The miracle of insulin

Mark WJ Strachan[1]

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Correspondence to:
Mark WJ Strachan
Metabolic Unit
Western General Hospital
Crewe Road
Edinburgh EH4 2XU
UK

Email:
mark.strachan@nhslothian.scot.nhs.uk

The discovery of insulin in 1921 was, at the time, little short of a miracle. The practice of 'physic' was largely based then around pharmaceuticals of dubious benefit and undoubted toxicity, such as the compounds derived from heavy metals to treat syphilis and heart failure. Prior to the discover of insulin, a child diagnosed with diabetes had an average life expectancy of only a matter of months. Survival could be extended by several further months by the rigorous application of a very low calorie and carbohydrate diet, as advocated by the American physician Frederick Allen, but the diet was miserably restrictive and ultimately the patient and their family faced a stark choice between death from starvation or death from diabetic ketoacidosis.

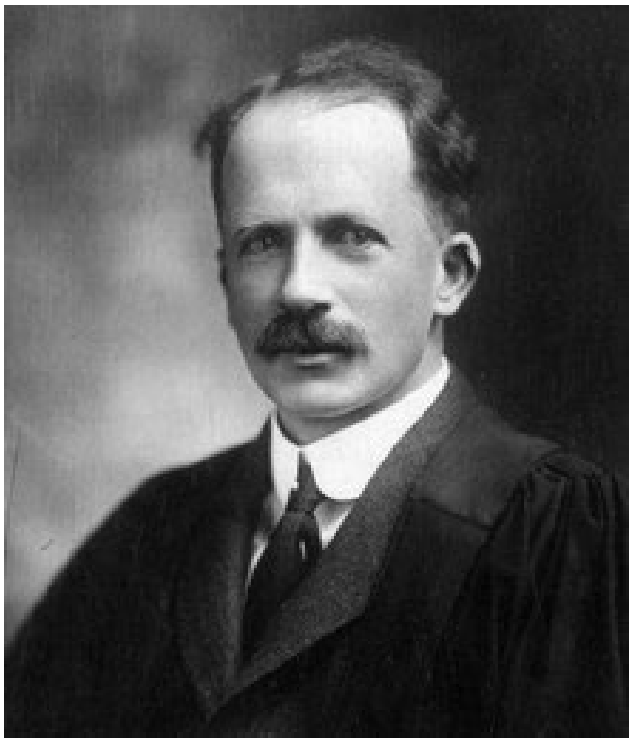
It had long been known that an 'internal secretion' of the pancreas (i.e., a substance distinct from the digestive enzymes, which ultimately entered the systemic circulation rather than be externally excreted) was important in regulating blood glucose. Pancreatectomy in animals resulted in their swift death from diabetes. Several scientists in the early twentieth century had come close to developing a pancreatic extract that lowered glucose, but the presence of pancreatic enzymes in the extract resulted in significant local toxicities after injection and variable effectiveness (presumably because the enzymes were degrading the internal secretion).

In the extremely hot summer of 1921, Frederick Banting and Charles Best started work on creating an extract of pancreatic internal secretion from dogs. Banting had a very unsuccessful career as an orthopaedic surgeon and then a general practitioner, before approaching the eminent Scottish physiologist, Professor James Macleod of the University of Toronto (Figure 1). Banting's 'idea' was that the internal secretion could be isolated by making a pancreatic extract several weeks after surgical ligation of the pancreatic duct of a dog. Banting postulated that pancreatic duct ligation would result in atrophy of the acinar cells allowing a 'purer' extract of the internal secretion, relatively free from the toxic effects of the digestive enzymes. Macleod had an international reputation in carbohydrate metabolism. Despite Banting's lack of any research training or experience in pancreatic surgery in humans, let alone animals, Macleod gave Banting laboratory space, resources and the services of one of his students, Charles Best. Such largesse was a credit to Macleod and something that would probably not be replicated today in any major research institute!

