

# The Discovery of Pancreatic Diabetes

## THE ROLE OF OSCAR MINKOWSKI

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In 1889 von Mering and Minkowski reported that total pancreatectomy in dogs was followed by severe diabetes. This was a discovery of historic importance. It demonstrated that diabetes occurs in the absence of the pancreas; and this finding furnished the starting point for research which proved that this organ produces an internal secretion, thus leading to the discovery of insulin and its application to the treatment of patients suffering from diabetes. Studies on carbohydrate metabolism were considerably extended, and it became possible to demonstrate the role of the liver in this metabolism and the regulatory functions of hormones secreted by several endocrine glands in normal conditions and in diabetes. This work was done in the laboratory of the Medical Clinic at the University of Strassburg, under the direction of Professor B. Naunyn, who in his book "Erinnerungen, Gedanken und Meinungen" refers to it in a statement which can be translated as follows:

"The discovery of pancreatic diabetes by von Mering and Minkowski gave a powerful impetus to our experimental research in diabetes. They had had a conversation about the extirpation of the pancreas. Next day Minkowski recounted that von Mering had upheld the dogma, accepted since Claude Bernard, that animals did not survive total pancreatectomy. He, Minkowski, had main-

tained that in dogs survival was possible; what did I think about it? I said: 'Since you have been able to remove the liver, you will also be able to carry out the removal of the pancreas, and if geese survive the liver operation, dogs will come through this one with even greater ease.' The next day Minkowski performed the first pancreatectomy in my laboratory; Mering assisted and then left on a trip. When Minkowski returned to the laboratory, 24 hours later, he could already report that the dog had severe diabetes with 5 per cent sugar. Incidentally, as long as he was in Strassburg, Mering did not perform pancreatectomy on his own, nor did he attempt to, and took little interest in following up the discovery."

When Naunyn's book was published, Thierfelder, a pupil of von Mering, wrote the following letter to Minkowski on May 5, 1926:

"You will be surprised to receive a letter from me. In fact, a special circumstance makes me write to you. It has to do with the description of the discovery of pancreatic diabetes given by Naunyn on page 457 of his 'Erinnerungen' (Memoirs). That description is undoubtedly mistaken, or at least incomplete. It not only minimizes Mering's contribution to this discovery, it completely suppresses it. This cannot remain unanswered, because it is already becoming current in medical literature. Thus, in the book written to commemorate the sixtieth birthday of Ludolf Brauer (reprint

from the *Zentralblatt für Herz-und Gefäßkrankheiten*, 1925, p.2), Büdingen says: 'According to Naunyn, his great teacher, this discovery of genius should be attributed solely to Minkowski; von Mering only helped him in the operation.' Because of my friendship with von Mering while he lived, you will understand that it appears to me to be my duty to defend his interests also after his death. Would you not wish to make use of the occasion to correct Naunyn's version in some appropriate place?"

I asked Minkowski's wife, who is now living in Buenos Aires, for information about the discovery of pancreatic diabetes and she gave me a copy of the letter written by Minkowski in answer to Thierfelder. This letter, written from Breslau and dated May 8, 1926, says:

"You are not fair to Naunyn if you imagine that in his account of the discovery of pancreatic diabetes he has unjustly belittled von Mering's contribution. Naunyn, as director of the Institute where the work was carried out, and as editor of the *Archiv für experimentelle Pathologia und Pharmakologie* in which it was published, kept in touch with the development of this research and guided the authors of the manuscript. Thus all that he wrote in his memoirs in his desire to be 'truthful even to harshness,' was very familiar to him.

"Nothing is further from my mind than the wish to detract from von Mering's memory. I never quarreled with him; I was friendly with him until his death and I always felt grateful to him for having suggested the operation of pancreatectomy to me in a conversation we had. I do not think he had any grounds for complaint of my behavior, at any rate he never expressed any, either on his visit to me in Cologne shortly before his death or when I returned his visit in Halle. There were, however, good reasons (and he agreed with them) why all the communications on pancreatic diabetes, such as those to the Medical and Natural Science Society of Strassburg, the First International Congress of Physiology at Basel, the Assembly of Natural Science Research Workers at Heidelberg and the Congress of Internal Medicine at Leipzig, should be presented by myself alone, and also why our joint work in the *Archiv für experimentelle Pathologie und Pharmakologie* should have been written by me only. The same reasons explain why further work on diabetes should be conducted by me while von Mering, as far as I know, did no further experimental work on the problem.

