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REVIEW

The discovery of insulin in Toronto: beginning a 100 year journey of research and clinical achievement

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Abstract

There has been a great deal of controversy regarding priority of discovery of insulin. Indeed, many scientists made important and, in some cases, seminal contributions to identifying the endocrine role of the pancreas and the potential for pancreatic extracts to have a glucose-lowering effect. The purpose of this article is to describe the early experiences with respect to research leading to the discovery of insulin in Toronto (ON, Canada). The experiments conducted at the University of Toronto resulted in the first demonstration that a pancreatic extract could be prepared that would consistently lower glucose, reverse ketosis and arrest the catabolic effects of type 1 diabetes. The remarkably rapid commercial production of insulin soon followed. The Toronto story begins on 17 May 1921, when Frederick Banting and Charles Best began their summer research project in the laboratory of John James Rickard Macleod, and we are now celebrating the 100th anniversary of this landmark achievement. The article herein outlines the steps leading up to the discovery of insulin and provides an overview of some of the key developments in insulin therapy over the past 100 years.

Keywords Banting · Best · Diabetes · Insulin · Review · Type 1 diabetes

Introduction

There has been a great deal of controversy regarding priority of discovery of insulin. Indeed, many scientists made important and, in some cases, seminal contributions to identifying the endocrine role of the pancreas and the potential for pancreatic extracts to have a glucose-lowering effect. However, it is not the purpose of this article to review the scholarly discussions with respect to priority of discovery of insulin, but rather to describe the early experiences with respect to insulin discovery in Toronto (ON, Canada). Irrespective, it is clear that the work described below, which occurred in Toronto, resulted in the critical event of demonstrating that an effective pancreatic extract could be prepared that would consistently lower glucose, reverse ketosis and arrest the catabolic effects of type 1 diabetes. This resulted in the remarkably rapid commercial production of insulin, saving millions of lives.

The Toronto story begins on 17 May 1921, when Frederick Banting and Charles Best began their summer research project in the laboratory of John James Rickard Macleod, and we are now celebrating the 100th anniversary of this landmark achievement [1–4]. Following their success, insulin was heralded in the lay press as a 'miracle substance', and for good reason. Prior to the availability of insulin, the treatment of type 1 diabetes mellitus primarily consisted of severe energy restriction. This negative energy balance, coupled with the progressive decline in endogenous insulin secretion as a consequence of the ongoing autoimmune destruction of the beta cells, resulted in continued weight loss, emaciation and, ultimately, diabetic ketoacidosis, coma and death. In fact, diabetes in childhood prior to 1922 was universally fatal. In contrast, the results of the treatment of the first 50 patients with insulin in Toronto highlights the truly dramatic clinical response of this lifesaving therapy. The following report was published in the *BMJ* in 1923 [5]:

> *Up to the present time over fifty cases of diabetes mellitus have been treated with insulin. ... Many of*

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the patients have come to the hospital in the state of extreme under-nutrition, suffering from great weakness along with an indisposition to any physical activity. On the first or second day of treatment, if sufficient insulin is given, the urine becomes sugar-free, and on the second or third day ketone-free. These patients become conscious of increasing strength before the end of the first week. ... Hunger is replaced by appetite; the thirst is lessened, oedema, which is common in these cases, disappears. Patients find they are less irritable and state that they begin to sleep well. The expression improves; the skin becomes less harsh and dry; even the hair becomes softer; in fact, the patient loses that appearance which characterizes the diabetic. In ten days a very considerable amount of physical vigour is restored. Some patients have been able to return to work after a month of treatment.
Frederick Banting, Walter Campbell, Almon Fletcher

Interestingly, despite this remarkable therapeutic response, the discoverers of insulin knew that their early treatment with insulin was only the beginning, with Macleod and Campbell indicating, in 1925, that in using insulin it would, of course, be ideal if it could be supplied so as to imitate the natural process. Indeed, the next decades (1930–1970) revealed the devastating microvascular and macrovascular complications associated with conventional insulin treatment of type 1 diabetes. These included an increased risk of visual impairment by 31%, stroke by 10%, amputation by 12%, myocardial infarction by 21% and renal failure by 22% [6].

