Insulin's centenary: the birth of an idea

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At 2:00 h on Oct 31, 1920, Frederick G Banting, a surgeon practising in London, ON, Canada, conceived an idea to isolate the internal secretion of the pancreas. The following week, he met with noted scientist John J R Macleod in Toronto, ON, Canada, and they developed a research plan. By August, 1921, Banting and his student assistant Charles H Best had prepared an effective extract from a canine pancreas. In January, 1922, biochemist James B Collip isolated insulin that was sufficiently pure for human use. On Oct 25, 1923, Banting and Macleod received the Nobel Prize in Physiology or Medicine for the discovery of insulin. Here, we recount the most relevant events before and after the fateful early morning of Oct 31, 1920, which culminated in the discovery and clinical use of insulin.

Lancet Diabetes Endocrinol 2020

Published Online
October 29, 2020
https://doi.org/10.1016/S2213-8587(20)30337-5

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Introduction

The discovery of insulin in Canada ranks among the leading triumphs of medical research; but is there an appropriate date to observe the centenary of this landmark achievement? There are several candidate milestones in the timeline that culminated in the isolation of insulin suitable for human use (figure 1). For instance, on May 17, 1921, Frederick G Banting and Charles H Best (under the supervision of John J R Macleod) commenced preclinical studies at the University of Toronto, Toronto, ON, Canada. On Aug 3, 1921, Banting and Best's crude extracts from the pancreas of a dog first showed activity in reducing hyperglycaemia in a pancreatectomised dog. Activity was first shown in humans on Jan 23, 1922, when Leonard Thompson, a 14-year-old patient with type 1 diabetes at Toronto General Hospital, Toronto, ON, Canada, responded spectacularly to injections of a purified insulin extract that was prepared by James B Collip. Any of these dates would merit consideration to commemorate insulin's centenary. However, we propose that the foundational event occurred months earlier in London, ON, Canada. The events that followed are well documented in numerous sources, including the definitive classic book, *The Discovery of Insulin*, written by the late historian Michael Bliss in 1982,[1] along with Bliss's biography of Banting[2] and others.[3–14] Here, we recount the events before and after the morning of Oct 31, 1920, which transformed the field of endocrinology.

Banting and London, ON, Canada

Sir Frederick Grant Banting was born on Nov 14, 1891, in Alliston, ON, Canada, a village 70 km north of Toronto, ON, Canada.[2] He was an average student, whose work ethic gained him entry into the University of Toronto, initially for theological studies. In 1912, he transferred to the Faculty of Medicine and chose surgery as his specialty. His classmate was Norman Bethune, who later served in Mao Zedong's army and helped to reform medical care in China.[15] Having already enlisted for service in World War 1, Banting completed his accelerated medical degree in December, 1916, and reported for duty as medical officer in the Canadian Army Medical Corps. Arriving in England in spring 1917, he was promoted to Captain and posted near the front line in France. At the Battle of Cambrai in September, 1918, he suffered a shrapnel wound to his dominant right arm, which became infected and healed slowly. Although he received the Military Cross for valour, he most likely endured post-traumatic stress disorder.[10]

After recovering and returning to Canada in early 1919, Banting worked at the Toronto Military Orthopaedic Hospital, Toronto, ON, Canada. That summer he entered a year-long surgical internship at the Hospital for Sick Children, Toronto, ON, Canada, under the departmental chief, Clarence L Starr. In 1920, Banting next ventured 200 km west of Toronto, ON, to London, ON, Canada, intending to establish a private medical and surgical practice in the midsized community. With his father's assistance, he bought a house at 442 Adelaide Street on the city's east side, now a national historic site and museum (figure 2; video). The ground floor of the yellow-brick home housed Banting's practice, whereas his living quarters were on the second floor (figure 2B). Business was slow from the outset: he cared for an average of two patients per month. By the autumn, concerns about cash flow forced him to work a second job as an instructor in the Departments of Surgery and Physiology at the Western University medical school, London, ON, Canada. He kept ahead of the undergraduate medical students and received favourable teaching assessments. He also volunteered as a research assistant to Frederick R Miller, Western University's Professor of Physiology, who studied cerebellar function in a feline model system.[16]

See Online for video

The birth of an idea

On Saturday, Oct 30, 1920, Banting dropped by the medical school library to review journals in preparation for his lecture on the pancreas, which was scheduled for the Monday. He noted an article of interest in his copy of the November issue of *Surgery, Gynecology and Obstetrics*.[8] That evening, having completed his lecture notes, he turned to the article by Moses Barron of the University of Minnesota, Minneapolis and Saint Paul, MN, USA.[17] Barron had published four case reports; in patient 4, a stone blocked the pancreatic duct, leading to atrophy of the exocrine pancreas, but preserving the islets of Langerhans.[17] The patient did not develop diabetes.

