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Review

Oskar Minkowski: Discovery of the pancreatic origin of diabetes, 1889

R. Luft

Department of Endocrinology, Karolinska Hospital, Stockholm, Sweden

This year, we are celebrating the 100th anniversary of one of the greatest advances in the history of diabetes and of experimental medicine in general: the demonstration by Oskar Minkowski and Joseph von Mering that diabetes mellitus follows total extirpation of the pancreas. This discovery furnished the starting point for research, which eventually proved that the pancreas produces an internal secretion, and also led to the discovery of insulin and its use in the treatment of patients with diabetes.

In my presentation I shall concentrate on the main discoverer, Oskar Minkowski; on the discovery as such; and on its place in the debate around "who discovered insulin?".

Fig. 1. This photograph of Oskar Minkowski (1858-1931) is taken from Fischer I (1933) Biographisches Lexikon. Urban & Schwarzenberg, Berlin Vienna

Oskar Minkowski

Minkowski's history is that of a Jewish family of East-European origin, whose ambition was to give their children a chance to higher learning - a tradition which was to exert such a marked impact on the natural sciences in Central Europe and the USA before World War II and thereafter. He was born in Alexota near Kaunas in Lithuania-Russia on 13 January 1858. His father was a grain-trader, who moved his family to Königsberg (now Kaliningrad, USSR) to escape the policy of anti-semitic persecution adopted by the Czar's government. One of Oskar's brothers, Hermann, became a world-famous mathematician, professor in Zürich - where he was a mentor of Einstein - and later in Greifswald. One of Oskar Minkowski's children, Rudolph Leo, was an astronomer who moved to the USA in 1935, where he became a Professor at the University of California at Berkeley and also a member of the National Academy of Sciences.

Minkowski attended school in Kaunas and Königsberg; then studied medicine in Königsberg, Freiburg and Strassburg (now Strasbourg, France), graduating as doctor of medicine at the University of Königsberg in 1881. His mentor was Professor Bernhard Naunyn who was to determine the direction of Minkowski's medical career in the years to come. Minkowski followed Naunyn to Strassburg, where he became Associate Professor of Medicine in 1891. Obviously, Minkowski's performances as teacher and physician and his achievements as clinical investigator attracted attention also outside Strassburg, but it would take a surprisingly long time until he was promoted. He was turned down from a chair in Halle. From written reports it can be noted that this was so because he was of Jewish descent - although a converted Christian (Kaiser and Wölker, 1981). Between 1900-1905 he was chief physician at a community hospital in Köln, and in 1905 was named Professor of Medicine in Greifswald. Not until 1909, at the age of 51, did he became "ordinarius" Professor in Breslau (now Wroclaw, Poland) where he remained and retired in 1926. During his Breslau years he joined a team of physicians called to Moscow in 1923 to attend to Vladimir Lenin after his final stroke - a sign of his high international standing as a clinician. After his retirement he moved to Wiesbaden, and in 1931 finally made arrangements to go to Berlin where his married daughter resided. However, at that time his health broke down, and he died the same year at the Schloss-Sanatorium in Fürstenberg of bronchopneumonia and secondary thrombosis.

Minkowski was married to Marie Siegel. She survived him but - probably in 1941 - had to leave Germany because of the persecution of the Jews. Her escape was made possible by generous economic support

from Charles Best. She eventually settled in Buenos Aires, where she received assistance from Bernardo Houssay. I had the privilege of meeting her at Houssay's house during the celebration of his 70th birthday.