Advances in insulin therapy have indeed been substantial over the past 100 years. In 1993, the landmark trial, the DCCT, demonstrated that with appropriate intensive diabetes regimens (insulin pumps or multiple daily injections), diabetes complications could be prevented in individuals without existing complications (primary prevention cohort), or the progression slowed in those with early complications (secondary intervention cohort) [7]. This landmark study conclusively established the validity of the glucose hypothesis: that hyperglycaemia is the principal cause of the microvascular complications of diabetes. More recently, the long-term epidemiological follow-up study of the DCCT, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, demonstrated that with improved glucose control, individuals with type 1 diabetes can achieve an essentially normal life expectancy [7, 8]. This 100th anniversary of the discovery of insulin and its subsequent development as a therapy for diabetes provides an opportunity to reflect on the history of the discovery of insulin, a story that has its beginnings in the 1800s.

Pivotal early research on diabetes

In 1869, Paul Langerhans, a medical student in Germany, identified irregularly shaped islands of cells throughout the pancreas. Although not realised at the time, these collections of cells (‘islets of Langerhans’) would subsequently be identified as the cells responsible for the production of insulin, glucagon and other peptide hormones. One of the earliest accounts of what would be later named ‘insulin’ dates back to 1889, when researchers in Germany were studying the effects of the pancreas on digestion [9]. Following total pancreatectomy in a dog, the researchers noted that flies and other insects could be found feeding on the dog’s urine. This was an early clue that the pancreas played an important role in glucose metabolism. Experiments conducted by M. Eugène Gley during the subsequent decade demonstrated that pancreatic extracts were capable of reducing glycosuria among depancreatised dogs [10–12]. Work by Georg L. Zülzer confirmed this observation via parenteral administration of a pancreatic extract to both dogs and people with diabetes [13]. He subsequently received a patent for the pancreatic extract, though the extract was not widely used.

Following the turn of the 20th century, Eugene Opie, an American pathologist, identified that the islets of Langerhans produced what would later be confirmed to be insulin [14]. He demonstrated that destruction of the islets of Langerhans would result in diabetes mellitus. Although controversial, it appears the term ‘insuline’ was first coined in 1909 by the Belgian biochemist Jan de Meyer [15]. The term comes from the Latin root *insula*, which means ‘island’.

By 1916, the Romanian physiologist Nicolae Paulescu developed an extract from the pancreas that was able to lower blood sugar levels in dogs with diabetes. His work, however, was stalled by World War I and it was not until 1921 that it was published [16]. Of note, while Paulescu and other researchers had demonstrated that pancreatic extracts lead to reductions in glucosuria, the reductions were not always sustained, were often associated with life-threatening reactions and conclusive studies in humans were not undertaken [16, 17].

One of the pivotal contributions prior to the work of Banting, Best, and Macleod occurred in 1919 [18]. Israel Kleiner, working at the Rockefeller Institute in New York City (NY, USA), was able to reproducibly demonstrate that administration of aqueous solutions of ground pancreas caused hypoglycaemia [18]. Prior experiments demonstrated reductions in glucosuria rather than blood glucose because the method to measure blood glucose was not well established prior to 1919. Regardless, the pancreatic extracts produced by Kleiner lacked the purity to be administered to people with diabetes mellitus. With the work of Kleiner and many scientists before him, the groundwork was laid for the ‘discovery’ of insulin by Banting and his team.

