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Review

The discovery of insulin

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ABSTRACT

The initiative for the work that led to the discovery of insulin in Toronto in 1921 came from Frederick G. Banting. He worked under the direction of John J. R. Macleod in the Institute of Physiology at the University of Toronto. He was assisted in his experimental program by the student Charles H. Best. In dogs with experimental diabetes, they demonstrated the blood sugar-lowering effect of pancreatic extracts. Thanks to the support of Macleod and the collaboration with James B. Collip, a biochemist from the University of Alberta who was on sabbatical in Toronto, the work was quickly crowned with success and the first applications of the extracts in humans became possible in January 1922. Soon after, in 1923, Banting and Macleod were awarded the Nobel Prize in Physiology or Medicine. Banting shared his half of the prize money with Best, while Macleod shared his half with Collip. That their research was successful in such a short time was due in large part to Banting's abilities as a surgeon, Best's enthusiasm as a student, Collip's abilities as a biochemist, and Macleod's guidance in bringing the group together and providing it with the necessary resources.

Introduction

In May 1921, the Canadians Frederick G. Banting and Charles H. Best began a series of experiments with pancreatic extracts, which led to the first applications in humans as early as January 1922. Insulin was introduced into the treatment of diabetes with clinical and social implications similar to those of the introduction of antibiotic therapy. The history of insulin is an impressive illustration of how advances in science and technology can lead to new and ever-improving treatments. For millions of people with diabetes mellitus, insulin ensured their survival, and at the same time it meant a new quality of life for people with diabetes.

Setting the stage for the discovery of insulin

Banting and Best experimented at a time and in an environment that was ripe for their discoveries [1]. Between 1893 and 1919, dozens of researchers developed a wide variety of pancreatic extracts to better understand the physiology of the endocrine pancreas and eventually to treat diabetes mellitus. The existence of this hormone – initially only postulated – was so obvious that the Belgian physiologist Jean de Meyer proposed the name "insulin" for this blood sugar-lowering principle as early as 1909. In the search for a therapy for diabetes mellitus, various researchers came close to breakthroughs well before the investigations in Toronto [2].

In February 1905, the French physiologist and endocrinologist Eugène Gley deposited a sealed envelope with the *Société de Biologie* in Paris containing a document entitled "Sur la sécretion interne du pancréas et son utilisation thérapeutique" [On the internal secretion of the pancreas and its therapeutic use], in which he described experiments he had performed on pancreatectomized dogs between 1890 and 1901. He wanted to test Gustave-Édouard Laguesse's hypothesis that the islets of Langerhans would secrete a substance that could lower the excretion of glucose through the urine. To this end, he first developed an aqueous pancreatic extract that, when administered to diabetic pancreatectomized dogs, reduced glucosuria and significantly improved diabetic symptoms.

In further experiments, he showed that the reduction was not due to the exocrine pancreas but instead to the islets of Langerhans. But it was not until 1922, after Banting and Best had published their discoveries, that he had the ominous envelope opened and read out. From today's perspective, Gley's secretive approach seems strange and incomprehensible. Apparently, this was not totally unusual at that time, if the author could not continue or complete his research for some reason.

At the beginning of the 20th century, Georg Ludwig Zülzer treated diabetic dogs in Berlin with alcoholic extracts from calf pancreases. As early as 1906, the first attempted treatment was given to a patient in a diabetic coma. The preparation used had been produced in a laboratory of the Berlin company Schering under the name Acomatol.

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Initially, the patient showed improvement, but then suffered severe side effects and died when the supply of Acomatol was exhausted. Zülzer subsequently conducted further experiments by injecting pancreatic extracts into five other diabetic patients, but the injections caused considerable fever, probably due to contamination. Other side effects that had already been observed in animal studies included tremors, sweating, and increased heart rate. From today's perspective, these symptoms would most likely be interpreted in the context of hypoglycemia.