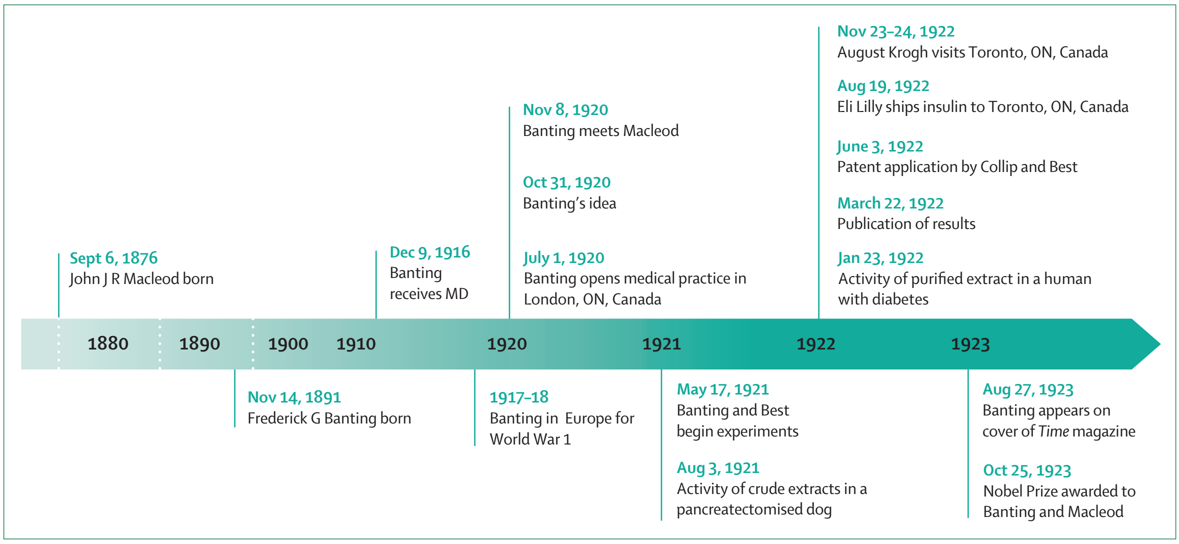

Figure 1: **Timeline related to the discovery of insulin**

Barron associated this observation with animal experiments in which the pancreatic duct had been ligated, but in which no diabetes (ie, no glycosuria) developed unless there was observable injury to the islets. Barron deduced that the islets secreted a hormone into the bloodstream that controlled glucose metabolism.

After reading this article,[17] Banting seemingly had a so-called eureka moment. He envisioned a potential approach to isolating a pancreatic extract related to diabetes. He was so enthused by his idea that he telephoned his neighbour and former classmate, William Tew, and engaged him in a long discussion.[18] Banting later wrote "It was one of those nights when I was disturbed and could not sleep. I thought about the lecture and about the article...Finally about two in the morning after the lecture and article had been chasing each other through my mind for some time, the idea occurred to me. I got up and wrote down the idea and spent most of the night thinking about it."[8] Figure 3 shows the page from his loose-leaf notebook where he scrawled "31" over the original entry of "Oct 30/20": "Diabetus. Ligate pancreatic duct of dog. Keep dogs alive till acini degenerate leaving Islets. Try to isolate internal secretion of these to relieve glycosurea." The spelling errors are ironic but are characteristic of Banting's personal writings. This note time stamps the initiating event for the discovery of insulin and all that followed.

The next week, Banting presented his idea to Frederick R Miller, who listened sympathetically. Western University was primarily a training institution, with neither the infrastructure nor scientific expertise to support the experiments required to evaluate Banting's hypothesis.[18] Fortunately, a world expert on carbohydrate metabolism, namely John J R Macleod, worked at the University of Toronto. Miller and his colleagues at Western University persuaded Banting to pitch his idea to Macleod.

