In the study of no other non-infectious disease has there been closer collaboration between laboratory and clinical investigators than in that of diabetes.¹

Leprosy has long had a reputation for being one of the most feared of all human diseases. In Canada today the disease is a rarity and the few existing cases are considered little threat to public health; however, this was not always the case. In the mid- to late nineteenth century an endemic leprosy was found to exist among the Acadian Population of New Brunswick, a discovery which caused much concern within the nation’s medical and legislative communities of the time. In this outbreak, which occurred prior to the discovery of the leprosy bacillus, the physicians involved with the situation were deeply divided as to the nature of the disease: was it hereditary or was it contagious? Their decision would prove fateful for the victims of the disease in this area. Furthermore, issues of race and class would become central in the discussion surrounding the appearance of leprosy in this population.

When J.J.R. Macleod wrote this statement in the February 1922 edition of The Canadian Medical Association Journal (CMAJ), he was referring to the contributions of numerous groups of scientists and physicians over many years, including his own Toronto-based team, to the study and treatment of diabetes mellitus. Macleod, a professor of physiology at the University of Toronto and assistant dean of the Faculty of Medicine, was the primary investigator who supplied the laboratory space, advice and medical science community clout that ultimately allowed F.G. Banting, C.H. Best and J.B. Collip to isolate the pancreatic hormone insulin and to be the first to use it to successfully treat diabetes mellitus. Macleod’s commentary prefaced Banting, Best and Collip’s preliminary report published in the same issue of the journal entitled “Pancreatic Extracts in the Treatment of Diabetes Mellitus.” This was the team’s first publication, which, although preliminary, indicated that their pancreatic extract (later named insulin) was able to control the clinical manifestations of diabetes mellitus in humans and in their opinion left “no doubt…that [insulin] was a therapeutic measure of unquestionable value.”² The impact of insulin can be regarded as one of the most dramatic events in the history of the treatment of disease and in 1923, the Nobel Prize was awarded for the discovery of insulin at Toronto.

In early November of 1920, Dr. Banting arrived in Toronto to meet Dr. Macleod after being directed there by Prof. Miller of the University of Western Ontario in London, Ontario. Upon reading volume XXXI, number 5 of “Surgery, Gynecology and Obstetrics” (1920), Banting, a struggling physician in London, was struck by an idea of how to make a pancreatic extract that contained the mysterious substance or internal secretion, which was hypothesized to control the metabolism of carbohydrates in blood.³ He was sent to Macleod, a specialist in diabetes, with the hope that he would give advice and laboratory resources. After two turndowns, Banting’s persistence was able to convince Macleod to provide him with eight weeks of lab space, experimental dogs and a bright young physiologist named C.H. Best to partially compensate for Banting’s lack of medical science research skills. In May of 1921, Banting and Best began what would be a tedious and tumultuous conquest to ligate the pancreatic ducts of dogs, wait for their pancreases to degenerate and isolate isletin, a working term for what was later called insulin. Upon injection into depancreatized dogs, it was hoped that the extract would counteract the clinical features of diabetes. On July 30th, 1921 Banting and Best found that injecting their extract into a diabetic dog’s veins was able to transiently reduce the blood and urine sugar levels and relieve the
Since 1887, when Von Mehring and Minkowski discovered that depancreatizing an animal renders it diabetic, many efforts had been attempted to devise methods for extracting the principle ingredient of the gland that mediated its anti-diabetic effects. However, no method was sufficiently robust to produce large enough quantities needed to sustain a diabetic animal once treatment had started while at the same time being pure enough to eliminate unwanted toxicity reactions. In an issue of the CMAJ, an editorial by Macleod recognizes Knowlton and Starling, Kleiner, Murlin, E.L. Scott and Paulesco as the investigators that provided the most notable evidence of an internal secretion before the Toronto team had done. He notes, however, that their “results...have been...insufficiently constant and significant to justify more intensive research with the object of securing preparations of greater potency that could be used for the treatment of diabetes in man.” Banting wanted to produce the elusive sufficiently constant results and Macleod apparently believed that he might be able to succeed.