Insulin discovery in Toronto: how the story commenced

Banting was born in London, Ontario, and completed his medical school training at the University of Toronto. He intended to become a surgeon; however, his applications for a surgical internship were unsuccessful and he returned to London, Ontario, where he opened a general medicine practice. In addition to his medical practice, he taught in the anatomy laboratory at London's Western University. In preparation for a lecture he was to give on carbohydrate metabolism, he reviewed a recently published paper entitled 'The relation of the islets of Langerhans with special reference to cases of pancreatic lithiasis' [19]. As Banting's bedside journal documents, he awoke from his sleep in the evening prior to the lecture and noted the following: 'Diabetus [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' [1, 20].

Although Banting had no formal research training, the idea that the difficulty of extracting insulin was caused by destruction of the islets of Langerhans when exposed to the other components of the pancreas captivated him and he returned to the University of Toronto. There, he approached Macleod, professor of physiology, to supervise his proposed summer research project. Macleod agreed and, while the work would be unpaid, he did provide Banting with laboratory space and equipment, dogs and a student assistant. The potential student, Charles Best, was keen to be involved with the project as his favourite aunt had recently died of diabetes [21]. After winning a coin toss, Best was assigned the role of student assistant.

Banting and Best first attempted to isolate insulin through a pancreatic duct ligation, whereby the duct connecting the pancreas to the small intestine was tied off [22]. Duct ligation atrophied the pancreatic acinar exocrine cells that produced digestive enzymes, thus leaving behind the islets of Langerhans. Duct-ligated dogs, in contrast to those receiving a pancreatectomy, did not develop diabetes mellitus. This observation further supported Banting's initial hypothesis about the importance of preserving the islets of Langerhans to isolate insulin, though a key challenge was keeping dogs alive long enough following pancreatic duct ligation.

By July of 1921, 2 months into their summer research project, Banting and Best had successfully isolated a solution of atrophied pancreas dissolved in normal saline [22]. They then injected this solution into a dog that had had its pancreas removed. Astonishingly, they were able to keep the dog alive with their pancreatic extract. Their results were encouraging, albeit preliminary, as they continued to struggle to produce stable and sufficient quantities of the pancreatic extract. At the direction of Macleod, by the latter part of 1921, they invited Collip to join their team.

Collip was a skilled biochemist and University of Toronto graduate who was on sabbatical from the University of Alberta (AB, Canada). His key contribution was helping the team—where nearly all previous teams had failed—to purify a safe and stable extract of insulin. The method of extraction involved a combination of varying concentrations of slightly acidic alcohol and cold temperature to inactivate the pancreatic enzymes, which required a neutral pH and a body temperature to be active, and, thus, extract insulin before it was digested by the pancreatic enzymes and without toxic contaminants. With his skillset, they were able to produce a pancreatic extract of sufficient purity and potency for human use.

First successful treatment of a patient with insulin

On 11 January 1922, an insulin extract termed 'Macleod serum' was administered to a 14-year-old boy named Leonard Thompson (7.5 cc [ml] into each buttock) [20]. While this pancreatic extract reduced the patient's glucosuria, the effects were modest, at best. Following further refinements to the pancreatic solution (principally by Collip), a second series of injections starting on 23 January 1922 resulted in a rapid reduction in glucosuria and resolution of ketonuria. This marked the first successful administration of insulin to a person with type 1 diabetes and, ultimately, led to the development of commercially available insulin. Interestingly, Leonard Thompson's chart also documents the first adverse reaction to subcutaneous insulin, with the development of an injection-site reaction (Fig. 1). Of note, this was a reaction to the initial pancreatic extract and not the preparation developed by Collip.

Following the successful administration of insulin to Leonard Thompson, a team of clinicians was formed to oversee the administration of insulin to other patients at Toronto General Hospital [5, 23]. Many of these patients were in a coma owing to their diabetes and, thus, the administration of insulin was truly lifesaving for these patients, as described by Campbell and colleagues [5, 23].

Widespread production of insulin

While the successful administration of insulin was a monumental achievement, problems began to arise in the subsequent months. A significant problem was that the team did not record the precise steps of their purification method and, by March 1922, the team was unable to re-produce insulin [24]. This was of immediate concern for patients who received insulin during the preceding 2 months and cast significant doubts about the possibility of widescale production.