Zülzer began a collaboration with Hoffmann-La Roche in 1911 and from then on was assisted by a chemist from the company, Camille Reuter. Finally, in 1914, he succeeded in producing larger quantities of a pancreatic extract from 114 kilograms of pancreatic tissue. Further experiments were not carried out, however, because at the beginning of World War I the hospital where Zülzer worked was converted into a military hospital. Zülzer himself was drafted. Although he had obtained patents in Germany, Great Britain and the USA, he was unable to resume his research after the war for various reasons.

At the University of Chicago, Ernest Lyman Scott studied pancreatic tissue extracts in his master's thesis written in 1911 and found a beneficial effect on glucosuria in pancreatectomized dogs. After completing his master's thesis, Scott moved to Kansas and then to Columbia University, but he did not resume his studies with pancreatic extracts. Although, he was later instrumental in developing methods for determining blood glucose.

At Rockefeller University, Israel Simon Kleiner studied pancreatic extracts in 1915. Kleiner demonstrated the blood sugar-lowering effect of intravenously administered pancreatic extracts in animal experiments. In his works, which were published in renowned journals from 1915 to 1919, he described essential principles of insulin action, in particular the triggering of hypoglycemia. However, his investigations were limited to animal experiments.

In 1916, the Romanian physiologist Nicolae Paulescu succeeded in demonstrating in extensive experiments the blood sugar-lowering and antiketogenic effect of an aqueous pancreatic extract he had obtained. He named the antidiabetic principle "Pancréine". He was never able to use it in humans due to significant local reactions and fever. Unfortunately, after an interruption caused by World War I, he could not resume his investigations until 1920. The following year, he published his results in three meeting reports of the Society of Biology in Bucharest and then, on August 31, 1921, in a more extensive publication in the *Archives Internationales de Physiologie, de Biochimie et de Biophysique* under the title "Recherches sur le rôle du pancreas dans l'assimilation nutritive" [Research on the role of the pancreas in nutrient assimilation]. In April 1922, he applied for a Romanian patent for his manufacturing process.

Banting's idea

Frederick Grant Banting, the son of a Canadian farmer, graduated from the University of Toronto in 1916 with a degree in medicine. Shortly after, he joined the Canadian Army and served as a medical officer during World War I. In the summer of 1920, he opened a practice in London, Ontario, about 150 kilometers west of Toronto. The practice was going badly, and Banting had to supplement the practice by teaching surgery and anatomy to medical students as a demonstrator at Western Ontario University in London.

In October 1920, while preparing a lecture on carbohydrate metabolism, Banting read an article by Moses Barron, an American pathologist, in *Surgery, Gynecology and Obstetrics* describing changes in the pancreas after experimental ligation of the pancreatic duct or after blockage of the duct by gallstones. Inspired, Banting developed the idea that by ligating the pancreatic duct and thereby inducing atrophy and degeneration of the exocrine tissue, it should be possible to obtain an islet cell extract without exposing the tissue to the destructive influence of pancreatic enzymes. In his notebook he wrote down: *"Diabetus. Ligate pancreatic ducts of dog. Keep dogs alive till acini degenerate leaving islets. Try to isolate internal secretion of these to relieve glycosuria."* The two misspellings (diabet**e**s and glycosur**i**a) are in keeping with the fact that, up to this point, Banting had been more inclined toward orthopedics than diabetes.

Fig. 1. Charles Herbert Best (left) und Frederick Grant Banting (right) with one of their experimental dogs (probably summer 1921).
[University of Toronto Archives; Public domain]

In order to implement his research ideas, Banting needed a laboratory and the facilities to perform animal experiments. He decided to take his idea to the University of Toronto to see the physiologist and diabetes expert, Prof. John James Rickard Macleod. Macleod was not particularly impressed by Banting, who at that time had no research experience, no publications, and not even a doctorate (which he only received in 1922!) [3]. Nevertheless, he gave him a chance and assigned Charles Herbert Best as his assistant. He was also provided a small laboratory and some experimental dogs (Fig. 1)