Macleod

John James Rickard Macleod was born on Sept 6, 1876, near Dunkeld, UK. An outstanding student at Aberdeen University, Aberdeen, UK, he received his Bachelor of Medicine and Bachelor of Surgery in 1898. In 1899, he studied physiological chemistry in Leipzig, Germany, on a scholarship. In 1900, he worked as a demonstrator of physiology at the London Hospital Medical School, London, UK, and in 1902, he earned a Diploma of Public Health from Cambridge University, Cambridge, UK. Remarkably, in 1903, he was offered the Chair of Physiology at Western Reserve University in Cleveland, OH, USA, where he initiated his lifelong interest in carbohydrate metabolism. He was a disciplined aggregator and synthesiser of knowledge. In 1913, he published a 1000-page textbook entitled *Physiology and Biochemistry in Modern Medicine*, of which he personally wrote more than 90%.

Macleod served on the editorial board of the *Journal of Biological Chemistry* and other journals, and procured leadership roles in professional organisations, rising, in 1922, to the presidency of the American Physiological Society. His publication record established him as a global authority on carbohydrate metabolism. In 1918 (more than a year after Banting had graduated) the University of Toronto used its growing endowment to recruit Macleod as Chair of Physiology.[1]

Banting meets Macleod

The week after reading Barron's article,[17] Banting was, by coincidence, in Toronto, ON, Canada, to attend the wedding of the daughter of his former mentor, Clarence Starr. Banting cold called Macleod and arranged a meeting on Nov 8, 1920.[2,7–9] Initially, after hearing Banting's idea regarding pancreatic duct ligation, Macleod was sceptical. He was well aware (as

 Published online October 29, 2020 https://doi.org/10.1016/S2213-8587(20)30337-5

Figure 2: **Banting House National Historic Site, London, ON, Canada**
(A) Banting's home at 442 Adelaide Street, London, ON, Canada. The home is now a national historic site, owned and operated by Diabetes Canada. (B) Interior of Banting's second-floor bedroom, where he conceived the idea of pancreatic duct ligation. (C) Commemorative plaque. Figure reproduced with permission from Banting House National Historic Site, London, ON, Canada.

Banting most likely was not) that several experienced researchers had reported more than 400 previous attempts to treat patients with diabetes by use of pancreatic extracts, however, none of these attempts were effective.[1]

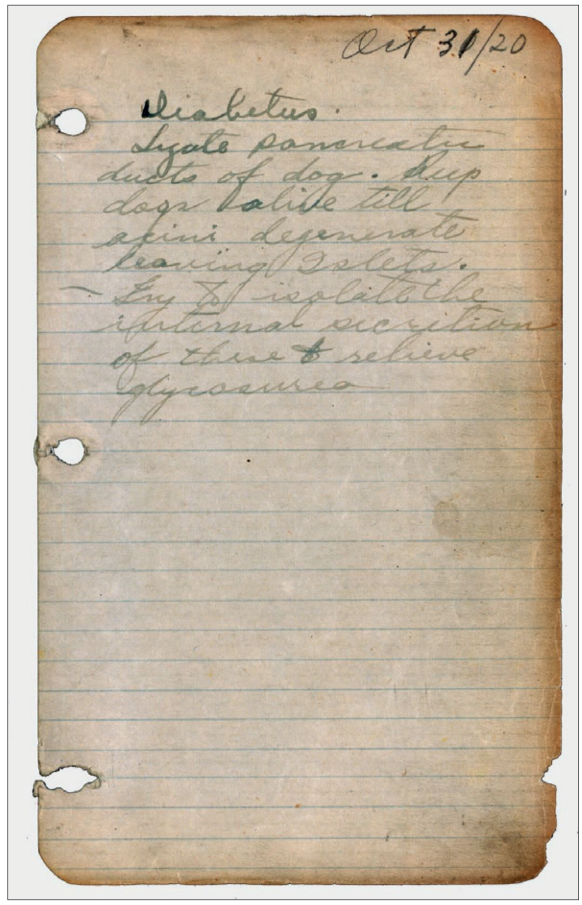

Figure 3: **Banting's notebook**
A page from Banting's notebook, dated Oct 31, 1920. Reproduced with permission from Thomas Fisher Rare Book Library, University of Toronto, Toronto, ON, Canada.

