

# The Discovery of Insulin: Is There Glory Enough for All?

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In October 2011, the University of Toronto and the Toronto-headquartered Gairdner Foundation partnered to celebrate the ninetieth anniversary of the discovery of insulin. In 1921, four scientists worked to discover, isolate, and purify insulin at the University of Toronto: Frederick Banting, John J. R. Macleod, James B. Collip, and Charles H. Best. The credit for this achievement has been assigned in varying ways. Popular opinion, in Toronto and worldwide, has bestowed the recognition for discovery upon Banting and Best. Indeed, many noted diabetolo-

gists have credited the achievement to this pair. However, the Nobel Committee awarded the Prize in Physiology or Medicine to Banting and Macleod in 1923. Michael Bliss, in his 1982 history of the discovery of insulin, revisited the question of who really is responsible for this wonder drug. Our essay will explore the pathway toward the discovery of insulin and seek to understand why the credit for this monumental achievement was apportioned in such different ways.

## THE IDEA

Frederick Banting was trained as a surgeon rather than as a research scientist, so his exposure to the nascent discipline of endocrinology was minimal (Figure 1). Born on a farm in Alliston, Ontario, Banting graduated from medical school at the University of Toronto in 1916, and served at Granville Hospital in England for thirteen months before being sent to the front line as a battalion medical officer in 1918 (University of Toronto, 2011a). Injured during the war, Banting convalesced in Britain, where he became a member of the Royal College of Physicians of London and the Royal College of Surgeons (Bliss, 1982). When he returned to Toronto, he began a residency in general surgery at the Hospital for Sick Children. Unable to secure a permanent surgical position at the hospital, Banting set up a private practice in London, Ontario. Banting's foray into private medicine was largely unsuccessful, and to supplement his income he worked part time as a demonstrator in surgery and anatomy at the University of Western Ontario, assisting Dr. F. G. Miller, a professor of physiology (Bliss, 1993a).

In 1920, Banting was introduced to the idea of a therapy for diabetes while preparing a lecture on carbohydrate metabolism for his physiology students. The night before his talk, he read a relevant article, "The Relation of the Islets of Langerhans to Diabetes with Special Reference to Cases of Pancreatic Lithiasis," by Moses Barron, in the November issue of the journal *Surgery, Gynecology, and Obstetrics*, which had just arrived in the mail (Barron, 1920). During a fitful night's sleep, Banting began piecing together a synthesis of carbohydrate metabolism and pancreatic ligation, writing the following idea in his journal:

*Diabetes [sic]*

*Ligate pancreatic ducts of dog. Keep dogs alive till acini degenerate leaving Islets. Try to isolate the internal secretion of these to relieve glycosurea.* (Bliss, 1986)

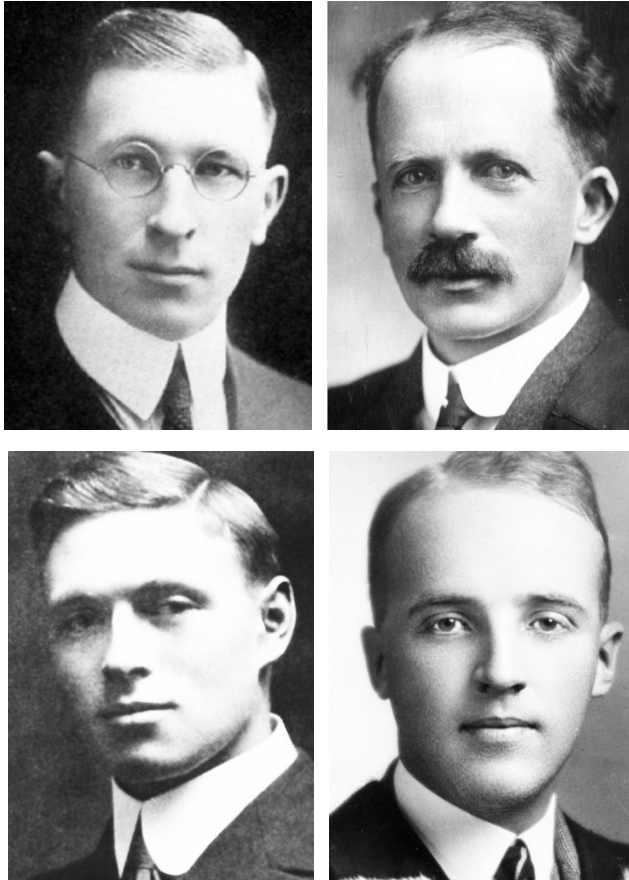
The next morning, Banting presented his idea to Dr.

