

100 years of therapy with insulin in Lower Silesia, Poland

100 lat terapii insuliną na Dolnym Śląsku

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The important contribution to the history of diabetology made by scientists from Wrocław University (at that time Breslau) [1–13].

At 11 o'clock on 23 January 1922, insulin was given for the first time to a patient with diabetes, Leonard Thomson [12]. At that time outstanding scientists devoted to diabetology were employed (working) at Wrocław University. They discovered the aetiology of type 1 diabetes and created the foundations of modern therapy for the disease. One of them was Prof. Oskar Minkowski. He was the discoverer of the aetiology of type 1 diabetes, and he called it pancreas diabetes. Oskar Minkowski was born on 13 January 1858 in Alexoto (Kaunas/ Kowno) Lithuania. In 1929, Prof. Minkowski established the relationship between the pancreas and diabetes, a critical milestone in understanding the aetiology of the disease. In collaboration with Mehring, he published "Investigation of Diabetes after Pancreatectomy" to demonstrate, using a canine model, that retransplantation of fragments of a previously resected pancreas reverses symptoms of diabetes.

It therefore became evident that the pancreas secretes an anti-diabetic substance that regulates carbohydrate metabolism. As early as in 1888, Minkowski discovered acetone in the urine of diabetic patients and hence administered sodium bicarbonate to them. In 1909 he became the director of the outstanding Department (Clinic) of Internal Diseases at the Wrocław (Breslau) University, where he worked with great satisfaction and a sense of fulfilment until his retirement in 1926. However, it took as long as 30 years before insulin was discovered by Banting and Best from Canada. In 1922, Prof. Minkowski received from Banting and Best the first vial of insulin, which

he presented during his lecture to the students stating: "I have always hoped that I would be the father of insulin, but that dream did not come true. However, I am very pleased to learn that Banting and Best called me the grandfather of insulin."

In 1923, Prof. Minkowski organized, for the first time in Germany, the Insulin Committee. With the participation of others, he supervised the production of the first batches of crystal insulin (Hoechst-Altinsulin), and the first German pancreatic extracts of insulin, commercially available as early as the end of 1923. The years 1888–1921, the period during which Minkowski discovered the role of the pancreas in diabetes and diabetology, were called the era of Minkowski. Prof. Oskar Minkowski died on 18 June 1931 in the presence of his assistants.

Since 1966 a "Minkowski Award" has been given at EASD meetings to accomplished diabetologists for their achievements in diabetological research. Many editions of "Minkowski Symposia" have been organized in Kaunas, Minkowski's birthplace, and in Wrocław Minkowski's workplace. In Wrocław, Minkowski developed and nurtured a team of outstanding physician-scientists devoted to diabetology. The Department building survived the Second World War, and the lecture hall in which Minkowski presented the first bottle of insulin to students remains fully operational. Another building, in which he had his private outpatient Clinic, was also unscathed. One of the streets near the Department's building has been named Minkowski street.

In summary: Prof. Oskar Minkowski was the founding father of diabetology, who contributed enormously to the theory and practice of the field. Prof. Minkowski, in the years 1902–1925 has been a five-time Nobel Prize nominee, but he has never won despite richly deserving it.

Another giant of diabetology associated with Wrocław was Prof. Karl Stolte (1881–1951), a paediatric diabetologist, known as the pioneer of modern therapy of type 1 diabetes. From 1904 to 1909 he worked in Strasburg, Wrocław (Breslau), and Berlin. In 1909 he was employed in the Paediatric Department (Clinic) at Wrocław University under the tutelage of Prof. Adalbert Czerny. Prof. Karl Stolte is known as the pioneer of modern therapy of type 1 diabetes, which remains the standard therapy of type 1 diabetes [1, 3, 5, 11].