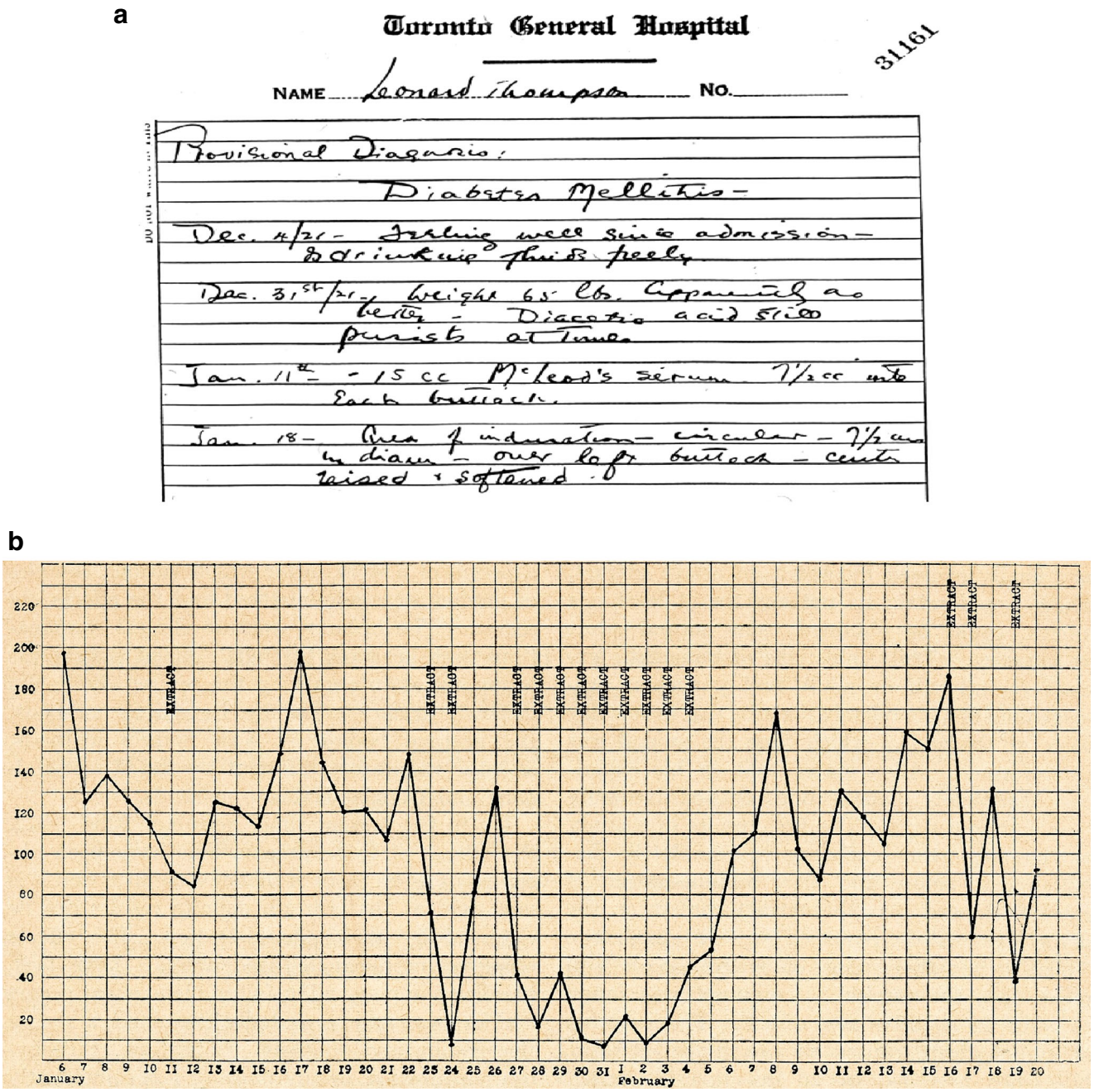

Fig. 1 Record from the administration of insulin in January 1922. (**a**) Medical record of Leonard Thompson (December 1921/January 1922), the first patient with type 1 diabetes to be successfully administered insulin, from the Toronto General Hospital. An initial dose of insulin extract, termed 'Macleod serum', was administered to the patient (7.5 cc [ml] into each buttock) on the 11 January 1922. This was followed by successful administration of insulin on the 23 January 1922. Also documented is the first adverse reaction to subcutaneous insulin: injection-site reactions. The text displayed in the record reads as follows:
Provisional Diagnosis: Diabetes mellitus -
Dec. 4/21 – feeling well since administration – is drinking fluids freely.
Dec 31st/21 – Weight 65 lbs. Apparently no better. Diabetic acid still persists at times.
Jan. 11th – 15 cc [ml] McLeod's serum. 7½ cc [ml] into each buttock.
Jan. 18 – Area of induration – circular – 7½ cm in diameter – over left buttock – centre raised + softened.
(**b**) Effect of administration of the insulin extract on glucose levels in urine from Leonard Thompson. On the *x*-axis, the date ranging from 6 January 1922 to 20 February 1922 is shown, while on the *y*-axis is the amount of sugar, ranging from 0 g to 240 g. (**a**) Used with permission from Thomas Fisher Rare Book Library, University of Toronto; (**b**) reprinted from [35], www.cmaj.ca. This figure is available as part of a downloadable slideset

By the spring of 1922, the Toronto team was again able to successfully produce insulin, but they realised they were ill-equipped for widescale production. Thus, they partnered with George H. A. Clowes of Eli Lilly and Company. Collip and Banting shared their 'recipe for insulin' and within weeks Clowes and the team at Eli Lilly were able to produce larger

batches, albeit with impurities and not quite at the scale necessary for the global demand.

Although they partnered with Eli Lilly, the patent for insulin was signed over to the University of Toronto for US$1. On an earlier version of the patent declaration, dated 3 June 1922, both Macleod and Banting declined to sign the patent. Banting reportedly felt, having sworn the Hippocratic Oath, that he could not, in good conscience, be party to the patent. Neither Best, a medical student at the time, nor Collip felt an ethical dilemma and were officially named as the inventors of insulin on the initial patent declaration.