Miller. Miller did not support the idea of embarking on this project, at least not under his auspices, but he suggested that Banting speak with J. J. R. Macleod at the University of Toronto, an expert in carbohydrate metabolism.

John James Rickard Macleod, a Scottish scientist, had studied medicine at the Marischal College of the University of Aberdeen and biochemistry at the Institute of Physiology of the University of Leipzig, Germany, while subsidized by an Anderson Traveling Fellowship. He earned his DPh degree from Cambridge University. Macleod began his teaching career as a demonstrator in physiology at the London Hospital Medical School, and was subsequently appointed lecturer in biochemistry. While in London, he also proved himself a skilled and energetic researcher. Then, from 1903 to 1918, he served as a professor of physiology at Western Reserve University (now called Case Western) in Cleveland, OH (Shampo and Kyle, 2006). During this time, Macleod became deeply interested in diabetes and carbohydrate metabolism, writing 12 lengthy papers in the *American Journal of Physiology* outlining new techniques for the study of carbohydrate metabolism. His work led him to become an authority in the field by 1913. He had reached the conclusion that contemporary attempts to lower blood glucose levels via the injection of pancreatic extract were unsuccessful. Macleod hypothesized that either the hormone producing the effect existed as an inactive precursor or it was inactivated by pancreatic enzymes during its preparation. Recognition of this work led him to Toronto, and what would become his legacy. Macleod was chosen to serve as an associate dean of medicine at the University of Toronto in 1918 before becoming director of its physiology lab (Williams, 2005).

On November 8, 1920, Banting met with Professor Macleod to discuss the possibility of researching the internal secretion of the pancreas. Macleod's encyclopedic knowledge of the field made him skeptical of the idea. He found that Banting was neither well versed in the subject nor sufficiently skilled in physiological research

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**Figure 1.** The four discoverers—Banting, Macleod, Collip, and Best—each of whom played an essential part in the discovery of insulin. Permission to use the images: University of Toronto. Images courtesy of the Thomas Fisher Rare Book Library, University of Toronto, Insulin Collection.

to undertake a project that had so many unknown variables (Bliss, 2005). This project ran the risk of being an expensive undertaking simply to discover that the internal secretion did not exist at all.

Macleod appreciated that the experiments of Oskar Minkowski and Josef von Mering, followed shortly by the work of B. Hedon in the closing decades of the 19th century, had prompted many first-rate scientists to search for and attempt to purify the internal secretion of the pancreas in vain. In the United States and Europe, George Ludwig Zuelzer, J. E. Scott, Israel Kleiner, and Nicolae Paulescu were among the most prominent failures (Bliss, 1982, 2005). The failures were often frustrating, with triumph tantalizingly close but never achieved. Why would his lab succeed where so many others had failed?

