

The discovery of insulin

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Introduction

The discovery of insulin is a landmark of medical history: it introduced life-saving treatment for a previously fatal disease and brought hope to millions. The research studies of Banting and Best in Toronto during the summer of 1921 have been recounted many times over. So also have the later contributions of Collip and Macleod, leading to refinements of the pancreatic extracts and their successful administration to Leonard Thompson in January of 1922.¹ The award of the Nobel Prize and the commercialisation of insulin are also well rehearsed postscripts to the discovery story, but comparatively little consideration has been accorded to events of the late 1800s and early 1900s that led up to the work in Toronto: these events are focused upon here.

'Islands' of Langerhans

The discovery of insulin is conveniently traced from research by Paul Langerhans when he was a medical student in Berlin. In 1869 Langerhans submitted a thesis on the microscopic anatomy of the pancreas in which he described the 'islands' of tissue that now bear his name: their function was unknown.² Although Claude Bernard had noted more than a decade earlier that animals could not be kept alive after pancreatectomy,³ the crucial link between the pancreas and diabetes had to wait for the work of Josef von Mering and Oskar Minkowski at the University of Strasbourg in 1889. While studying the role of the pancreas in fat digestion their technician observed the polyuria and glucosuria of a pancreatectomised dog. Minkowski and von Mering recognised these features to be typical of diabetes.⁴ They pancreatectomised further dogs to confirm the findings, and Minkowski later reported partial reversal of the diabetes by subcutaneous implants of pieces of pancreas.^{3,5}

Around the same time (1890-93) a French scientist, Edouard Hedon, also conducted experiments showing that subcutaneous auto-implants of pancreatic tissue could partially reverse the diabetes of pancreatectomised dogs and it was recalled that there had

been reports (such as those of Etienne Lancereaux) that atrophy of the pancreas was often observed at autopsy of people with diabetes.^{6,7} However, even though it was recognised that pancreatic duct ligation could cause pancreatic atrophy without destruction of the pancreatic islands and without glucosuria, the pancreatic islands were yet to be implicated in the prevention of diabetes.⁸

Extracts of pancreas

The possibility that the islands of Langerhans might produce an internal secretion that prevents glucosuria was suggested by Gustave Laguesse in 1893, fuelling the emerging concept of endocrine glands.⁹ However, therapeutic studies for diabetes continued to focus on pancreas pieces and very crude extracts of pancreas: some short-term successes were reported with animal studies, but attempts to treat human diabetes with pieces of animal pancreas were unsuccessful.⁷ For example, Patrick Watson-Williams in Bristol in 1894 implanted pieces of sheep pancreas under the skin of a 15-year-old boy who was severely ill with diabetes: the boy died several days later.

The question of an antidiabetic principle from the islands of Langerhans was revisited in 1901 when the American pathologist, Eugene Opie, described degenerated fibrotic islets in a patient with diabetes.¹⁰ Similarly, interest was rekindled in 1906 when Wilhelm Heiberg reported fewer islands in pancreatic tissue from diabetes patients,¹¹ and in 1907 John Rennie and Thomas Fraser in Aberdeen reported that fish islet extracts slightly reduced glycosuria sometimes in five diabetes patients.¹² More encouraging progress came from Berlin, where Georg Zuelzer had been experimenting with injections of pancreas extracts into pancreatectomised dogs. In 1908 he obtained a pancreas extract (Acomatol) from a local pharmaceutical company and reported how injections of the extract kept a diabetes patient alive until supplies ran out: his own extracts were only temporarily helpful in this and other patients.¹³ Sadly, he was unable to continue his work as his pharmaceutical sponsors felt that he would do better to concentrate on what is now recognised as type 2 diabetes.

Studies that stimulated Banting

Following the work of Zuelzer, several laboratories reported studies in diabetic animals, confirming that injections of pancreas extracts could reduce glycosuria and prolong survival.¹¹ Most notable of these were the studies of Ernest Scott (Chicago, 1911), John Murlin and Benjamin Kramer (New York, 1913), and Israel Kleiner (New York, 1919).¹⁴⁻¹⁶ John Macleod, Professor of Physiology in Toronto, met Scott but he did not encourage him. Although no successful clinical studies emerged from these

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sources, the latter two are cited by Banting and Best in their seminal publication, indicating that they were key to Banting's rationale for selecting pancreatectomised dogs as the model in which to test his extracts.¹⁷ Also stimulating Banting's thoughts on diabetes was a paper by Moses Barron from Minneapolis in 1920 which described a fibrotic pancreas with intact islets. This reminded Banting of animal studies of pancreatic duct ligation, and suggested to him that he "might obtain the internal secretion free from the external secretion".^{18,19}

Parallel research

One of the most intriguing stories surrounding the discovery of insulin is the work of the French physiologist Eugène Gley. In Paris between 1900 and 1905 Gley prepared pancreas extracts and recorded that they reduced glycosuria and increased survival when injected into pancreatectomised dogs.²⁰ The next steps he did not publish but described in a sealed document which he deposited with the Société Française de Biologie in 1905, asking that it be opened only when he so requested.¹¹ In 1922, when the work of Banting and Best became known, Gley asked for the document to be opened: it appears that Gley had conducted studies around 1900 with extracts made from mainly islet tissue of pancreatic duct-ligated animals and had found these extracts to be particularly potent in preventing glycosuria in diabetic animals.¹¹

Another important piece of parallel research with pancreatic extracts was undertaken by physiologist Nicolae Paulesco in Bucharest. In 1916, Paulesco prepared and injected pancreatic extracts into pancreatectomised dogs and noted the reduction in blood sugar. The work was interrupted by World War I and was not published until August 1921; it had not proceeded as far as clinical studies.²¹

Successful clinical outcome

As the histological studies of Langerhans became subsumed into the initial concepts of endocrinology the nomenclature evolved and in 1909 the Belgian physiologist Jean De Meyer suggested the name 'insuline' for the putative antidiabetic internal secretion of the islands.²² The same name ('insulin') was independently proposed by English physiologist Edward Sharpey-Schäfer in 1916, but it was not until well into the 1920s that reasonably purified preparations became available. Even the refined pancreatic extracts prepared for clinical use by Collip in early 1922 were still the consistency of a sludge and probably the source of infections that accompanied the initial injections.^{1,23} Further purification on a large scale was vital to the possible clinical usefulness of pancreatic extracts. Collip and Macleod formed a close association with Eli Lilly (and in particular with George Clowes) who were able to purify the extract further and also to assist Connaught Laboratories in Toronto to produce clinically useful extracts.

The question of who deserved the Nobel Prize remains a matter for debate, and more credit should perhaps have been given to Paulesco, whose critical paper was mistranslated by Best and therefore was not quoted in the seminal paper by Banting



Key messages

- Discovery of insulin was one of most important developments in medicine of last 150 years.
- It took decades for the initial suggestions of the role of the islets of Langerhans in diabetes to be translated into treatment for humans
- No single person or group was responsible for identifying the source of insulin, its extraction and therapeutic significance

and Best. That said, we acknowledge with grateful thanks the contributions of all concerned in the pre-insulin research that provided the foundation for the achievements of the group in Toronto during 1921 and early 1922. We have seen how so many came so close to preparing a clinically effective pancreatic extract but did not achieve a successful clinical outcome. This awaited the enthusiasm and concerted efforts of Frederick Banting, the diligent assistance of Charles Best, the guidance and facilities provided by John Macleod, the biochemical expertise of James Collip, the support of Eli Lilly and the desperation of the mother of a 13-year-old son in diabetic coma with no more than days to live.

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