"I am sorry I did not publish a detailed history of the discovery of pancreatic diabetes while von Mering was still alive, as he could only have confirmed my statements. It is not very pleasant for me to do so after his death because my account of the affair can easily be misinterpreted. Personalities seem to me to be of no importance compared with the value of positive results. However, your prejudice against Naunyn's statements forces me to describe exactly what happened as it has remained engraved in my memory.

"You know I worked in the laboratory of the Medical Clinic at Strassburg while von Mering was working at Hoppe-Seyler's Institute when you were an assistant there. One day in April 1889 I went over to your Institute to consult some chemical periodicals in your library, which were not available in our Clinic, and there I met von Mering, who shortly before had recommended 'Liparin,' an oil with 6 per cent free fatty acids, as a substitute for cod liver oil in the belief that its favorable therapeutic effects might be due to its free fatty acid content.

"Do you use Liparin frequently in your clinic?' von Mering asked me.

"Oh, no,' I answered. 'We give our patients only good fresh butter, not rancid oil.'

"Don't scoff,' he replied. 'Healthy men must split fats before absorbing them. If, however, the pancreas does not function properly, fats already split must be given.'

"Have you proved this experimentally?' I asked.

"That is not so easy,' he answered, 'since pancreatic lipolytic enzymes pass into the gut even if one ties the pancreatic duct.'

"Well, then,' I said, 'remove the whole pancreas!'

"That is an impossible operation,' he replied.

"As I did not know that Claude Bernard had stated that animals could not be kept alive after total pancreatectomy, and my youth led me to presumptuous overestimation of the results I had already obtained in my surgical experiments, I exclaimed: 'Bah! there are no impossible operations; pancreatectomy cannot be more difficult than hepatectomy; give me a dog and I will remove its pancreas today.'

"Good, I have dog which I can let you have now. So try it.'

"That same afternoon in Naunyn's laboratory, with von Mering's help, I took out his dog's pancreas. Perhaps, as a lucky coincidence, that particular animal possessed especially favorable anatomical conditions; they vary considerably in different animals. The whole gland was removed and the abdominal wall sutured; the animal remained alive and apparently well for nearly four weeks. I intended to return it to von Mering for his experiments on the utilization of fats, so I did not bother much about it; but because there was no suitable cage available it was kept tied up in one part of the laboratory. The day after the operation, von Mering had to go to Colmar urgently because his father-in-law was seriously ill with pneumonia. He had to stay there over a week. Meanwhile the dog, which was house-trained, very often micturated in the laboratory. I scolded the servant for not letting it out frequently enough, but he said: 'I do, but the animal is queer; as soon as it comes back it passes water again even if it has just done so outside.'

"This observation induced me to collect some of the urine in a pipette and do a Trommer's test. Finding the urine reduced strongly, I made a 10 per cent solution

with 1.5 cc. I still had in the pipette and found it contained 12 per cent sugar.

"I thought at first that the glycosuria might be due to the fact that von Mering had treated his dog for a long time with phloridzin. So I immediately pancreatectomized three more dogs with no sugar in their urine previous to the operation. The second and third animals died two days later of necrosis of the duodenum, but both had glycosuria before they died. The fourth animal survived and from the second day after pancreatectomy had a persistent diabetes just like the first animal's.

"It was then von Mering returned, but did not come at once to the laboratory. I met him again on the first of May, the Anniversary of the foundation of Strassburg University at the festival celebration in the auditorium. Purely by chance, I was sitting behind him and I said over his shoulder, 'Do you know, von Mering, that all pancreatectomized dogs become diabetic?'

" 'That's interesting,' he replied, 'we must follow up this question.'

"I then operated on a whole series of dogs, assisted sometimes, but not always, by von Mering. Once he tried to operate, but the animal died of hemorrhage on the operating table so he gave up trying.

"He took part in some of the work, in particular the glycogen determinations with which he was familiar. He was prevented by other circumstances from coming regularly to the laboratory of the medical clinic and he left me to finish the work alone. At the end of the semester I proposed to von Mering we should publish the results of our research together and that I would carry on the further conduct of the work alone. He agreed and also left me to prepare the manuscript of our work. When it was finished and ready for the press, von Mering was away on vacation and as I did not wish to delay its publication, I was unable to let him see it. Naunyn had no scruples about publishing the manuscript I had prepared in his *Archives*, so von Mering read the paper for the first time in proof and praised its make-up. Because I had written it, I put his name first, out of courtesy and also because von Mering was somewhat older than I and his name came before mine in alphabetical order. It is curious that because of that order, 'von Mering and Minkowski,' some have inferred that von Mering's contribution was necessarily greater than mine.