Best was still a student and was just about to finish his bachelor's degree in physiology and biochemistry. He and his close friend Edward Clark Noble were both to work as summer students in Macleod's lab and then begin a master's program at the University of Toronto in the fall. They reportedly flipped a coin for the job with Banting. Best won, and the plan was that he would assist Banting for the first month. Afterwards, Noble would take over. Having taken practically a month to learn his surgical duties, Best wanted to stay with Banting and continue the experiments he had just begun. Noble himself recalled this decision as follows: *"It was also agreed that we should change over at the month's end; however, when this time arrived, Best had become proficient in assisting Dr. Banting in his surgical techniques so it was mutually agreed, in the best interest of the experiments, that Best should continue to work out the full time with him."*

Banting and Best's experiments

In May 1921, Banting and Best began their first animal experiments, aiming to induce atrophy of the exocrine pancreatic tissue by

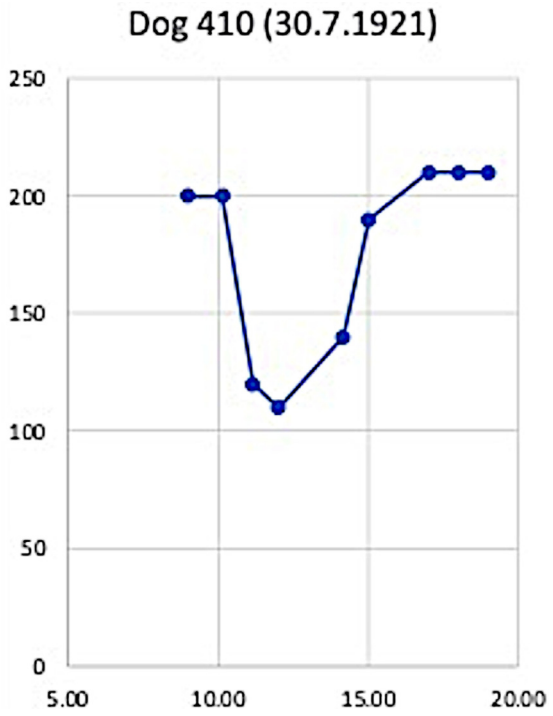

Fig. 2. On July 30, 1921, Banting and Best injected 4 cc of their extract into the dog 410. As a result, the blood sugar dropped from 200 mg/dl to 120 mg/dl. On administration of sugar through a stomach tube, the values rose again to the initial range.

ligating the pancreatic duct [4]. They hoped to subsequently extract the postulated blood glucose-lowering principle from the remaining islets of Langerhans. As inexperienced researchers, they had to overcome technical difficulties with the pancreatectomies and the ligation of the pancreatic duct. In addition, the glucose determinations in urine and blood also presented difficulties that had to be solved. Since quite a few dogs died during the procedures, they also bought street dogs, sometimes from rather dubious suppliers. In this difficult phase they were completely on their own because Macleod had left Toronto for a trip to Europe, which lasted several months.

On July 30, 1921, it all came together. They had a pancreatectomized dog with well-established diabetes, and they had two dogs in which the ducts had been successfully ligated so that they could prepare a suitable pancreatic extract. Thus, for the first time, they were able to inject a pancreatic extract intravenously into a pancreatectomized dog and document its blood sugar-lowering effect. Indeed, blood glucose dropped from 200 mg/dl to 110 mg/dl over about 2 hours (Fig. 2). Banting and Best experimented further and performed pancreatectomies or duct ligation on dogs in a rather unsystematic manner, prepared pancreatic extracts, injected the extracts into the diabetic dogs and documented the effect on blood glucose levels of the test animals. They also conducted certain control experiments in which they proved that extracts obtained in an analogous manner from other organs (liver, muscle) had no effect on blood glucose levels. In their notes from the beginning of August, they gave their extracts the name "Isletin" for the first time [5].