By the end of the summer of 1922, Eli Lilly was increasing production of insulin, though further refinements were needed to improve production yield and 'purity'. A major breakthrough came that Autumn, when chemists applied isoelectric precipitation to produce insulin. The method of isoelectric precipitation provided a reliable method for mass production of insulin. By 1923, nearly all insulin was being produced by either Eli Lilly in the USA or Connaught Laboratories in Canada.

In 1922, August Krogh, a Danish professor in zoophysiology and Nobel Laureate, visited Toronto to learn about insulin [25]. His interests were both scientific and personal, as he was married to Marie Krogh who was a physician caring for patients with diabetes mellitus who herself had diabetes. By early 1923, Professor Krogh and Hans Christian Hagedorn, a Danish chemist and physician, began producing insulin in Copenhagen, Denmark, at their Nordisk Insulin Laboratory and had successfully administered it to patients with diabetes.

Development of insulin analogues

During the 1920s, patients with diabetes mellitus would typically receive 3–4 doses of insulin each day [26–28]. There was a clear demand for longer acting forms of insulin to limit the number of daily injections required. The core problem, though, was that the time course of insulin action was relatively short and multiple daily injections would be required.

By the mid-1930s, attempts were made to create a longer acting form of insulin. The first success was by Hagedorn (in Denmark), who identified that basic proteins (e.g., protamine) could be added to the insulin molecule to stabilise it [29]. At the same time, in Toronto, researchers identified that other substrates could be used to prolong insulin's half-life, most notably zinc. These advances allowed for long-acting insulin to be used in conjunction with the originally available shorter acting version. These longer acting forms of insulin became widely available in the late 1940s, and by the mid-1950s, even longer acting forms existed (e.g., lente insulin).

