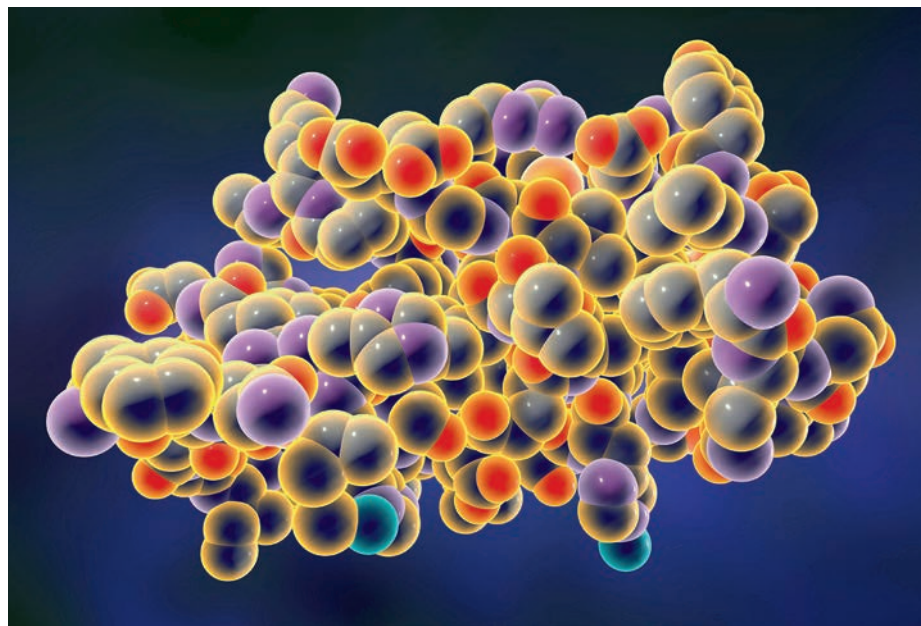


Milestone 1



A history of insulin: initial discovery to first use in the treatment of T1D

In 1921, Frederick Banting and Charles Best designed a series of experiments to identify how the pancreas was involved in carbohydrate metabolism. Their work, published in 1922, built on findings from studies over the previous 40–50 years showing that the pancreas, and more specifically the islets of Langerhans, was key for carbohydrate metabolism and might be involved in the pathogenesis of the disease we now know as type 1 diabetes (T1D). This work led to the identification of insulin.

Together with John Macleod, Banting and Best hypothesized that carbohydrate metabolism was either controlled by the blood being modified while passing through the pancreas, or by the islets of Langerhans producing an internal secretion. Banting and Best began by removing the pancreases from several dogs, which then went on to display signs of diabetes, including increased blood and urine levels of glucose. The dogs were then injected with different pancreatic extracts, after which blood and urine levels of glucose fell and their overall health improved. Banting and Best noted that the degree of the effect varied depending on

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how concentrated the extract was. They also found that extracts containing pancreatic juices (containing digestive enzymes) negated the positive effects of the pancreatic extract on glucose levels. These results demonstrate that a pancreatic secretion was involved in carbohydrate metabolism.

Following these findings, the researchers started work to purify the extract. Early use of this pancreatic extract in patients was unsuccessful, owing to its high protein content. James Bertram Collip then joined the team in order to help purify the pancreatic extract further, to give insulin. The researchers went on to devise a method to produce larger quantities of insulin, so that they could start to administer it to patients.

Work began at Toronto General Hospital, Canada, to administer insulin to a small number of patients with T1D, under close supervision. Leonard Thompson (14 years old) was, famously, one of these early patients – and was potentially the first patient to be administered with insulin. Similarly to the earlier animal work, blood and urine levels of glucose dropped following administration of insulin in these patients. The patients also reported complete resolution of the subjective symptoms associated with T1D.

Reporting on the case of Leonard Thompson, the researchers noted his low weight, lethargy and high blood and urine levels of glucose. Following daily administration of insulin, Leonard quickly began to feel better and was more alert, and his blood and urine levels of glucose reduced. On withdrawal of treatment for 2 days, his symptoms returned. In their 1922 paper in the *Canadian Medical Association Journal*, the researchers note that “These results taken together have been such as to leave no doubt that in these extracts we have a therapeutic measure of unquestionable value in the treatment of certain phases of the disease in man.”

The researchers noted that their early findings were positive enough to warrant further work to refine the treatment regimen and improve patient outcomes. The following decades saw rapid advances in the use of insulin to treat T1D, such as the discovery in the 1930s that the action of insulin can be prolonged with the addition of protamine.

Banting and Macleod were awarded the Nobel Prize in Physiology or Medicine for their work in identifying insulin. Recognizing the key involvement of Best and Collip, Banting and Macleod decided to share the prize money with their two colleagues. As Banting noted in his Nobel Prize lecture, insulin is not a cure for T1D; it is instead a treatment that enables people with T1D to metabolize carbohydrates. T1D research has advanced considerably in the 100 years since Banting and Best’s seminal paper, but a cure has remained elusive. It is to be hoped that a cure will be found in the next few years.

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Nature Reviews Endocrinology

Milestone study

Banting, F. G. & Best, C. H. The internal secretion of the pancreas. *J. Lab. Clin. Med.* **7**, 465–480 (1922)

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