When Macleod returned to Toronto at the end of the summer, Banting presented their results to him. Macleod was somewhat skeptical and questioned some of the results, which infuriated Banting and resulted in a massive verbal conflict. Banting issued an ultimatum, threatening to leave the University of Toronto unless he was given better laboratory space and a permanent position for himself. Banting had been working without pay up to this point [6]. Within a few days, Macleod managed to find better laboratory facilities, a lab boy, and employment for Banting in pharmacology. Banting and Best were even retroactively financially compensated for their work.

November and December 1921 saw a number of groundbreaking new developments:

- Banting realized that they could not produce sufficient quantities of their extract from pancreases of dogs and decided to produce new extracts from pancreases of calf fetuses, which they obtained from slaughterhouses. They swiftly succeeded in proving their blood sugar-lowering effect. In addition, Banting and Best learned the methodology of alcohol extraction from Macleod. This meant that extracts could now be produced and tested in larger quantities and with higher potency.
- Macleod asked Banting and Best to present the experiments conducted at a local journal club on November 14. Banting was inexperienced as a presenter and uncertain. More confident, Macleod took over large parts of the presentation and Banting once again became annoyed with his supervisor. An important result of this otherwise somewhat unfortunate event was the suggestion of one participant to test for long-term experiments whether pancreatectomized dogs could be kept alive in the longer term by Isletin. On November 18, a pancreatectomy was performed on the dog Marjorie, who was kept alive with daily injections for 70 days. This long-term success was an important basis for subsequent testing in humans [7].
- On November 23, one of the researchers – presumably Banting – injected himself subcutaneously with an extract in a self-experiment: "One of us had 11/2 cc Berk. ext. subcut. No reaction." ("Berk." refers to Berkefeld filters used to sterilize the compound). There followed no other toxicity tests in humans.
- At Banting's suggestion, Macleod asked the biochemist James Bertram Collip, who was a professor in Edmonton at the University of Alberta on sabbatical in Toronto, to join the team in mid-December. Collip, as a biochemist, was quickly able to substantially improve the purification of the extracts with precipitation using concentrated alcohol.
- On December 30, the results were presented to a wider audience in New Haven at a meeting of the American Physiological Society. The program announced a presentation by Macleod, Banting, and Best on "The Beneficial Effects of Certain Pancreatic on Pancreatic Diabetes". Numerous critical comments and questions were raised in the discussion, and Banting once again seemed rather helpless in answering them [8]. Macleod had to support him. Many years later, Elliott Joslin recalled: "Banting spoke haltingly, Macleod beautifully". Banting himself was extremely disappointed by the reactions, and especially by the fact that his poor presentation had contributed much to the unflattering response.
- In February 1922, Banting and Best published these animal experimental results under the title "The Internal Secretion of the Pancreas" in the *Journal of Laboratory and Clinical Medicine*. In this work, they also cited Paulescu: *"He [Paulescu] states that injections into peripheral veins produce no effect and his experiments show that second injections do not produce such marked effect as the first".* Quite obviously this interpretation was wrong and in a letter to Professor Ion Pavel on October 15, 1969 Charles Best apologized: *"I regret very much that there was an error in our translation of Professor Paulescu's article. I cannot recollect, after this length of time, exactly what happened [. . .]. I do not remember whether we relied on our own poor French or whether we had a translation made. In any case I would like to state how sorry I am for this unfortunate error and I trust that your efforts to honor Professor Paulescu will be rewarded with great success."*

First clinical applications

In early January 1922, the group was then ready to dare to use their pancreatic extract on humans for the first time. It was Leonard

Thompson, a 14-year-old boy with diabetes mellitus, who received the first subcutaneous injection of a pancreatic extract prepared by Banting and Best on 11 January 1922. Banting had insisted on using "his" extract. However, the effects on blood sugar and glucosuria were minimal. Banting was extremely disappointed and tensions grew enormously between him and Macleod and Collip respectively [9].