The concept of a pancreatic internal secretion was at least 30 years old. In 1890, Josef Freiherr von Mering and Oskar Minkowski (Strasbourg, Germany) reported a dog that survived a total pancreatectomy but surprisingly developed polyuria, caused by glycosuria from hyperglycaemia, implicating the pancreas in diabetes.[19] Between 1905 and 1920, scientists from around the world, including Georg Ludwig Zülzer (Berlin, Germany), Ernest Lyman Scott (Chicago, IL, USA), Israel Kleiner and Samuel Meltzer (New York City, NY, USA), John Murlin and Benjamin Kramer (Rochester, NY, USA), and Nicolae Paulescu (Bucharest, Romania), reported preparation of pancreatic extracts that, to varying degrees, suppressed glycosuria and reduced blood sugar in animals in experiments.[20–25] However, a seemingly insurmountable hurdle for each project was translation to humans. Administration of these extracts to patients was marked by an absence of activity, often followed by local abscess formation, infections, fever, sepsis, and other toxic reactions.[1,20–25] At this stage, these efforts were typically abandoned. The accepted wisdom was that impurities were inextricably linked to the pancreas'

For more on **Banting House National Historic Site** see https://bantinghousehsc.wordpress.com

Figure 4: **Recognition for the discovery of insulin**
(A) 1923 Nobel Prize certificate in Physiology or Medicine. The accompanying citation reads in part: "The Professorial Staff of the Caroline Institute has considered the work of Banting and Macleod to be of such importance, theoretically and practically, that it has resolved to award them the great distinction of the Nobel Prize. Professor J Sjöquist, Nobel Committee for Physiology or Medicine". Reproduced with permission from Thomas Fisher Rare Book Library, University of Toronto, Toronto, ON, Canada. (B) Proposed design for the CA$5 banknote, recognising Banting, Macleod, Best, and Collip as co-discoverers of insulin. Figure reproduced with permission from Banting House National Historic Site, London, ON, Canada.

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internal secretion, either destroying or contaminating it, thus precluding safe administration in humans.[1,6]

Macleod believed that although the pancreatic internal secretion was real, its isolation in a pure soluble form from the mammalian pancreas could be a lost cause. Parenthetically, during Banting and Best's experiments, Macleod directed half of his research funds towards projects in monkfish and cod, species in which the islets are anatomically detached from the exocrine pancreas.[26] In these fish models, Macleod showed that islets were the source of insulin,[27] although in quantities that were insufficient to be commercially viable.[28]

Launching a collaboration

Perhaps Banting's energy and enthusiasm impressed Macleod.[2] Banting was unburdened by circumspection that might have discouraged a more experienced researcher with a deeper background understanding.[2,10] Despite reservations, Macleod eventually agreed to allow Banting, a battlefield surgeon with minimal research experience, to enter the academic world as a volunteer in his laboratory and pursue a hypothesis that was neither novel nor guaranteed to be correct. When Macleod became serious about providing direction plus laboratory space and animals, Banting transiently had doubts. He hesitated about shutting down his nascent medical practice and selling his newly purchased home to produce "negative results of great physiological importance".[1] The meeting ended with Banting telling Macleod that he would consider his offer carefully.

In December, 1920, Starr intervened and advised Banting to stay in London, ON, Canada. Starr's advice seemed to make Banting question himself and delay his decision. On March 8, 1921, Banting contacted Macleod to inquire whether the offer to do the research was still available. It was, but Banting was still unsure. Financial security in London, ON, Canada, was not progressing at the pace that he would have liked. He inquired about enlisting in the Indian Medical Service and almost joined an oil expedition to NT, Canada.[8] The breakdown of a serious romantic relationship also figured into his decision. On May 14, 1921, Banting locked up his house. He invigilated the final examination for Western University's graduating class, who gave him a box of cigars in appreciation for his teaching. That afternoon, Banting left London, ON, Canada, although he avoided commitment to the decision by continuing mortgage payments on his home.[18]