Would Banting’s idea—ligating the pancreatic duct and allowing the acini to atrophy—be the key? Research budgets were slim. Embarking on a project that had no foreseeable gains seemed like a wasteful use of funding that could be allocated elsewhere. Macleod was familiar

with the Barron article that had inspired Banting, and he knew that the ligation story was not new. Furthermore, he knew that in fish, the islets of Langerhans, the presumed site for synthesis of “insuline,” were naturally separate from the acini. Fish might have proven to be a better path to success. As they discussed the topic, they arrived at a hypothesis that Macleod supported: ligate the pancreatic duct to induce pancreatic atrophy and test to see if it contained the alleged internal secretion (Bliss, 1989). The experiment had not been conducted by previous researchers, and the results could be valuable. Under these research conditions, Macleod agreed to accommodate Banting in his laboratory at the University of Toronto.

Macleod also mentioned at this meeting that James Bertram Collip might be of help. Collip, a Canadian biochemist educated in Toronto, had received an appointment as an associate professor of biochemistry at the University of Alberta. Collip’s earliest research focused mainly on the comparative blood chemistry of vertebrates and invertebrates. His contributions to the medical literature began in December 1916 with the publishing of his paper “Internal Secretions” (Collip, 1916; Noble, 1965). After receiving a Rockefeller Traveling Fellowship in 1921, Collip took a sabbatical to begin studying the effect of pH on blood sugar under Macleod at the University of Toronto (Browne and Denstedt, 1966). It was that same year, when Banting went to discuss the project with Macleod, that Collip and Banting first met.

Banting’s commitment to carrying out his proposed experiments wavered, but he ultimately arrived in Toronto in April 1921. Macleod introduced Banting to two of his students; one would serve as Banting’s assistant to help him with the blood and urine tests that were to be used to detect diabetes. The two students flipped a coin to see who would begin the research with Banting over the summer (Rosenfeld, 2002). Charles Herbert Best won.

The son of a physician, Best served as a sergeant in the Canadian army and then graduated in 1921 from the University of Toronto’s Honor Physiology and Biochemistry course. Previously, Best had worked as a research assistant in experimental diabetes and was therefore knowledgeable about blood-sugar analysis (Bliss, 1993b). The experiments began in May 1921.

**THE EXPERIMENTS**

Under Macleod’s supervision, with detailed instructions, Banting and Best began their experiments. The process proved more difficult than expected; the first few dogs on which they operated died from excessive blood loss and infection. After the scientists improved their surgical technique, they worked on two populations of experimental dogs to account for the endo- and exocrine duality of the pancreas. One set of dogs had to be completely

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void of pancreatic function so as to make them diabetic. These dogs were fully pancreatectomized and became the models for experimentation. The other set of dogs was a living biochemical factory of sorts: their pancreatic ducts were ligated to remove the exocrine capacity of the glands. With the conduit for exocrine secretions removed, the exocrine cells would begin to atrophy, leaving only the endocrine pancreas intact. These dogs were used to harvest the internal secretion that was central to the experimental foundation of Banting and Best's work (Bliss, 1982). When Macleod went on vacation during the summer, he left specific instructions along with information about how to reach Collip, the biochemist whom Banting had briefly met, in case any pressing questions arose.

By early July, it was clear that the experiments had fallen short of expectations. Banting and Best had operated on 19 dogs, 14 of which had died, mostly from causes unrelated to the planned experiments (Bliss, 1982). At the end of the month, the pair prepared their first extract of the hypothetical internal secretion from degenerated pancreas that had been ground up and filtered. The filtrate did not cause a decrease in blood sugar in the first dog, but upon further oral administration of sugar, the extract prevented a spike in blood glucose. Further, less sugar was found in the urine. This gave early confirmation that the extract had an effect on these diabetic dogs. Repeated results gave birth to the name "isletin" for this extract in the experimenters' August notes (Bliss, 1982).

For a second round of experiments, the pair decided to do complete pancreatectomies on two dogs. The extract was administered to one, and its health was compared with that of the dog that was left untreated. To the delight of the scientists, the control dog was barely able to walk, whereas the experimental dog was in "excellent condition does not appear tired or sleepy walks about as before operation" (Bliss, 1982; Figure 2). As Banting and Best further pursued their experiments, they uncovered a wide range of methods for obtaining the best possible extract, including using a whole pancreas and even a fetal pancreas.

