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PERSPECTIVES

The roots of SGLT inhibition: Laurent-Guillaume de Koninck, Jean Servais Stas and Freiherr Josef von Mering

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SGLT inhibitors, are contemporaneously considered a "hot topic" in the field diabetology and as an introduction, it is commonplace for presentations on this topic to start with a historical retrospect on the discovery of phlorizin and its glucosuric effect. In point of fact, it was mentioned during the presentation of a major trial during the 2017 ADA Scientific Sessions, as well as in recent publications, that phlorizin was discovered by "French" chemists. The reality, however, is that phlorozin was discovered in Belgium by Belgian researchers. Furthermore, it is often cited that Josef von Mering discovered the glucosuric effect of phlorizin. Nonetheless, what is perhaps not so widely known is the fact that Freiherr Josef von Mering had already described the glucose lowering effect of phlorozin and had postulated that the action of phlorizin occurs in the kidney—a hypothesis which was latterly proven to be correct by Oscar Minkowski.

Hence, the roots of SGLT inhibition are actually Belgian and German and not, as is so often echoed, French.

Phlorizin was discovered by Laurent-Guillaume de Koninck together with Jean Servais Stas. De Koninck was born in Louvain on March 5th, 1809. At this time, Louvain was part of the French Empire, eventually becoming part of the Netherlands in 1814. Ultimately, the city of Louvain became a part of the Kingdom of Belgium following the "Belgian revolution" in 1830.

De Koninck studied in Louvain, graduating in Medicine, Pharmacy and Natural Sciences. His main interest, however, was chemistry. A grant, awarded by the Belgian government, gave him the opportunity, during the period of 1834–1835, to visit two of the most distinguished chemists of that time, Gay-Lussac in Paris and Justus Liebig in Giessen. He also visited laboratories in Berlin, Bonn, Magdeburg, Heidelberg, Jena and Göttingen—an early illustration of the efficacy of awarding travel grants to young European scientists [1].

Jean Servais Stas (1813–1891) received his M.D. in 1835 [2] and became assistant to his former professor of chemistry, Jean-Baptiste Van Mons (1765–1842). Van Mons himself was a renowned expert in pomology whose experiments on fruit trees, particularly pear trees, brought him much recognition. Here is where destiny, and luck, came into play—Van Mons also happened to own an apple nursery, and, when this nursery needed to be displanted, Stas and Van Mons's other assistant, De Koninck, were fortuitously supplied with a large supply of fresh apple tree roots. It was from these roots, or, more specifically the bark of these roots, that they isolated a crystalline glycoside which they named phloridzine—later called phlorizin.

De Koninck published the discovery, in German [3], in 1835. Customarily, however, the half page report on the discovery which was published in a French Journal is quoted as being the original publication. This report mentions Stas and de Konninck (sic!) [4]. Contemporary authors gave the distinction for the discovery of phlorizin to de Koninck and Stas as early as in May 1835 [5].

Stas continued his research on phlorizin. In 1837, he moved to Paris where he performed a detailed study on phlorizin, splitting it into phloretin and glucose [6]. De Koninck was employed by the University of Liège to teach chemistry. His main interest moved to palaeontology and he went on to become a renowned specialist of Palaeozoic fauna. Today a street in Liège is named in his honour.

De Koninck communicated that he had attempted to treat fever with phlorizin with "some success" [3]. Others had also experimented with phlorizin as an antipyretic and this may have been the reason why Prof. Freiherr Josef von Mering became interested in this substance half a century later. Von Mering, born in Cologne in 1849, worked in the University of Strassburg in the department of biochemistry headed by Prof. Hoppe-Seyler. The German University of Strassburg was, at the time, the best funded place for medical research

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Prof Freiherr von Mering—scientific "Grandfather" of SGLT 2 inhibitors and insulin

Prof Laurent-Guillaume de Koninck—the first to describe "Phloridzin" in 1835

in the German Empire, possibly the world—the German Emperor wanted to influence the local opinion in favour of Germany. It attracted a myriad of scientists who went on to achieve fame. Names such as Adolf Kussmaul, Friedrich Daniel von Recklinghausen, Hans Chiary, Bernhard Naunyn, Wilhelm Konrad Röntgen, Oswald von Schmiedeberg and Emil Fischer to name but a few were all associated with this prestigious place of learning.

Von Mering was interested in numerous different topics including pharmacology. For reasons which we may never know and without any hypothesis related to diabetes, Von Mering decided to administer phlorizin to dogs. By happenstance, he discovered glucosuria in dogs after oral and subcutaneous administration of phlorizin [7]. However, "*le hasard ne favorise que les esprits préparés*"—von Mering was, after all, an expert in diabetes research. It was following his stay in the distinguished Institute of Physiology in Leipzig, headed by Prof. Ludwig, that he published a superlative study about glucose metabolism [8].

In 1886, von Mering reported that phlorizin decreased glycaemia in dogs and assumed that the substance "may induce glucosuria by changing something in the kidney" [9]. He reported a year later that in people with diabetes (from Prof. Kussmaul's department) phlorizin (15–20 g) induced a glucosuria of 6–8% [10]. Von Mering noticed that his "phlorizin-diabetes" was very different from the disease diabetes due to the fact that in diabetes glucosuria occurred with hyperglycaemia whereas in "phlorizin-diabetes" glycaemia decreased with increasing glucosuria [10]. At a later stage Oskar Minkowski, in a straight forward experiment, proved that phlorizin acts in the kidney—he took the kidneys in healthy and pancreatectomised dogs out whereupon he observed that without the kidney, phlorizin lost its blood-glucose lowering effect [11].

In April 1889, von Mering met Oskar Minkowski—a young physician who had just arrived from Königsberg with Prof. Naunyn, the successor of Prof. Kussmaul. This meeting, which took place in the library of the Hoppe-Seylers institute of biochemistry, led to them working together to perform the pancreatectomy of a dog to study fat absorption. As a result of this procedure, pancreatic diabetes was discovered—serendipity again, much like the discovery of "phlorizin-diabetes" [12]. Minkowski tested the urine of the dog for glucose because the lab technician had reported polyuria in the dog. However, this particular dog, which was provided by von Mering, had been treated previously with phlorizin. This is the reason why Minkowski repeated the experiment with other dogs. The first two of these dogs did not survive but Minkowski persevered, with success.

Following the presentation of the discovery of pancreatic diabetes in the first world congress of physiology in Basel in September 1889, von Mering and Minkowski became famous worldwide. Despite their work and recognition,

only Oskar Minkowski continued with research in diabetology. Three reasons which may explain why von Mering did not continue diabetes research are, first, that following some unsuccessful applications Josef von Mering was nominated in 1890 in the University of Halle an der Saale and, therefore, moved with his wife and his four children from Strassburg to Halle in April 1891. The second reason is that in Halle he had signed up for an incredibly multitasking life—becoming director of the Medical Polyclinic (which included medical teaching), lecturing on otorhinolaryngology, medical chemistry and legal medicine as well as becoming head of department in a Catholic hospital in Halle. The third reason is that von Mering worked, with great success, in many different areas of research. He, together with the Noble prize winner Emil Fischer, discovered the first barbiturate. Indeed, von Mering also holds the accolade of having published the first clinical paper on paracetamol [13].

After a complex history and an ambiguous beginning involving Belgian apple roots, modifications to the phlorizin molecule have provided clinical diabetology with today's SGLT inhibitors.

130 years after von Mering's original discovery, the first clinical trial based upon this mechanism was published.

Compliance with ethical standards

Conflict of interest The author declares that they have no competing intrest.

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