt, the third presenter died, he only spoke of a precursor as well). After I told Lomedico that I had succeeded already in the fall of 1973 to see a precursor, he never challenged my claim.

The controversies surrounding the discoveries of anti-diabetic hormone and/or insulin have been well documented and show the brilliance of many researchers to advance science and cure diseases, but also demonstrated the weakness of human nature, especially if the prize is the Nobel Prize.

The discovery of insulin itself, in my opinion, nobody can claim. There were many pancreatic extracts. They became over time more purified. Later on the full purification took place in pharmaceutical companies.

With regard to the discovery of proinsulin, I propose a committee should be formed or more research be done as to who truly discovered proinsulin. Over the years, I have repeatedly asked the American Diabetes Association to help, unfortunately to no avail. Should such effort confirm my doubts about the extent of Steiner's role and his candor, it would raise questions about his unattributed references to preproinsulin and its discovery. In any event, I believe my account of preproinsulin's discovery in 1975, and coining of the term—now universally used—sets the record straight.

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DOI:10.31579/2693-4779/176

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