By mid-September, Macleod had returned to Toronto. He was updated on the progress of the Banting and Best experiment, only to find Banting requesting more funding and facilities. Macleod was initially hesitant to provide much additional funding for this project, as it had greatly exceeded the budget he had originally allotted to them, and other research projects would consequently suffer. Banting, convinced of the gravity of the project, was offended that Macleod did not seem to hold it in the same regard. This was the first of many points of contention between the scientist and the surgeon. After a heated conversation, Macleod ultimately relented, encouraging the pair to delve deeper into their experiments to convince their scientific colleagues of the veracity of their findings. He was specifically

interested in an experiment that eliminated the possibility that the decreases in blood sugar were due to a dilution of the blood rather than to the action of the extract. Banting, empowered by the positive results, was more interested in veering off in other directions. At this point, Banting suggested expanding the experimental team. Macleod, however, urged them to continue on their own. Experiments resumed in October (Bliss, 1982).

By November 1921, Banting and Best started writing their first paper together. It detailed the results of their experiments from the summer up to that point (Banting and Best, 1922; Bliss, 1982). Why Macleod chose not to put his name on the paper is unclear, but several theories have been posited. After a brief presentation of their work at a journal club on the university campus, the suggestion was made that the next experiment, termed the "longevity experiment," should demonstrate that regular administration of the extract could prolong the life of a diabetic dog. It began smoothly and then ended abruptly when the dog began to exhibit twitches and periods of unconsciousness. The dog died within a day. Another longevity experiment made it clear that impurities in the extract were undermining its curative capacity. In December, Collip began to help the researchers purify their extracts, and by the end of the month, he had prepared an extract that appeared to be medically potent (Bliss, 1982).

#### INITIAL RECEPTION

As an esteemed member of the American Physiological Society, Macleod received a call for papers for the society's annual meeting, to be held in New Haven during the Christmas holiday. Macleod encouraged Banting and Best to present their findings in this forum. A number of renowned diabetologists, including Elliot Joslin, Frederick Allen, Israel Kleiner, and the research director of Eli Lilly and Co., George H. A. Clowes, attended this meeting in anticipation of these findings. Banting presented the work, but members of the audience, including some who had attempted a similar feat, were well versed in the diabetes literature and began asking pointed questions directed at the experimental methods. Watching Banting struggle with these gaps in his presentation, Macleod redirected the discussion, focusing on the reduction in blood glucose observed in the dogs and their increased survival rates. The meeting drove a deeper wedge between Banting and Macleod (Bliss, 1982). Banting believed that Macleod had ruined his moment of fame by usurping the discussion, and his use of the term "we" implied that Macleod had been in the lab performing the experiments. After that meeting, Banting claimed that Macleod was stealing his work. An important positive result of the meeting, however, was that Clowes saw past the inadequacies of the experimental process and the mediocre presentation and was convinced of the potential for a future collaboration to produce insulin commercially (Bliss, 1982).