Prof. Stolte was the creator of the idea of patient self-control. He was the director of the Paediatric Department from 1916 to 1945, when he emigrated with all his patients after the end of the war [1, 10]. Beginning in 1929, only seven years after the discovery of insulin, Stolte developed the idea of intensive education of diabetic patients and their parents, of a “free diet”, and multiple, precisely calculated doses of short-acting insulin in children with type 1 diabetes [7]. Therefore, he preceded by about 50 years the current standard approach to therapy in type 1 diabetes. The key difference was that he monitored the glucose level in urine (the only method possible at that time) rather than in blood, as it is done today. Prof. Karl Stolte died in 1951, during a congress in Heidelberg, where he was inducted as an honorary member of the German Paediatric Association.

Professor Stolte firmly believed that diabetic patients should be treated in a much more individualized fashion than the experimental animals that receive exactly the same amount of food daily [1, 4, 7, 10]. He postulated treating patients with type 1 diabetes with insulin doses exactly matched to the patient’s needs and an unrestricted diet. As we all know, this need-adjusted insulin dosing became a universally accepted standard of care. He further insisted that treatment with multiple doses of insulin, appropriately calculated to meet the actual needs, results in the normal development of diabetic children, without any growth retardation, and with good metabolic control and vastly improved quality of life. In the early 1930s, Stolte began to emphasize the importance of education for patients and their families [7].

He published a comprehensive, periodically updated report: “Instructions for the Therapy of Children After Discharge from the Clinic”. However, diabetologists at that time did want, or were unable, to accept the concepts of Prof. Karl Stolte. His first report on the new therapy of type 1 diabetes: “Insulin Doses Adequate to the Need”, which reported on three-year observations, was met with enormous criticism, especially in Germany and Austria.

A prominent Viennese diabetologist, Carl von Noorden, called Prof. Stolte a heretic; he said that his proposed therapy for children and adolescents with type 1 diabetes was a crime, and that the obtained positive results of the therapy were pure luck. In this response, Stolte stressed that type 1 diabetes is a disease of a hormonal deficiency, and therefore the supplementation of insulin must result in the regression of the disease, without a need for dietary restrictions. He believed that the time of a restrictive diet was over and that full advantage should be taken of the availability of insulin with appropriate dosing. In 1939 he adamantly opposed the therapy of diabetic children

and adolescents with long-acting insulin. He postulated that therapy with insulin with proper dose adjustment (adaptation) to the actual requirement is possible only with quick- and short-acting insulin. He also believed that it would be ideal to treat diabetes without the need for frequent insulin injections. However, he recognized that this would be accomplished only in the distant future. He believed also that to recapitulate the physiological secretion of insulin in healthy people, it was necessary to administer multiple doses of insulin. Prof. Karl Stolte declared that, should another method with better therapeutic outcome be developed, he “would rapidly accept it. But for now, I will treat my patients according to my method with multiple daily doses of short-acting insulin, exactly calculated to the actual requirement and an unrestricted diet”. Indeed, paediatric diabetic patients treated according to this method, including simultaneous intensive education of the patients and their parents, developed normally and reached a normal height.

Because of very strong opposition, Prof. Stolte’s therapeutic method did not gain widespread application. This method was applied in children and adolescents, and later, gradually also in adults with type 1 diabetes only in Wrocław. As much as 30 years after Prof. Stolte’s death his pioneering contributions to the field of diabetology were widely recognized.

The Prof. Karl Stolte Award was, for the first time, given during the 25th German Diabetological Congress in 1990 in Düsseldorf. In February 1994, a commemorative plaque, in both Polish and German, was unveiled in the Endocrinological Department (Clinic) for Children and Adolescents in the presence of the Rector of Wrocław Medical University, the Presidents of the Polish and German Diabetological Associations, the Polish National Consultant for Diabetology, and representatives of the Diabetological Departments in Düsseldorf and in Wrocław. The sponsor of the plaque was one of the most accomplished diabetologists: Prof. Michael Berger (1944–2002). The plaque reads “In memory of Karl Stolte (1888–1951), the creator of intensive therapy with insulin. As a clinician, scientist, practitioner, and a role model for European paediatrics and diabetology”. Many positive comments were published in German medical magazines, and Prof. Renata Wasikowa was designated as successor of Prof. Karl Stolte.