Banting and Best's initial studies were unsuccessful, not the least because of high mortality in the dogs operated on by Banting. Their scientific method was chaotic by modern standards and lacked rigour. However, despite this, progress was made. The key turning point was the decision to abandon Banting's original idea, and instead to try and purify the internal secretion from the pancreas glands of cows, which were readily available from the local abattoir. At Macleod's suggestion, the biochemist James Collip joined the group and his input proved vital in the efforts to purify the internal secretion, now known as insulin. On 11 January 1922, Leonard Thomson, a 14-year-old boy dying of diabetic ketoacidosis, became the first human to receive an injection of insulin. The circumstances around the initial use of insulin in Thomson would certainly not meet the standards of therapeutic research in humans today, but Thomson quickly recovered from ketoacidosis and would go on to live for a further 13 years. The Toronto scientists became internationally renowned, but Banting and Macleod had a spectacular disagreement. Banting felt that Macleod was taking credit for a discovery that had been due to his idea and work; Banting did not recognise the substantial intellectual and practical contributions that Macleod had made to the

[1]Consultant in Diabetes and Endocrinology, Western General Hospital, Edinburgh, UK

Figure 1 Professor James JR Macleod, Professor of Physiology, University of Totonto. Photo reproduced from *J R Coll Physicians Edin* 2013; 43: 366–73.



scientific achievement. In 1923, Banting and Macleod were awarded the Nobel Prize in Physiology or Medicine. It was the shortest interval between a scientific discovery and the award of a Nobel prize and was testament to the magnitude of the impact the discovery had on people with diabetes. It was a truly remarkable achievement, but Banting and Macleod would never speak to each other again.

Overnight, the discovery of insulin transformed diabetes (and in particular what we now recognise as Type 1 diabetes) from a terminal illness to one where prolonged survival was possible. However, it was not a cure for diabetes and in the years that followed it became evident that insulin injections alone could not restore normoglycaemia. Increased longevity came at the price of terrible advanced complications of diabetes: blindness, kidney failure and lower limb amputation. Patients had to live with the perpetual risk of hypoglycaemia and indeed fear of hypoglycaemia would prove to be a major barrier in achieving strict glycaemic control, as glucose was maintained at high levels to reduce the risk of 'a hypo'.

Pharmaceutical companies played a pivotal role in the evolution of insulin as a therapeutic agent. Initially, their input was vital in enhancing the purity of the extracts and in turning the 'cottage industry' in Toronto into large-scale production. Later, companies developed basal insulins whose durations of action were prolonged by the addition of protamine or zinc. Until the 1980s, commercially available insulin continued to be derived from cow and pig pancreas glands, but in 1978 insulin became the first human protein to be synthesised through biotechnology, using recombinant DNA technology in *Escherichia coli*. Human-sequence insulins were introduced in the 1980s and proved to be less immunogenic than the animal-derived insulins. In subsequent years, analogues of insulin were created, with modifications to the amino-acid sequence of insulin or the addition of chemical moieties to the insulin molecule itself, that had either much shorter or longer durations of action. These evolutionary changes to insulin, coupled with the introduction of capillary blood glucose testing, allowed individuals with Type 1 diabetes to improve glycaemic control, experience fewer episodes of hypoglycaemia and ultimately have a lower risk of complications and improved life expectancy.

However, people with Type 1 diabetes still have to live with marked excursions in blood glucose, with substantial variability across a 24-hour period and from day-to-day. The ever-present risk of hypoglycaemia has intrusive effects on countless activities of daily life, including work, driving and sport. Serious complications of diabetes still occur, and life expectancy is reduced compared to the general population. The fundamental issue is that the delivery of exogenous insulin is not inextricably coupled to the prevailing blood glucose. Once a dose of exogenous insulin is administered, it will lower blood glucose whatever the prevailing level. Human factors are also important, and all too often doses of insulin are omitted (either accidentally or deliberately) or inappropriate doses administered. Delivery of insulin has moved on from the initial glass syringes, through pen devices (initially pioneered in Scotland by Sheila Reith and John Ireland) to insulin pumps. The ability to monitor glucose has also developed substantially and now continuous glucose monitoring is becoming the standard of care in Type 1 diabetes in high-resource settings.

The future is very bright. Linked insulin pumps and continuous monitoring systems now provide that crucial tethering of delivery of insulin to blood glucose levels, creating 'artificial pancreas' systems. There are even 'bionic pancreas' systems in development that contain separate syringe drivers of insulin and glucagon, and which use artificial intelligence and machine learning, with the aim of achieving near-normal blood glucose with minimal input form the user. As we approach the centenary of the discovery and first clinical use of insulin, we have the real prospect of a 'technological cure' for Type 1 diabetes. However, these diabetes technologies are expensive and have the potential to exacerbate inequalities in diabetes care worldwide. While these systems should be cost effective in the long term by reducing complications of diabetes, funding these new technologies will be a major challenge in the short to medium term. The Toronto investigators would no doubt regard these technological developments as 'miraculous', but 100 years on it is right that we pay tribute to their amazing discovery.

Suggested reading

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