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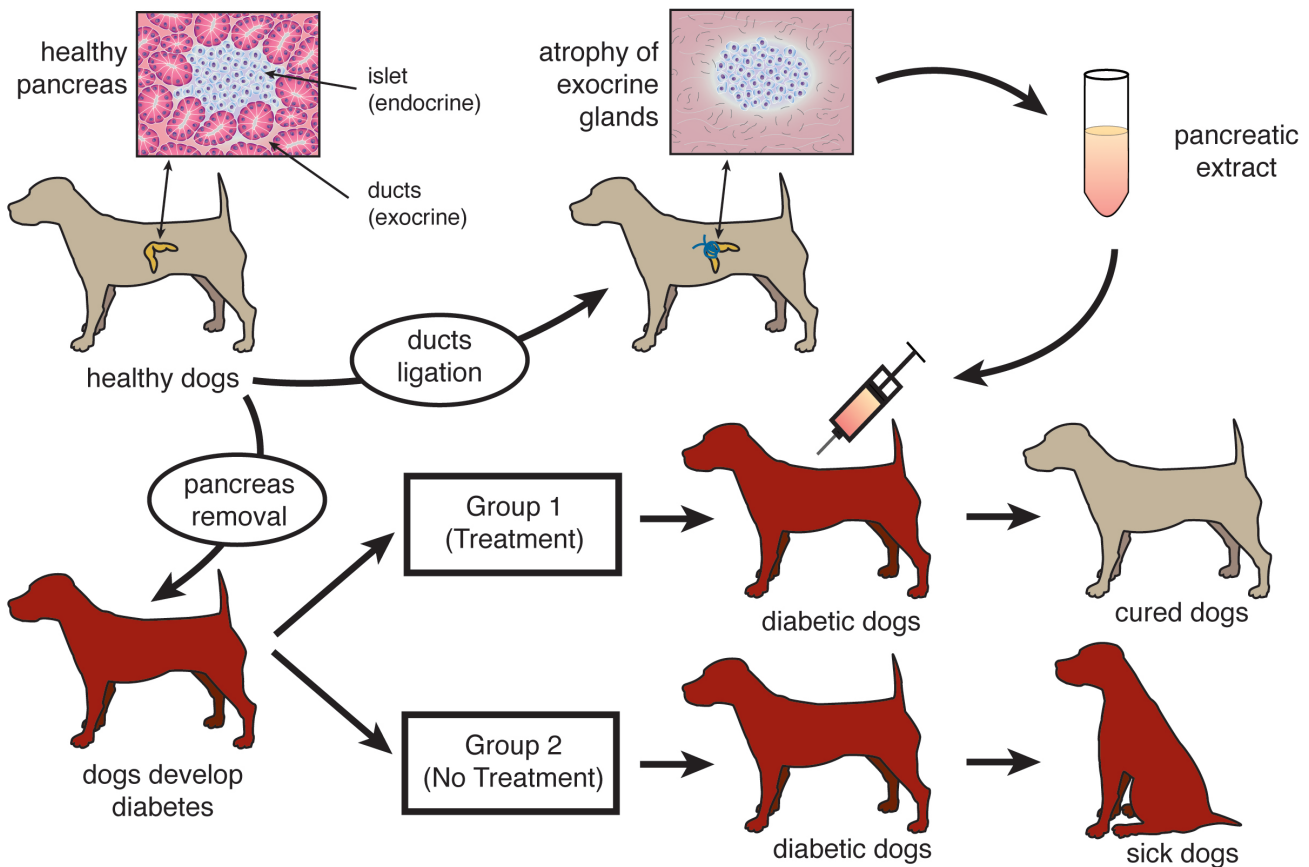


Figure 2. Schematic of Banting and Best's early experiments. Figure courtesy of Lorenzo Agoni, MD, MS (*EJBM* Staff).

Following the meeting in New Haven, the research group began to expand, and new experiments were performed. The inaugural clinical testing began under the supervision of Drs. Walter R. Campbell and A. A. Fletcher in their diabetes clinics. On January 11, 1922, at Toronto General Hospital, Leonard Thompson, a 14-year-old diabetic patient, was given a pancreatic extract made by Banting and Best that incorporated some of Collip's improvements. The extract failed to produce significant results and was discontinued. Toward the end of January, Collip had discovered a method to produce an extract whose purity far exceeded that of previous attempts. When Collip went to Banting and Best to announce his findings, he stated that he would not reveal his new method. Banting physically accosted Collip; Best had to rescue him (Bliss, 1982).