Aware of the progress that Banting and Best had accomplished in dogs and perhaps foreseeing the potential of clinical implications, Macleod expanded the Toronto team, at the request of Banting, to include the biochemist and endocrinologist J.B. Collip in mid-December 1921. At this point, Macleod had shifted the focus of his other research interests and instructed his whole staff to work to purify insulin (the Toronto team had now used the term insulin for their extract, coined years earlier by Sir A.E. Schafer). It was Collip’s principle task to work on Banting and Best’s newly discovered extract in order to refine its purity and increase its yield through the use of more sophisticated biochemical techniques. The priority was to produce enough pure insulin for use in human testing — the hurdle that so many other researchers had failed to leap.

It was merely six months later, on January 11, 1922, a refined version of the extract used in the summer was injected into 14-year-old Leonard Thomson in Ward H of the Toronto General Hospital (TGH). Many significant events occurred within this time period. Most notably, the extract was able to prolong the life of a depancreatized dog named Marjorie (referred to in lab note books as dog #33) for 70 days beginning in the last week of November until it was sacrificed. These long-term results were a significant and unprecedented achievement and it was the formula for this extract that was chosen by Macleod to be used in Leonard Thomson, heralding the first clinical trial of insulin.

Interestingly though, the extract injected into Leonard Thomson, was of Banting and Best’s formula that they had been using on Marjorie since November, a month before Collip began working on the project. In fact, Collip’s extracts were only starting to be used on January 23, 1922, which was 12 days after the first clinical trial of insulin in Leonard. Perhaps the mixed experimental results were sufficient to convince Macleod that Banting and Best’s extract was refined and safe enough to be injected into a human. Insulin’s first patient, Leonard Thomson was 14 years old when he was admitted to TGH on December 2nd, 1921 as “poorly nourished, pale, weigh[ing] 65 pounds, hair falling out, odour of acetone on [his] breath...abdomen large and tympanic...dull, talked rather slowly [and] quite willing to lie about all day.” He had been diagnosed with a case of severe juvenile diabetes with ketosis and according to Macleod, Banting, Best and the rest of the Toronto group, his “careful dietetic regulation [(the prevailing treatment for diabetes at the time)] failed to influence the course of the disease. [B]y January 11th his clinical condition [was]...definitely worse.” Banting et al., made it evident in their 1922 CMAJ publication from which these excerpts are taken that it was Thomson’s unpromising and grave circumstance that prompted them to inject what was described as a “thick brown muck” into the boy’s buttocks – this muck, as described by Walter Campbell, the chief clinician at TGH at the time, was 15 cc. of beef pancreas extract made by Banting and Best.
The effect of this first clinical test with Banting and Best’s extract was not spectacular. In the Banting et al. CMAJ paper, it is described with one sentence:

The extracts given on January 11th were not as concentrated as those used at a later date, and, other than a slightly lowered sugar excretion and a 25% fall in the blood sugar level, no clinical benefit was evidenced.2

More extracts were administered to patients at TGH beginning on January 23rd. It was these injections that justified insulin’s eventual fame as a wondrous therapeutic because they resulted in immediate improvement to the diabetic patient’s clinical and emotional condition. But the extracts that provided these positive results, which, were given subsequently to the one that Thomson received, were made from Collip’s formula and not Banting and Best’s. On January 19th, 1922 Collip recalled, “I discovered a way to get the active principle free from all the ‘muck’ with which it appeared to be inseparably bound.”9 With additional insulin therapy, approximately 85 units per day for 13 years, Leonard Thomson was able to live a “more or less normal life” until he died on April 20, 1935 of complications due to pneumonia.9 Collip had accomplished the duty to which he was specifically assigned. He had prepared a more pure extract by refining Banting and Best’s method and, in doing so, as Macleod had requested, made available an extract that was more suitable to be injected into a human for clinical testing. The result was that for the first time in recorded history, an extract of pancreas had been unambiguously successful in having a distinct antidiabetic effect on a human. Now, millions of people worldwide who suffer and would surely die from diabetes mellitus are offered life and the hope of fulfilling their goals and achieving happiness.

References

9. The Discovery of Insulin at the University of Toronto: An Exhibition Commemorating the 75th Anniversary. K Martyn, M Bliss, M Vranic. Toronto: University of Toronto Library, 1996.