The next major milestone occurred in 1955, when the British biochemist Frederick Sanger sequenced insulin. It was the first protein to be fully sequenced, an achievement that secured Sanger the 1958 Nobel Prize in Chemistry [30]. The sequencing of insulin paved the way for a shift from animal-based insulin to synthetic 'human' insulin. With the development of recombinant DNA technology, it became possible to produce human insulin in large amounts, independent of the need to obtain beef or pork pancreases. The production of human insulin essentially resolved the problem associated with the development of anti-insulin antibodies leading to lipoatrophy and antibody-mediated insulin resistance [31].

While multiple forms of insulin were clinically available by the 1980s, they did not approach physiological insulin replacement. Specifically, there was a growing need for both a more rapid-acting insulin for mealtime use and longer acting forms of insulin for between mealtimes or basal coverage. By the 1990s, the first form of rapid-acting insulin analogue was approved (insulin lispro) and by 2000, the first truly long-acting insulin analogue was approved (insulin glargine). Progress continued and, to this date, newer insulin analogues have been developed that have superior pharmacokinetic and pharmacodynamic properties. In 1989, one of the authors (BZ) published an article in the 'Drug Therapy' section of the *New England Journal of Medicine* entitled 'Physiologic replacement of insulin: an elusive goal' [32]. Thirty-two years later, and 100 years since the discovery of insulin, we are closer to this goal, but it still remains elusive. With the subcutaneous injection of newer insulin analogues, we are able to approximate the insulin profiles characteristic of meal responses and overnight basal requirements. However, to duplicate physiological secretion, the insulin would have to be released into the portal system, reproducing the high concentration achieved in the liver, where it has important effects on hepatic metabolism [33]. In contrast, when insulin is injected subcutaneously, the hepatic and peripheral insulin concentrations are similar. It is unclear whether this difference has any clinical relevance other than somewhat higher peripheral insulin concentrations. In addition, and consistent with most hormonal systems, closed-loop feedback would be required. Designer insulins, with superior pharmacokinetics and pharmacodynamics, provide important advances, but on their own they will not achieve physiological insulin replacement.

Insulin discovery in Toronto: what happened next?

For their work, Banting and Macleod received the Nobel Prize in Physiology or Medicine in 1923, 18 months after their remarkable accomplishment. Banting shared his prize money with Best, and Macleod shared his with Collip. Although there was controversy regarding the appropriate recognition of the

