Rethinking the "discovery" of insulin

Cite as: *CMAJ* 2021 October 25;193:E1636-7. doi: 10.1503/cmaj.211401

The centenary of the discovery of insulin is being marked this year by publications and commemorative events across Canada and around the world. Without doubt, the advent of insulin is worthy of celebration. What bears closer inspection, however, is our use of the term "discovery" in describing the events at the University of Toronto from 1921 to 1923.

Michael Bliss' 1982 book, *The Discovery of Insulin*,[1] is acclaimed as the definitive account. Until its publication, any Canadian schoolchild likely would have said insulin was discovered by Banting and Best. In painstaking detail, Bliss reconstructed the investigations day by day, dog by dog, and made the case that the insulin discovery actually resulted from the teamwork of Frederick Grant Banting, Charles Herbert Best, James Bertram Collip and John James Rickard Macleod. In the decades since 1982, the less alliteratively appealing, but more accurate formulation of "Banting, Best, Collip and Macleod" has become accepted by scholars. All 4 figures are now reflected in popular accounts, ranging from the graphic on the World Diabetes Day website to the tightly scripted new *Heritage Minute* video created by Historica Canada.

Bliss dissected the creation and promotion of the "Banting and Best" myth,[2] but even in recent years and in the work of historians, it is not hard to find insulin still described as the work of "Banting and Best." When Collip is mentioned, he is typically said to be the biochemist brought aboard to purify the insulin. This rendering of the story suggests that Collip's role was rather like that of a sous-chef who plates the chef's masterful creation. It belies the fact that the purification — more precisely, the preparation of an extract pure enough to be used continuously in human therapy — was really the entire point of the enterprise.

For decades, researchers in many parts of the world had tried to make an extract of the pancreas as a treatment for diabetes.

Commemorative banner of the discovery of insulin on Confederation Boulevard, Ottawa, with images of Frederick Banting and Charles Best. Department of Canadian Heritage. Photo taken by Carlo Magaard-Romano.

Macleod estimated there had already been some 400 such attempts. Several were particularly notable, such as those of Georg Zülzer in Berlin, Ernest Lyman Scott in Chicago, Israel Kleiner in New York, John Murlin in Rochester and Nicolae Paulescu in Bucharest. A century later, the priority claims of these investigators continue to have their champions. The ongoing and often fervent debates — coloured by institutional and national pride — illustrate the complex nature of scientific discovery and the futility of locating it to a single "eureka" moment.

Banting, a physician and general surgeon, and Best, a new graduate in honours biochemistry and physiology, worked with the support and supervision of Professor Macleod, a respected expert in carbohydrate metabolism. From May to December 1921, they made exciting progress in the laboratory, creating an extract of the pancreas and showing that it reduced blood glucose in depancreatized dogs. They had not, however, discovered anything that had not already been accomplished and published by other researchers years before. They and several of their predecessors showed that a pancreatic extract could alleviate 1 or more symptoms of diabetes. These extracts, however, were full of toxic materials that caused fever, abscesses and other harmful adverse effects. What none of them had been able to accomplish — what remained the Holy Grail — was to make an extract that could be used safely to treat a person with diabetes. This was the feat that Collip managed to accomplish in a flurry of activity over a remarkable 42 days from Dec. 12, 1921, to Jan. 19, 1922.

Collip was an associate professor in the Department of Physiology and Biochemistry at the University of Alberta, on sabbatical leave in Toronto that year. As a seasoned biochemist, he set to work systematically, and with an appreciation of the scientific literature and the broader physiologic context. Although his ostensible task was to purify the extract, he understood his work not simply as an effort to rid the extract of toxic impurities, but rather as part of a larger, collaborative scientific endeavour to understand the principle's nature and physiologic function. As an experienced experimental scientist, he was soon able to find ways to speed up the research. He figured out that he could use normal rabbits rather than depancreatized dogs as a relatively inexpensive and readily available subject with which to evaluate the potency of the extract. He adopted a new method of blood glucose analysis that allowed quick, convenient measurements with a small volume of blood. In rapid succession, Collip made several key contributions. First, he proved that the extract reduced ketones in urine. Second, he showed that it allowed the body to convert glucose into glycogen in the liver. These findings were evidence that the extract actually restored the ability of the diabetic body to metabolize sugar. Third, Collip identified the hypoglycemic reaction when he observed that 1 of his test rabbits went into convulsions after receiving a dose of extract, but that the subject could be revived by the administration of sugar.