Banting and Best's experiments

After arriving in Toronto, ON, Canada, Banting met with Macleod on May 17, 1921, to begin the project. They were joined by an undergraduate student assistant, Charles Herbert Best (born Feb 27, 1899 in West Pembroke, ME, USA), who either won or lost a coin toss with another student to work with Banting over the summer. Macleod's rigorous protocol made use of Banting's surgical skill to produce two types of animals: pancreatic duct-ligated dogs to provide the source material and pancreatectomised dogs with diabetes to receive the preparation. Best was trained in the latest real-time laboratory methods to measure sugar in small blood volumes and urinary sugar, acetone, and nitrogen. This expertise proved to be crucial to the efficacy of the experiments.[29] Macleod also outlined a preparation method for the pancreatic extracts, assisted on the first operation, and oversaw the experiments.[9] A month later, Macleod departed for a sojourn in Scotland but kept in touch with the young researchers over the summer.[1,7–9]

 Published online October 29, 2020 https://doi.org/10.1016/S2213-8587(20)30337-5

On Aug 3, 1921, enduring sweltering heat, poor conditions, and repeated setbacks—eg, an animal mortality rate of 70% (seven of ten) of dogs—Banting and Best began an experiment that eventually showed that their extract, which was administered four times over four days, reduced glucose and improved the status of a dog with diabetes. They called this preparation isletin, which was later renamed insulin. Other researchers had previously suggested various names (eg, insuline,[30] acomatrol,[20] pancreine,[25] and even insulin[31]) for a hypothesised pancreatic endocrine secretion. Banting wrote to Macleod of their findings on Aug 9, 1921.[2] Over this time, Best provided both technical and psychological support for the volatile Banting.[1,2] The results were sufficiently promising that Banting decided to abandon London, ON, Canada.[1] He returned in September to sell 442 Adelaide Street and dispose of furniture and unused medications from his drug cabinet, before he left London permanently.[2,18] He lived in Toronto, ON, Canada, for the rest of his life.

Inviting Collip

After Macleod's return to Toronto, ON, Canada, from Scotland, on Sept 21, 1921, he guardedly provided additional resources and required replication of results. During this period, the relationship between Macleod and Banting began a protracted downward spiral. Banting's insecurity and suspicious nature were exacerbated by Macleod's tendency (according to Banting) to disproportionately credit himself at scientific meetings over the next year.[1,2] Macleod recounted that he had gone out of his way to consistently acknowledge Banting.[9] But Banting, as the originator of the idea and hands-on experimentalist, believed that he (and possibly Best) deserved most of the recognition. Bliss contended that Banting might not have appreciated the value that a supervisor brings to a project through providing strategic direction, resources, funding, and infrastructure.[1,2]

Macleod honoured Banting's request to invite James Bertram Collip (born Nov 20, 1892, in Belleville, ON, Canada) into the project to help purify the crude extract. Collip was an innovative biochemist with an interest in hormones,[32] who conveniently was visiting Macleod's department. After starting work on Dec 12, 1921, Collip developed a standard insulin-activity assay in rabbits.[7–9] Then, he devised an extraction protocol by use of 90% alcohol, a key improvement that allowed insulin to be soluble, whereas other impurities precipitated.[33] This technical breakthrough solved insulin's so-called last mile problem and elevated Banting and Best's preparation to one that was pure enough for human use. On Jan 23, 1922, Collip's isolate substantially improved the status of Leonard Thompson, a 14-year-old patient with type 1 diabetes; less than 14 days earlier, Banting and Best's preparation had caused only sterile abscesses in the same patient. The use of insulin in patients was soon published with clinician coauthors.[34,35]