Fortunately, Collip made progress with the development of his extraction technique, allowing Leonard Thompson's therapy to resume on 23 January. The blood sugar dropped from 520 mg/dl (on January 23) to 120 mg/dl (on January 24). By the end of January, Banting, Best, Collip and Macleod had signed a tight cooperation agreement with the Connaught Laboratories of the University of Toronto to ensure the production of the extracts on a larger scale. By February, 6 more patients were treated. Still in February, they had sufficient clinical results to publish Pancreatic Extracts in the Treatment of Diabetes Mellitus". The authors were Banting, Best, Collip, Campbell and Fletcher [10]. The last two authors were the internists at the General Hospital under whose supervision the injections were given. Macleod was not among the authors of this seminal paper in the *Canadian Medical Association Journal*.

The further course of Leonard Thompson's treatment was fraught with several complications: insufficient effectiveness of the insulin, on the one hand, and hypoglycemia on the other. At least he was able to lead a relatively normal life. He went to school, albeit intermittently, and even played baseball occasionally. He had to continue to adhere strictly to the high-fat diet recommended by most diabetologists at the time and was only allowed to eat 160 grams of fat, 50 grams of protein and 10 grams of carbohydrates. In the spring of 1935, Leonard Thompson died of pneumonia after 13 years of insulin treatment. By this time, he had developed severe generalized arteriosclerosis.

Among the first patients to benefit from insulin therapy, Elizabeth Hughes is particularly noteworthy: In 1918, at the age of 11, she developed diabetes mellitus. She then followed a strict starvation diet of no more than 850 calories per day, and by the time she was able to start lifesaving insulin therapy in 1922, her weight had dropped from 34 to 21 kilograms. She was treated by Banting himself, but with a more liberal diet and insulin injections twice daily. She married, gave birth to three children and was able to control her diabetes in a relatively stable manner for years [11]. Aside from a cataract, she developed no diabetes-specific late complications. She finally died of heart failure at the age of 73 after 58 years of insulin treatment.

Towards protecting intellectual property

In order to better adapt to an international audience, the tongue twister "Isletin" was replaced by the name "Insulin", which had already been proposed by de Meyer in 1909. By the end of January 1922, there were already massive differences and tensions in the group over the question of how the invention of insulin should be handled in terms of patent protection. At one-point Collip even threatened to leave Toronto and file a patent on his inventions. Banting and Macleod, as physicians, were philosophically opposed to applying for a patent. The economic gain often sought by a patent was contrary to their understanding of the Hippocratic Oath. However, to prevent others from patenting their inventions, in April 1922 Banting, Best, Collip, Macleod, and Fitzgerald (of the Connaught Laboratories) proposed to the president of the University of Toronto that the "laymen" of the group (Best and Collip) would file a patent and assign it directly to the University of Toronto (Fig. 3). Subsequently, Best and Collip obtained a Canadian patent and assigned it to the University of Toronto for the symbolic price of one dollar [12].

Registering a U.S. patent proved more difficult: The Collip-Best patent was in fact rejected by the United States Patent Office because

Fig. 3. Insulin vial produced by Connaught Laboratories, Toronto (1923). *[Sanofi Pasteur Canada Archives; UTL Insulin Digital Library].*

of a conflict with the patent granted to Georg Zülzer in 1912. Subsequently, an extended patent application was filed by Banting, Best and Collip that included additional purification steps developed by Ely Lilly. Finally, in January 1923, Banting, Best and Collip were granted the U.S. patent for insulin. They sold the patent to the University of Toronto for one dollar each. Banting is reported to have said, "Insulin doesn't belong to me, it belongs to the world." He wanted anyone who needed access to insulin to get it. In addition, they also published numerous aspects of both the "Banting and Best" method as well as the "Collip" method, making them generally available and thus no longer patentable [13]. The University of Toronto, which now held the patents, generously granted licenses to use the patent in Europe and elsewhere. As early as 1923, various companies in several countries were producing insulin from frozen pancreatic tissue obtained from slaughterhouses and extracted with acidified alcohol.