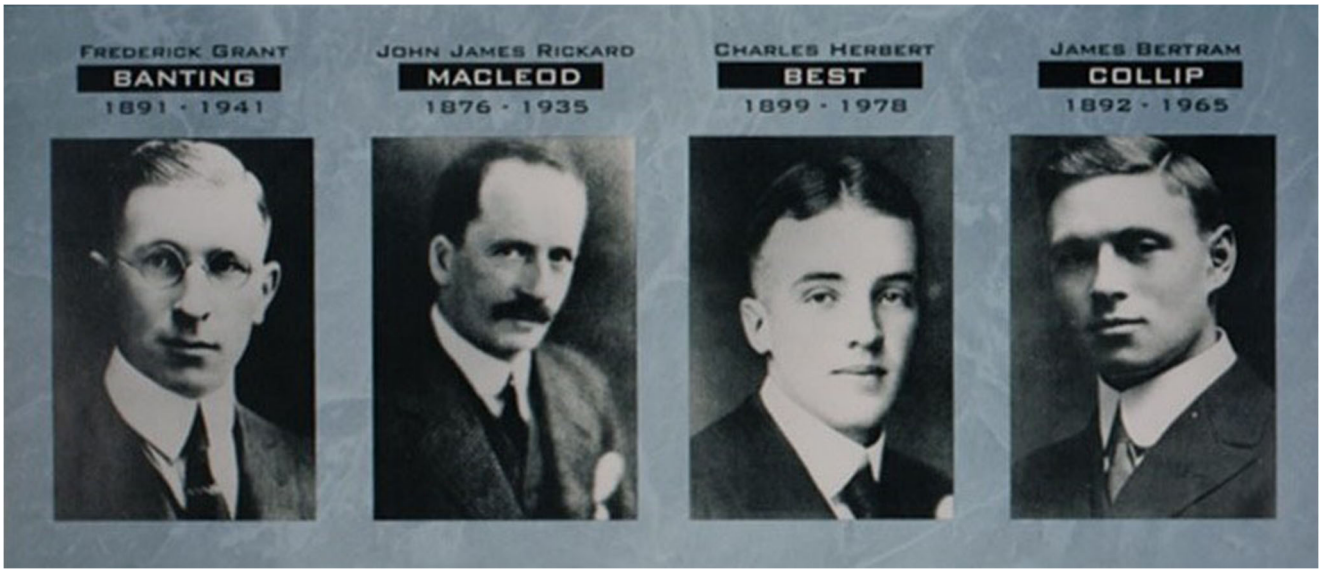

Fig. 2 Toronto's key players in the discovery of insulin. Banting conceived the idea and research plan for isolating insulin and Best assisted Banting with the experiments. Macleod supervised Banting and Best and provided them with the necessary laboratory space and equipment to conduct their research. Collip played an integral role by developing a method to purify a safe and stable extract of insulin. Image courtesy of Banting House National Historic Site of Canada. This figure is available as part of a downloadable slideset

various members of the insulin discovery team, the 1988 television movie (based on the Michael Bliss book, 'The Discovery of Insulin' [1]) got it right in titling the movie 'Glory enough for all' [34]. Indeed, each member of the research team made important and critical contributions to the successful isolation and clinical application of insulin for diabetes (Fig. 2).

Macleod would return to his home in Scotland in 1928, where he lived until his death in 1935. Collip returned to the University of Alberta before leaving for McGill University (QC, Canada), where he would go on to be one of the first scientists to isolate parathyroid hormone. He also served as Dean of Medicine there from 1928 to 1941, followed by Dean of Medicine at the University of Western Ontario from 1947 to 1961. Best continued his research into the physiological activity of insulin, though his scientific interests expanded beyond insulin; in the 1930s, he and his team were the first in the world to purify heparin, which allowed it to be safely used in humans. In 1978, Best died at 79 years of age, owing to a ruptured aortic aneurysm. Banting continued his research following the discovery of insulin. Banting died in a plane crash in Newfoundland on his way to England in 1941, during the second world war.

Leonard Thompson, the 14-year-old boy who received the first successful administration of insulin, would live for another 13 years. Although it pales in comparison with current life expectancies for people with type 1 diabetes, if it were not for the discovery of insulin by the Toronto team, Leonard would probably not have seen his 15th birthday.

The discovery of insulin in Toronto in 1921 and its first administration to a patient with type 1 diabetes in 1922, followed by the remarkably rapid transition to a widely available commercial product in 1923, is truly something to celebrate. Although there continues to be a debate about priority with respect to the isolation of an active glucose-lowering pancreatic extract that lowered glucose in animal experiments, there should be little controversy that the events in Toronto changed the lives of countless individuals with type 1 diabetes. The year 2021 will be recognised as a centennial year globally, marking an amazing 100 years of progress in insulin therapy with the prospect of completing the goal of physiological insulin replacement.

Supplementary Information The online version contains a slideset of the figures for download available at https://doi.org/10.1007/s00125-020-05371-6.

Authors' relationships and activities BZ reports serving on scientific advisory boards for Eli Lilly, Novo Nordisk and Sanofi. MF declares that there are no relationships or activities that might bias, or be perceived to bias, their work.

Contribution statement MF wrote the initial draft of the article. Both authors were responsible for revising it critically for important intellectual content and approved the version to be published.

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