**CONVINCING THE WORLD**

In April 1922, the group prepared a paper that summarized Banting's idea, Banting and Best's early experiments, Collip's purification, and the clinical results. The paper, "The Effect Produced on Diabetes by Extracts of

Pancreas," was co-authored by Banting, Best, Collip, Campbell, Fletcher, Macleod, and E. C. Noble (Banting et al., 1922). The essence of this paper was presented by Macleod at the annual meeting of the Association of American Physicians in Washington, DC (University of Toronto, 2011b). This time, the experimental data from the lab supported by success in diabetic patients convinced an enthusiastic audience. Banting and Best had chosen to stay behind in Toronto, saying that they could not afford to make the trip; nobody believed them.

**WHO DESERVES THE CREDIT?**

In less than a year, from initial experiments to the first successful injection, the Toronto team had given the world an effective treatment for diabetes. The group was able to achieve an isolated and purified extract of the internal secretion of the pancreas, a result that no other previous scientist had been able to obtain, though many had come quite close. Each member of the team brought his unique talents to the table. Banting provided the passion behind the project; without him there would have been no impetus to search for insulin in Toronto. Best was the stabilizing force in Banting's

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scientific life, keeping him focused. Collip's expertise in biochemical technology was the key to formulating a clinically useful drug. Macleod had the sophistication to guide the research from spark to clinical trial. It is impossible to isolate the most important contributions. The difficult dynamic among the collaborators that began early on in the experimental process manifested itself in its ugliest form as each scientist fought for his place in history. At the center of all the tension was Banting, paranoid that Macleod was trying to steal his life's work. Unfortunately for Macleod, he was never able to gain Banting's trust or mollify his anger.

The first instinct of the international medical community was to praise Macleod. This reaction was strengthened by his international recognition as a well-known research scientist who was an expert in this field prior to the insulin project.

Banting and Best were absent from the meeting in Washington where Macleod announced the discovery. Yet because Best was directing Canada's insulin production, and Banting was the point person for all clinical questions related to insulin, Canada's popular opinion considered these two scientists the discoverers. This may in part have been because Canada was interested in elevating two of its own as breakthrough scientists of the 20th century. Michael Bliss mentions that Banting had several high-placed friends in Toronto medical circles, and a complex campaign was orchestrated to recognize Banting as the single discover of insulin, the success of which was reflected by a lifetime annuity awarded to him by the Canadian government (University of Toronto, 2011a). In later years, Best succeeded in convincing Canadians that he deserved equal credit.

The tension over the credit awarded for the discovery became complicated by the prospect of a Nobel Prize. In November 1922, Danish biomedical scientist and Nobel laureate August Krogh arrived in Toronto. The purpose of his visit was twofold. First, he wanted to investigate the claims of discovery with an eye to awarding the Nobel Prize. But there was also a personal consideration—Krogh's wife was diabetic, and he wanted to bring the technology back to Denmark. He and Dr. H. C. Hagedorn successfully did so, and they established the Nordisk Insulin Company (Bliss, 1982).

Nominations for the Nobel Prize poured in. Professor G. N. Stewart of Western Reserve University nominated Macleod. Dr. George Washington Crile of Cleveland and Francis G. Benedict nominated Banting. Krogh nominated Banting and Macleod together. There were other noteworthy demonstrations of recognition as well. In early 1923, Macleod won the University of Edinburgh's Cameron Prize given for distinction in therapeutics, and was the keynote speaker at the Eleventh International Physiology Congress (Bliss, 1982). In March of the same year, Dr. George W. Ross, an instructor at the University

of Toronto, and Sir William Mulock, the chancellor of the university, started a campaign to secure government funding for Banting. In May, Ontario's legislature passed the Banting and Best Medical Research Act, which established the Banting and Best Chair of Medical Research at the University of Toronto (Nobel Foundation, 2011). This later grew into the Banting and Best Department of Medical Research. And the Academy of Medicine declared that Banting and Best had priority in the discovery of insulin (Bliss, 1982).