In 2002, the International Symposium dedicated to the memory of Prof. Karl Stolte was organized in Hanover by Prof. Thomas Danne. It focused on therapy with personal insulin pumps in children with type 1 diabetes. The team from Wrocław Department of Endocrinology and Diabetology for Children and Adolescents was invited to the meeting. Its Chair, Prof. Renata Wasikowa, conducted the plenary lecture. In 1996, after the stay of Prof. Renata Wasikowa as a visiting professor in Düsseldorf in Prof. Berger’s Clinic, therapy with insulin pumps was introduced to diabetic children in the clinic in Wrocław. In Poland, therapy with pumps in children was used for the first time in Wrocław, even earlier than in Germany (Hanover).

In summary, Prof. Karl Stolte, a pioneer of modern therapy in diabetes, the creator of intensive education of diabetic patients and their families, was an outstanding scientist, a precursor to the currently used therapy of type 1 diabetes, and

an exceptional person. He developed his own highly original ideas, protested against unfounded critiques, and contributed enormously to the field of diabetology. However, first and foremost, he was an excellent physician caring for his young patients. He was a scientist who was about 50 years ahead of this time. Efficiently tolerating and rebuffing unjust criticism, he introduced intensive therapy with insulin, which is now used by diabetologists around the world (it is actually standard therapy in type 1 diabetes).

Prof. Alfred Lublin (1895–1956), who was born in Bishofsburg in Eastern Prussia, was another Silesian physician with significant contributions to diabetes, its diagnosis, and therapy. Professor Lublin joined Wrocław University Department (Clinic) led by Oskar Minkowski as an assistant professor in 1920. With Minkowski's guidance, Prof. Lublin investigated the pathogenesis of diabetes, in particular the metabolism of carbohydrates. In 1922 Prof. Lublin developed the micromethod of measuring acetone and beta-hydroxybutyric acid in the peripheral blood. From 1923 Prof. Alfred Lublin investigated the topic of ketoacidosis, and from 1924 the problem of gravidity in diabetic woman. In 1926 he published the report "The influence of Insulin on Carbohydrates in a Non-Diabetic Organism. Contribution to the Subject of Therapy with Insulin". He significantly expanded the knowledge about the influence of insulin on carbohydrate metabolism in healthy subjects.

In 1925 Prof. Lublin was promoted to Associate Professor, and in 1932 to full Professor (he was only 37 years old). In 1932,

together with Dr. Robert Kroner, Prof. Lublin published the book *Active Care in Diabetic Patients*. Together with Prof. Katsch, Prof. Lublin prepared a program for the therapy of diabetes with adequate insulin doses, an appropriate diet, physical activity, and education for the patients. The meteoric career of this extremely talented young scientist was dramatically interrupted in 1934 by the Nazis. Professor Alfred Lublin was dismissed from the University and forced to emigrate to Bolivia, where he worked as a doctor. After the end of the Second World War he planned to come back to Germany. He received an invitation from Prof. Katsch to the 500th Anniversary of the University in Greifswald. Unfortunately during arrangement of the necessary documents, he died of a cardiac infarct. As well as Prof. Lublin, there were many other very talented, outstanding assistants to Prof. Oskar Minkowski, such as Erich Frank, Adolf Magnus Levy, Ferdinand Blum, Georg Zulzer, Otto Meyerhof (received Nobel Prize Award), Fritz Albert Lipman, Konrad Bloch, Gharry Theresa, and Ferdinand Covi.

While commemorating the centennial of insulin discovery we have to keep in mind that the steady progress in diabetes therapy, notwithstanding this ground-breaking discovery, was not followed with other ones of this calibre, and understanding of the various types of diabetes remains elusive [12, 13]. Consequently, Nobel Prizes may still be awarded for deciphering their pathogenesis. The "Flame of Hope" was designed to burn outside the home of Banting in Ontario [12] until diabetes mellitus becomes a fully curable disease.

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