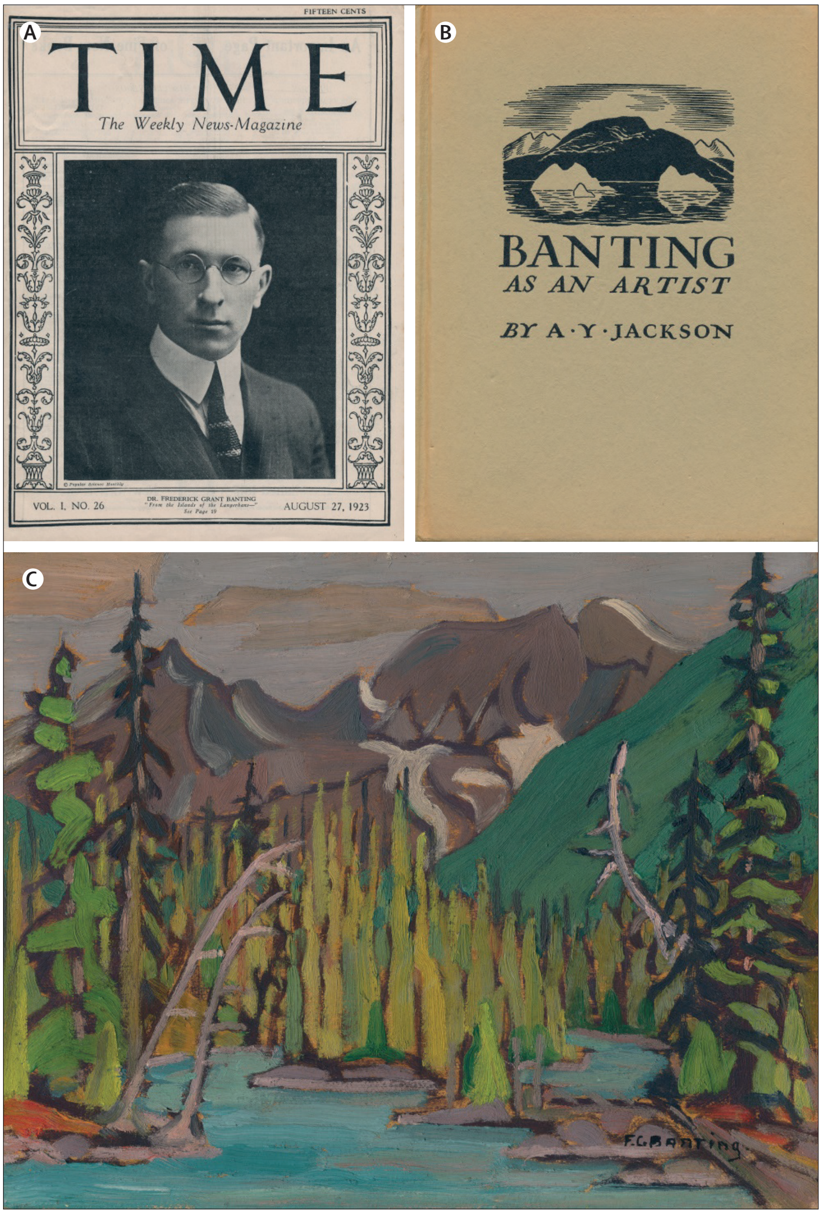

Figure 5: **Recognition and diversion for Banting**
(A) Cover of *Time* magazine on Aug 27, 1923. (B) Cover of the book *Banting As An Artist*,[45] written by the famed Canadian artist A Y Jackson. (C) Painting by Frederick Banting (1891–1941), *Rocky Mountains—Calgary* (1934), gift of W L Tew, 1984. Figure reproduced with permission from Banting House National Historic Site; London, ON, Canada.

The university and pharma step in

Establishing Toronto insulin as the global standard benefited from the support of the University of Toronto and its affiliated hospital and laboratories. By the summer of 1922, insulin was being produced with sufficient quality and quantity that patients with diabetes from Canada and around the world began coming to Toronto, ON, Canada, for treatment.[36] Banting assumed the role of treating physician, initially in a private clinic and later at Toronto General Hospital, to the irritation of academic physicians,

For more on **Banting House National Historic** Site see https://bantinghousehsc.wordpress.com who regarded him as an unqualified interloper.[2] However, the substantial effects of insulin profoundly affected the general public and international diabetologists, such as Elliott Joslin,[37,38] who later wrote “By Christmas of 1922 I had witnessed so many near resurrections that I realized I was seeing enacted before my very eyes Ezekiel’s vision of the valley of dry bones.”[1,10]

Concurrently, a partnership between the University of Toronto and Eli Lilly brought on board the resources of pharmaceutical companies. The first US patent application for insulin was filed in the names of Collip and Best on June 3, 1922.[39] In the autumn of 1922, George Walden, an Eli Lilly scientist, used isoelectric precipitation to drastically increase both the purity and yield of insulin.[11] Furthermore, in November, 1922, a visit to Macleod’s laboratory by the Danish Nobel Prize winner August Krogh was consequential in two ways. First, after meeting the principal investigators personally, Krogh wrote nomination letters to the Nobel Prize committee.[40] Second, Krogh received approval from the University of Toronto to produce insulin in Denmark at the Nordisk Insulinlabatorium, which he founded and later became Novo Nordisk.[11]