Nobel prize for Banting and Macleod

A few months later in 1923, Banting and Macleod received the Nobel Prize in Physiology or Medicine for their group's landmark discovery. Best and Collip went away empty-handed. Banting was furious that Best had not been nominated and thought about not accepting the prize. He had repeatedly gotten the impression that Macleod wanted to steal their results. Only discussions with two trusted people (John Gerald Fitzgerald, the head of the Connaught Laboratories at the University of Toronto, and Colonel Albert Gooderham, a member of the board of governors of the University of Toronto) persuaded him to accept the prize after all. After only a few days, he announced that he would split his share of the prize money with Best. Macleod came under pressure and as a result finally announced that he, in turn, would share his prize money with Collip.

Among others, Schack August Steenberg Krogh had nominated them. Krogh himself had received the Nobel Prize in Physiology or Medicine in 1920 for his discovery of the capillary motor regulatory mechanism. Because of this honor, he was invited to a lecture tour of universities on the east coast of the United States in 1922 [14]. On this trip, Krogh and his wife kept hearing reports of diabetics being treated with the new insulin. It was his wife, herself a physician and recent sufferer from adult-onset diabetes mellitus, who persuaded him to visit Macleod and the University of Toronto together. The Krogh couple quickly realized that the work of the Toronto group was a clinically remarkable discovery and secured the rights to manufacture insulin for Scandinavia. Back in Denmark, Krogh, together with the Danish physician Hans Christian Hagedorn, founded the

"Nordisk Insulinlaboratorium" which quickly began insulin production and was able to market the first insulin preparation as early as the spring of 1923.

Banting and Macleod were both nominated separately for the Nobel Prize. Why Krogh proposed Macleod as a laureate in addition to Banting can be deduced from the nomination letter, he sent to the Nobel Prize Committee: *"With the information which I personally have obtained in Toronto, and which also, although less clearly so, emerges from the published works, one may conclude that the credit for the idea behind the work which led to the discovery, undoubtedly goes to Banting, who is a young and apparently very talented man. However, he would definitely not have been able to carry out the investigations, which from the start and during all stages, have been supervised by Professor Macleod."* By the time of the aforementioned visit to Toronto, Collip had probably already returned to Alberta. Thus, it is quite conceivable that Krogh underestimated Collip's part in the investigations and also that of the student Best. Either way, the Nobel Prize Committee could have named a maximum of three people as Nobel Prize winners [15].

From an academic point of view, it is regrettable that Gley did not publish his results in the usual way. He was certainly the first to isolate a blood sugar-lowering principle from pancreatic tissue. However, he himself never claimed to be the discoverer of insulin and he congratulated Macleod for "*une grande simplification*" [a great simplification] of the methodology. Zülzer and Paulescu, however, complained directly to the Nobel Prize Committee that they had not been considered for the prize. However, the two had not been nominated for the prize at all. In view of the fact that the group in Toronto had carried out important physiological experiments on insulin action, had established insulin production on a small scale and later on a larger scale, and had successfully used it in the therapy of diabetes mellitus, it seems justified that the Nobel Prize went to Toronto. There was a great debate about Macleod's part in the investigations. In any case, many would have rather seen Banting, Best and Collip as laureates. At the time of the 50th anniversary of the discovery of insulin, Paulescu's role was examined in more detail, and the view was increasingly expressed that he, on the one hand, and Banting and Best, on the other, would have been the worthiest Nobel laureates [16].

With his appointment as a Nobel laureate, Banting suddenly became arguably the most famous Canadian of the time. With the prize money, the university salary and a lifetime annuity of the Canadian Government, he had also become a wealthy man. He held a chair in medical research and worked as a consultant physician. Macleod, for his part, was increasingly burdened by the whole polemic over the legitimacy of the awarding of the Nobel Prize, so much so, that in 1928 he left Toronto and accepted a physiology professorship in Aberdeen. Best then followed Macleod in 1929 as professor of physiology at the University of Toronto.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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