"Naunyn, who was in a position to judge, considered I had shared too much with von Mering in not keeping the work on diabetes for myself and leaving him to follow up the further work on fat absorption. I knew, however, that I owed the discovery of diabetes to a lucky accident, and that I had not, any more than von Mering, imagined until then the importance the pancreas had in carbohydrate metabolism. Moreover, perhaps I would never have tried the extirpation of the pancreas if that conversation with von Mering had not taken place. I thought it only decent to invite him to collaborate in the work on diabetes, and I have never omitted to place his name together with mine even in

recent times, as for example in my report on insulin in the Kissingen Congress of 1924.

"You must remember that in work done over many years I alone defended the doctrine of pancreatic diabetes and the internal secretion of the pancreas against many attacks, in particular against those of Edward Pflüger; also that I have contributed new proof of my ideas by experiments with transplants, duodenal extirpation, etc. In all these discussions von Mering took no part or interest. It is also peculiar, perhaps because he did not master the technique of pancreatectomy, or because he had no further interest in the problem, that he did not resume the work on fat absorption after pancreatectomy. With his consent, I suggested that Mr. Abelman in the laboratory of Naunyn's clinic should examine fat absorption after pancreatectomy. Later Burkhardt and Lombroso in my clinic in Greifswald busied themselves with this question which even today merits further research.

"I do not intend to publish this information. I shall, however, leave a copy of this letter in a suitable place, for at some future time a student of the history of diabetes may be interested in the true facts. Only if you or anybody else were to take a definite attitude against Naunyn's account, would I consider myself obliged to take action to clarify the circumstances."

It is not worth while to report or discuss the innumerable versions of the story of the discovery of pancreatic diabetes, some of which have been published while others have passed into the oral tradition of laboratories.

Professor E. Frank, now of Istanbul, and himself a pupil of Minkowski, is in possession of a copy of this letter and quotes its contents in his book written in 1949. The letter was deposited by Minkowski in the Medical Section of the "Schlesische Gesellschaft für Vaterländische Kultur" in Breslau. When Hitler came to power in 1933, the General Secretary of this section, Professor Rosenfeld (the same who coined the slogan, "The fats are burnt in the fire of the carbohydrates") and Professor Frank were asked to resign from membership. Professor Rosenfeld abstracted this document and, being an elderly man, gave it to Professor Frank.

Oscar Minkowski was born in Alexoten (Kowno, Russia) on January 13th, 1858, and in 1872 became a naturalized Prussian. He studied in the Gymnasium at Kowno from 1867 to 1872 and in the old Gymnasium of Königsberg. His inaugural thesis for the doctorate in medicine was accepted in 1881.

He was an assistant to Professor Naunyn in the Medical Clinic at Strassburg and later became Professor of Internal Medicine at Greifswald and afterwards at Breslau. He died in Fürstenberg (Mecklenburg) on June 18, 1931. Naunyn refers to Minkowski in his Memoirs in the following terms:

"In Minkowski I found a force of the greatest magnitude. When a student, he went back from Freiburg to his home in Königsberg, before taking the State Examination, and he asked me for a subject for his thesis. I proposed the following: Changes in the excitability of the psycho-motor cortex of the brain caused by experimental variations in the blood circulation. Perhaps the subject was the reason that no important results were obtained. In the course of this work, however, I came to appreciate Minkowski so much that when Stadelmann left I gave him the latter's position. This was a great acquisition for us, because Minkowski was a man of rare intelligence. The agility, clarity and universality of his mind, and the quickness and accuracy of his observations and opinions, endowed him with powers for exact judgment and for research in natural science. In his experimental work his great manual dexterity was very useful to him. It was surprising how easily he adapted himself to different circumstances. His elder brother, a business man of great ability, recounted to me how Oscar (my friend), when a student, frequently did his homework in his father's shop. Thus he sometimes saw samples of wheat which were passed from hand to hand. Not long after, his advice used to be asked and he would give his verdict with as much assurance and sometimes more accuracy than the experts. The removal of the liver and the removal of the pancreas were surgical achievements of the first quality, and several years passed after he had taught them before they were performed in other laboratories than my own. He had never done microscopic work; however, when we worked together on polycholic jaundice he prepared the slides and from the beginning he made them perfectly; I have never seen better sections. Already at that time we found the 'Kupfer cells,' before they were given Kupfer's name. When he was in Strassburg, a gentleman came to see me in whom I found a small polyp placed exactly on the anterior commissure of the larynx. It is very difficult to see these small tumors in this place and even more difficult to operate on them. As at that time there was nobody in Strassburg who cared to operate on this case, I asked Minkowski to do so. Minkowski, who had never even thought of operating on the larynx, laughed and would not do it. Finally, he made up his mind and practiced during a few days. About fifteen days later he told me he had 'removed the polyp completely and cleanly in one session.' 'It is not easy, but it can be done.' He was never interested in surgery; however, he was fascinated by problems. When a problem was suggested to him, with astounding acuteness he saw the decisive aspects and knew how to cope with them. Even today I 'dip my flag' to the powerful intelligence which endowed Minkowski for all this, but at times I overestimated his capacity. That spirit which pushes us into research and tortures us, and is only appeased by work done in its service, was not always alive in him and sometimes it was necessary to stimulate it. When it awoke, Minkowski worked powerfully; otherwise, my friend could also live without an absorbing task. Ambition and the wish for official places were foreign to him. Minkowski ar-