Recognition

The climax event occurred on Oct 25, 1923, when the Karolinska Institute awarded the Nobel Prize in Physiology or Medicine to Banting and Macleod for the discovery of insulin (figure 4A).[41,42] This award represents a rare example in the Nobel archives: a scientific achievement was recognised for having been accomplished during the preceding calendar year, adhering to the prize’s actual terms of reference. But animosity between Macleod and Banting grew in proportion to insulin’s notoriety. They were not on speaking terms, and each scientist split his financial share: Banting with Best and Macleod with Collip.[1,2] All four individuals made essential contributions at various times (figure 4B). Other diabetes researchers contested the decision to award the prize to the Toronto researchers but were unconvincing.[24,43,44] History now judges that, if only two of the scientists could be recognised, Krogh’s initial case for Banting and Macleod was appropriate, but an argument could be made that all four should have been co-recipients.[1] Ultimately, the prize mainly acknowledged the importance of insulin’s discovery, which transcended specific individuals.

Aftermath

After their work on insulin, the four scientists’ careers diverged widely. Banting attained near-mythological status in Canada (figure 5A), receiving a lifetime government endowment to continue medical research.[2,46] To date, Banting is the youngest recipient of the Nobel Prize in Physiology or Medicine. He also pursued his artistic interests, becoming a well regarded landscape painter (figure 5B, C).[47] He died in an aeroplane crash on Feb 21, 1941, while serving in World War 2.[48,49] Macleod, whose standing in Canada had been besmirched by Banting and Best’s admirers, returned to Aberdeen University, Aberdeen, UK, as Chair of Physiology and died in 1935.[50,51] His role and reputation have been rehabilitated through historical scholarship. Best became Chair of Physiology at the University of Toronto, continuing teaching and research until his death in 1978.[52] Collip grew into a person of great importance in endocrinology, having isolated parathyroid hormone, thyroid stimulating hormone, and follicle stimulating hormone, among other hormones.[53–57] He became Dean of Medicine at the University of Western Ontario, ON, Canada, and died in 1965.[58,59]

The final irony

Ironically, Banting’s original idea was physiologically flawed. There was no need to ligate the pancreatic duct to preserve the β cells or insulin. Although trypsinogen, the precursor of trypsin, is resident in the acinar cells, it does not directly possess digestive capacity until it becomes activated in the intestinal lumen. Neither Banting nor Macleod realised this fact at first. Banting and Best eventually found that whole fresh pancreas, non-duct ligated, could serve as the source of insulin. Trypsin was not the problem, but rather other impurities that were removed by Collip’s strong alcohol method. The practical consequence of eliminating duct ligation was upscaling of the pancreatic supply from slaughterhouses, which was the standard until human insulin came into widespread use in the 1980s.[60]

Nowadays, as society seeks accelerated development of cures (eg, Operation Warp Speed to find a COVID-19 vaccine), the example of insulin is miraculous. Less than 3 years after Banting read Barron’s paper, insulin was in widespread clinical use. As we enter the centenary of the insulin era, the morning of Oct 31, 1920, is an appropriate date for tribute. Banting was alone inside the room on the second floor of 442 Adelaide Street when he jotted down his idea, which set in motion a chain of events that led to the most important medical discovery of the 20th century in Canada. The effect of the discovery of insulin on endocrinology, medicine, and society reverberates 100 years later.

Contributors

RAH and GMM both contributed to the literature search; article design; data collection, analysis, and interpretation; and writing.

Declaration of interests

RAH declares consulting fees from Acasti, Aegerion, Akcea and Ionis, Amgen, HLS Therapeutics, Novartis, Regeneron, and Sanofi. GMM declares no competing interests.

Acknowledgments

We thank Amanda Berberich for the helpful comments. RAH is supported by the Jacob J Wolfe Distinguished Medical Research Chair, the Edith Schulich Vinet Research Chair in Human Genetics, and the Martha G Blackburn Chair in Cardiovascular Research; and operating grants from the Canadian Institutes of Health Research (foundation grant) and the Heart and Stroke Foundation of Ontario (G-18–0022147).

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