On Jan. 11, 1922, Leonard Thompson, a 13-year-old boy with diabetes, received an intravenous injection of an extract made by Banting and Best. The results were disappointing; no clinical benefit was observed, and what's more, a painful abscess formed at the site of injection. In the days that followed, Collip threw himself into the purification problem. On Jan. 19, working alone late at night, using a succession of different concentrations of alcohol, he discovered a way to trap the antidiabetic hormone in a semipure form. This extract was tested the following Monday, Jan. 23, on Thompson and the results were dramatically different; there were marked improvements in blood glucose and in urinary sugar and ketone levels. Thompson felt stronger, brighter and more active. This was the first unambiguously successful clinical use of a pancreatic extract in a person with diabetes.[3]

Getting from a single application to the large-scale manufacture of a safe, stable and reliable supply of insulin would be a monumental task, requiring the combined efforts of many more people in the departments of physiology, pharmacology and medicine at the University of Toronto, the Connaught Laboratories and Eli Lilly and Company of Indianapolis, along with a network of clinical collaborators. By 1923, the method devised by Collip had been improved upon and superseded several times by the work of other researchers, including David Scott, Peter Moloney and George Walden, resulting in insulin that was up to 100 times more potent than the material Collip had captured that wintery night.[4]

Collip would modestly say that he had only done what any good biochemist would have done, but more importantly, he recognized the collaborative nature of the endeavour. Years later, when philanthropist Gladys Muttart, herself a person with diabetes, wrote to Collip of plans to donate a Wurlitzer organ in his honour, she suggested a plaque engraved: "In recognition of the contribution of James Bertram Collip to the discovery of insulin." Collip replied, saying he was deeply touched, but asking for a change in wording. Instead of "the discovery of insulin," he substituted, "the development of insulin therapy for diabetes." He said, "although I have been guilty of using the word 'discovery' on occasion myself, generally speaking I do not like it. Most so called discoveries represent simply the last but important step in a long series of previous steps, representing contributions of many others through the years in the scientists [sic] search for truth."[5]

In celebrating the centenary of insulin's arrival, we might slip into using "discovery" as a shorthand for this outstanding achievement, but let us not forget the far richer history of contribution and collaboration that is contained within that term, one featuring numerous investigators, administrators, and clinical and industrial partners, in a heroic effort spanning several nations and many years.

Alison Li PhD
Toronto, Ont.

References

1. Bliss M. *The discovery of insulin: the twenty-fifth anniversary edition*. Toronto: University of Toronto Press; 1982.
2. Bliss M. The eclipse and rehabilitation of JJR Macleod, Scotland's insulin laureate. *J R Coll Physicians Edinb* 2013;43:366-73.
3. Li A. *J.B. Collip and the development of medical research in Canada*. Montreal: McGill-Queens University Press; 2003.
4. Rutty C. Insulin 100. Defining Moments Canada. Available: https://definingmomentscanada.ca/insulin100/ (accessed 2021 Aug 9).
5. Muttart MD. Letter to: Dr. James B. Collip 1959 August 7; Collip, J.B. Letter to: Mrs. M.D. Muttart, 1959 August 13. Papers of Dr. James Bertram Collip, Dean of Medicine, University of Western Ontario, London, 1913–1964. Archives and Research Collections Centre, Western University.

This article has been peer reviewed.

Competing interests: Dr. Li reports being the author of *J.B. Collip and the Development of Medical Research in Canada* (McGill University Press) and of the foreword to the forthcoming special centenary edition of *The Discovery of Insulin* by Michael Bliss (University of Toronto Press), for which she receives royalties.