Minkowski happened to appear on the medical scene during a period when German medicine was on its way out of the idealism of its "Naturphilosophical" heritage toward a more empirical approach: the interpretation of physiological phenomena through direct observations and analysis of chemical aspects of physiological processes. Naunyn was one of the prime movers of this transition, and concentrated his interest on metabolic processes (Stoffwechsel) or metabolic pathology. He opened in Königsberg one of the first laboratories for experimental pathology. This environment, where experimental pathology was combined with clinical work, suited Naunyn's favourite pupil, Minkowski, and he readily adopted this new direction. This is well illustrated by so many of his scientific contributions, which one recalls with astonishment and admiration: e.g., the identification of beta-hydroxybutyric acid in the urine and its relation to fat metabolism; the lowered carbon dioxide tension of the blood in diabetic coma, and the introduction of alkali treatment for it; total removal of the liver in larger birds and its impact on metabolic processes, e.g., those of bile pigments, and the role of the liver in haemolytic jaundice. He described familial haemolytic anaemia and its origin in disturbance of blood pigments (Chauffard-Minkowski disease), and made important contributions to the field of gastric disease. He described Korsakoff's syndrome before Korsakoff, and suggested a pituitary origin of acromegaly (1887) three years before the publication of Pierre Marie.

These and other scientific discoveries - in addition to that of the pancreatic origin of diabetes - were accomplished before the turn of the century when Minkowski was 42 years old. It is obvious from reports and letters that he was considered to possess the rare combination of talents, a razor-sharp intelligence, intuition and the dexterity of a gifted surgeon. Naunyn said about him that "confronting his enormous intelligence, I strike sails". The giant in German surgery during the early part of this century, Sauerbruch, called Minkowski "the greatest experimental pathologist of his time".

Diabetes after total pancreatectomy - an illustration of serendipity

Serendipity is the ability to search for one thing and to end up by discovering another. The discovery of diabetes after pancreatectomy illustrates this in an excellent way. As Minkowski describes the situation:

He and a colleague at the University of Strassburg, Joseph von Mering (1849-1908), were discussing whether free fatty acids were essential for fat absorption, a problem which, at the time, occupied von Mering. The pancreas probably played a major role in the process, and von Mering had tried to resolve this by ligation of the pancreatic ducts, however without success. Minkowski proposed total pancratectomy in dogs to prove von Mering's theory, a procedure which the latter considered impossible to perform. However, Minkowski with experience of removal of the liver in birds - perhaps in youthful recklessness - asked von Mering to procure a dog for the purpose. von Mering did so the same day, and assisted Minkowski in the total removal of the pancreas. The operation, without any special preparations, was successful, and it was planned shortly to use the dog for von Mering's fat studies - von Mering had to leave the place for a few days. It is obvious that neither of them had in mind the possibility of diabetes appearing after pancreatectomy. While von Mering was absent, things happened which were to make medical history. As Minkowski reports in a second article in Zbl Klin Med 1889:

After extirpation of the pancreas in dogs, diabetes appears. It starts some days after the operation, and lasts for weeks until the death of the animal.

Glycosuria appears and, in addition, polyuria, marked thirst, severe hunger as well as severe weight loss and asthenia in spite of ample supply of nutrients.

One pancreatectomized dog after fasting for 48 h excreted 5-6% of sugar in the urine.

A 16 kg dog, on a pure meat diet, excreted daily one litre of urine containing 6-8% of sugar. After a glucose meal, urinary sugar transitorily reached a value of 13%, and most of the glucose given was excreted unchanged.

The urine of the operated animals also contained appreciable amounts of acetone.

Blood sugar was considerably elevated; in one dog it amounted to 0.30%, in a second one 0.46%.

The glycogen content of the organs virtually disappeared.

The solar plexus was not damaged during surgery and, therefore, the diabetic state must be regarded as a direct consequence of the removal of the pancreas.

Transfusion of blood from a diabetic dog into the vein of a healthy dog did not induce glycosuria in the latter.

Fat resorption was markedly hampered, and so was the utilization of administered protein.