On October 25, 1923, the Nobel Prize was awarded to Banting and Macleod. The joint prize made a bad situation exponentially worse. Banting was livid that he had to share the glory of a Nobel Prize with his rival, Macleod. His first instinct was to reject the prize altogether, but instead he made a public pronouncement that he had chosen to share his prize money with Best. Macleod followed suit and recognized Collip with half of his prize, although not with the same zeal that Banting had demonstrated. The University of Toronto held a special convocation in honor of its Nobel laureates, at which Banting and Macleod were awarded honorary doctor of science degrees.

Best tended to be mentioned only in the context of Banting's work and was often neglected in the early years following the discovery. In a letter written to Elliot Joslin, Best laments that he was not invited to the tenth anniversary celebration of the discovery, held in Toronto (Cooper and Ainsberg, 2010). Over time, however, he achieved greater fame on his own. Best rose to the top of his medical school class and became involved in biomedical research, discovering the anti-allergic enzyme histaminase, as well as isolating choline and studying its role in metabolism. When Macleod left Toronto in 1928 (his departure due, many speculate, to the uncomfortable situation created by Banting), Best succeeded Macleod as professor of physiology at the University of Toronto at age 29. He also took over the Banting and Best department, and in 1953, the university erected the Best Institute alongside the Banting Institute of 1930.

In 1922 Collip returned to Alberta as professor of biochemistry, and earned his DSc (1924) and MD (1926) there. He was highly praised at his parent institution, and a banquet in his honor was held in Edmonton, and a luncheon in Calgary. He continued his work in endocrinology research, and his skill in isolating peptides was highlighted by his success in isolating parathyroid hormone and adrenocorticotrophic hormone (Barr and Rossiter, 1973).

### INSULIN TODAY

Ninety years after its isolation and introduction as a therapeutic agent, insulin is used ever more widely, remaining irreplaceable and lifesaving for patients with type 1 diabetes. It is also now commonly prescribed as

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an add-on treatment for patients with type 2 diabetes who are not achieving their glycemic targets with other medications. Insulin is the standard primary therapy for gestational diabetes, the hyperglycemia that afflicts some women during pregnancy. More recently, it has been used in the treatment of the transient hyperglycemia that can accompany severe acute illness and trauma in nondiabetic patients, such as after stroke and surgery. This “stress hyperglycemia,” which in the past was typically left untreated except in extreme cases, is now considered undesirable and is treated with intravenous insulin (LeRoith et al., 2003; Van den Berghe et al., 2001). These varied uses for insulin are perhaps beyond the scope of what the Toronto group could have imagined. However, the early investigators of insulin were certain that their discovery would have an immense clinical impact. The significance of the discovery stands in contrast to its tumultuous history; it is unfortunate that such a rich legacy has been tarnished by such unnecessary strife. Lewellys Barker, a Canadian professor of medicine at Johns Hopkins, declared at Toronto’s 1923 Nobel Prize dinner, “In insulin there is glory enough for all” (*Toronto Star, 1923*, cited in Bliss, 1982).

### CONCLUSION

From Michael Bliss’s careful dissection of the history, it becomes clear that each of the four scientists had a specific role in the discovery of insulin. The supportive role of the pharmaceutical companies should be also appreciated, since they supplied the raw materials to keep the insulin project afloat. The work of each scientist alone was not sufficient and would not have resulted in the discovery of insulin. The key was a combination of their work, despite their personal and professional differences. The discovery made by the team was greater than the sum of its parts.

What swayed the cognoscenti? The carefully documented books, lectures, and scholarly articles written by Bliss have been the major force. The passing of the Old Guard and of the devoted acolytes and relatives of Banting and Best has also helped. At the celebratory dinner in Toronto, an eloquent scholarly toast was raised to each member of the team—Banting, Macleod, Collip, and Best—and the first monument to the achievement was unveiled at the university, honoring the four. The discoverers’ struggle for credit arose from a desire to make a place for themselves in history. Perhaps they did not realize that in the history of medicine, there would be glory enough for all.

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