rived too late at a position which gave him independence and free reign to his genius. Even today I feel indignant when I think he was almost fifty years old when he obtained his first appointment. When eventually he went to Greifswald he was again passed by for many years, while places that were right for him were occupied by others. I was so annoyed by this that I decided to take a very unusual step. I sent a personal memorandum to the Prussian Minister of Education, in which I drew attention to the importance of Minkowski and to the fact that, in my opinion, this man of great worth was continually being passed over for incomprehensible reasons. I have cause to believe my request was given due attention in Berlin. In the meantime my friend found in Breslau a position worthy of him and a place where his genius could develop, but I still bear a grudge against the faculties of medicine who overlooked him for so long; my whole school suffered because its most outstanding member was forgotten. I was always having to exert my influence in favor of Minkowski to the detriment of others."

The discovery of pancreatic diabetes is usually considered as the result of chance; but luck favors those who deserve it, that is to say, those who are prepared to make use of it. The discovery was made in Naunyn's clinic, where diabetes was the main subject of study and where experimental work on problems of pathology and pharmacology was being done. A factor in this discovery was the boldness which youth sometimes brings to research, as was the case with Minkowski in 1889 and Banting in 1921. Minkowski's surgical ability and his previous training in experimental work made his achievement possible. The discovery was correctly understood from the beginning, and through many years Minkowski gave further proof of his interpretation of it by means of patient and cleverly performed experiments. He was not only an able man, he was also fair to von Mering and associated him in the publication of the results as was his due. Later both discoverers had distinguished scientific and medical careers. Undoubtedly, however, the discovery of pancreatic diabetes was due to Minkowski's determination and technical dexterity; it was he who removed the pancreas from a dog and found sugar in its urine. This experiment opened a new and fruitful era in the study of diabetes and its treatment, in metabolic research and in endocrinology.

Von Mering carried out a very distinguished scientific career; he discovered phloridzin diabetes and, in collaboration with Emil Fischer, he developed veronal. The true fact is that von Mering did not discover pancreatic diabetes nor did he do research in this field after his first publication with Minkowski.

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 THE MORAL RESPONSIBILITY TO BE INTELLIGIBLE

*Clinical research is predicated upon the belief that its significant results should be communicated and used by others. How miserably this is accomplished is any contemporary editor's tale of woe and any thoughtful reader's sorrow. The pseudo prestige of long and difficult words transcends the useful scientific term and diffuses widely through our papers. Simple things are made complicated and the complex is made incomprehensible. Chaos reigns. The so-called medical literature is stuffed to bursting with junk, written in a hopscotch style characterized by a Brownian movement of uncontrolled parts of speech, which seethe in restless unintelligibility. Every day we realize that the iron curtain which disbars us from sampling in adjacent fields of science is not so much the erudition of our colleagues as the tropical jungles of verbiage and gobbledegook in which this erudition lurks, unobserved save by the initiated. Has this unfortunate situation any corrective? If some small fraction of the time and effort which goes into the techniques of research were spent on study and perfection of the simple techniques of writing and speaking clearly, paths could be made in the jungle. Those who start late must read and study good models of exposition. Learn the simple rules: write, rewrite, delete, polish. For sage advice, Allbutt's "Notes on the Composition of Scientific Papers" has lost none of its cogency, and elegantly combines precept with example. For a contemporary view Gower's "Plain Words" is equally good. With such guides our scientific writing must improve. Correct grammar, thoughtfully combined with rhetoric, might lead through grace to that elusive quality, style, and make a worthy medium for telling of significant work.*

—From "A Testament of Duty," by William Bennett Bean, M.D., *Journal of Laboratory and Clinical Medicine*, January 1952.