This remarkably pertinent, precise report of a brilliant experiment was published in 1889 by von Mering and Minkowski in a paper occupying three-quarters of a page in Zbl Klin Med, followed by more extensive reports in Naunyn-Schmiedebergs Archive (1890) and in Arch Exp Pathol Pharmakol (1893). Minkowski should be credited with the priority of the discovery. von Mering, whose prior main contribution to diabetes research was the discovery of phloridzin diabetes, assisted at the first operation, but otherwise did not participate in the studies on the diabetic state. When going over the relevant literature, I did not find any claims by von Mering to the discovery. It is to Minkowski's credit that he put

von Mering's and his own name in alphabetical order on the first reports of the work.

It is of special interest that Minkowski later reported on transplantation experiments in dogs - confirmed by Hédon in Montpellier - in which he removed the greater part of the pancreas, and attached a small remaining piece, with intact blood supply, subcutaneously to the wall of the abdomen. No diabetes resulted until after this remnant was removed. This certainly strengthened Minkowski's suspicion that the pancreas produced "something" indispensable for carbohydrate metabolism elsewhere in the body, the lack of which caused diabetes.

Minkowski admittedly had not examined the pertinent literature before the first pancreatectomy, but later did so in detail. Two reports deserve special attention. In 1683, Conrad Brunner in his book "Experimenta circa pancreas" reported experiments in which he tried to remove the pancreas in dogs. One dog obviously demonstrated symptoms, i.a., polyuria which, in retrospect, might be ascribed to a diabetic state. N. De Dominicis in Münch. med. Wschr. in 1891 reported on pancreatectomies in dogs, in which he sometimes noted glycosuria. However, he expressed doubts that the pancreas per se would be of prime importance in diabetes.

Minkowski made his pioneering discovery more than a decade before the term hormone had been introduced, and endocrine physiology had been put on the map by Starling in 1902. Minkowski's original work, and that to follow, was a solid proof of the endocrine function of the pancreas.

As pointed out to me by Rachmiel Levine, Minkowski saw far ahead in the matter of defining and understanding the role of internal secretion in metabolic control. He and Naunyn even felt that the pancreatic internal secretion controlled the storage of glucose as glycogen rather than the utilization of glucose.

"Who discovered insulin?"

It was obvious from the experiments by Minkowski, and shortly afterwards those of Hédon that the absence of the pancreas was a prerequisite for diabetes. But by what mechanism? Laguesse already in 1893 had proposed that the islet cells of the pancreas - which he named the islets of Langerhans - might be involved in the regulation of carbohydrate metabolism. Eugen Opie in 1901 supplied another link by showing a possible connection between human diabetes and damage to the islets of Langerhans. From then on, it was generally believed that the islets of Langerhans produced the internal secretion of the pancreas, insulin, and that absence of this secretion was the key to diabetes. A host of investigators started endevours to isolate this secretory product. Minkowski himself tried unsuccessfully (1892), but later a number of scientists produced extracts of the pancreas which increased the utilization of glucose and had a blood sugar lowering effect in animals or patients with diabetes: e.g., Blumenthal in 1898, Zuelzer in 1908, and Paulesco in 1921. The extracts unfortunately also exerted toxic side effects. This period came to an end in 1921 with the extraction of insulin by Banting assisted by Best, which was then purified by Collip.

But who really discovered "insulin" and, thereby, complied with the prime condition for the Nobel prize worded in Mr. Alfred Nobel's will: "a discovery". To my mind, Minkowski presented the first proof of the impact of the pancreas in diabetes, and that the disease was the consequence of the lack of pancreatic substance transported by the blood stream. This work was the real impetus for all later work to extract insulin. It was certainly an original discovery, and the most important one in the history of diabetes.

Minkowski's contribution remains a monument in medical research. It complies with what the ageing Faust considered most desirable: "Es wird die Spur von seinen Erdetagen nicht in Äeonen untergehn". The mark of Minkowski's discovery has not effaced with time. Therefore, it is most appropriate to celebrate the centenary of this remarkable achievement.

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Prof. Dr. R. Luft
Department of Endocrinology
Karolinska Hospital
S-104 01 Stockholm