Hidden Gems

Tim Holt
Contributing Editor

Shining a light into the past for the articles that continue to shape our diabetes clinical practice today

This issue: Banting FG, Best CH, Collip JB, Campbell WR, Fletcher AA (1922) Pancreatic extracts in the treatment of diabetes mellitus: preliminary report. *CMAJ* 12: 141–6

This classical article by Banting et al describes the basic research leading up to and including the first administration of "pancreatic extract" to humans with diabetes. In terms of its historical importance and later impact on clinical practice, this report is perhaps without equal in the literature of diabetes. Within a year of its publication, a marketable product, insulin, was available, and its mass production followed soon after.

Historical context

There has been an established link between the pancreas and diabetes for well over 100 years. It was evident in 1889 that pancreatectomised dogs rapidly became hyperglycaemic (Von Mering and Minkowski, 1889), and it was first demonstrated in 1916 by Paulescu (1921) that the administration of pancreatic tissue extract would reduce their blood glucose levels. However, the effect was transitory, the nature of the responsible substance in the extract was unknown, and World War I largely prevented further research. It took until after the war for Paulescu to publish his findings.

The discovery of insulin as the active principle, and the identification of its origin within the beta cells of the islets of Langerhans, is now a familiar story. During 1921, Canadian physician and surgeon Frederick Banting was given use of a University of Toronto (Canada) laboratory by the physiologist John J Macleod. Whilst Macleod was away for the summer, Banting conducted new experiments on dogs to investigate the relationship between the pancreas and diabetes. One experiment involved ligation of the pancreatic duct, which led to atrophy of the exocrine tissue with relative sparing of the islets of Langerhans. This provided a means of protecting endocrine secretions from the destructive effects of digestive enzymes also produced by the pancreas. With the help of a PhD student Charles Best (who is said to have won a coin toss over another student to join Banting's project), a new pancreatic endocrine extract was derived. The extract was clearly effective at reducing blood glucose levels in dogs and was purer than the substance used by Paulescu. By January 1922, it was considered pure enough to risk a trial in humans with diabetes.

The Hidden Gem

The report by Banting et al describes the crucial next step in the discovery of insulin by trialling the pancreatic extract in humans. The authors describe a series of experiments using the still unnamed substance, initially in dogs and then in seven in-patients with diabetes.

Until this report, the beneficial effect of pancreatic extract in diabetes was very limited, largely because the active substance was destroyed by the digestive enzymes. Banting hypothesised that ligation of the pancreatic duct would produce degeneration of the pancreatic tissue and suspected that the acinar cells producing the digestive enzymes would be more sensitive to this procedure than the endocrine tissue. If the pancreas was removed 10 weeks after ligation, the authors believed that there would be a relative preservation of the "internal secretion". Banting also recognised that further benefit might come from tying off the arteries supplying the gland, again producing selective destruction of the exocrine tissue. It was then possible to extract a substance that more safely and effectively reduced hyperglycaemia, at least in dogs. As controls, the investigators also injected extracts of liver and spleen into dogs with diabetes, with no resulting effect on blood glucose or urinary glucose excretion. This identified the pancreatic tissue that had survived the ligation process as the source of the therapeutic substance.

In preliminary experiments reported in this article, the authors further noted that foetal calf pancreas at 5 months' development did not require ligation to isolate the pancreatic extract as the digestive enzymes had not yet formed, and they also successfully prepared bovine pancreatic extract from adult oxen. They injected either extract into a "completely diabetic" dog daily, increasing its survival from an expected 14 days to 70 days. The potential for a fundamental breakthrough in the treatment of diabetes was clear.

Once pancreatic extract was known to have a beneficial effect on diabetes, the next step was to make it safe for use in humans. Allergic reactions from the proteins in the extracts had been observed in dogs and other animals, so the biochemist James B Collip, who

Affiliation
Academic Clinical Lecturer, Nuffield Department of Primary Care Health Sciences, Oxford University

Hidden Gems

Figures 1 and 2. The effect of pancreatic extract injection on ketonuria and blood sugar in the first person with diabetes to be injected (from Banting et al, 1922).

Figure 1. Showing the cessation of ketonuria following administration of extract

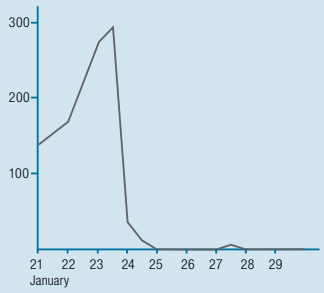
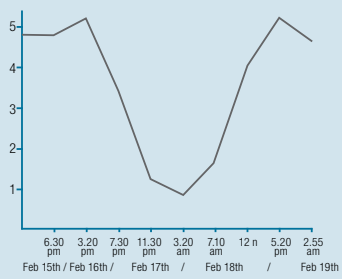


Figure 2. Effect of one injection of extract on blood sugar (mgs. per c.c.e=tenth per cent)



was particularly skilled in these purification techniques, isolated an extract that was sterile, highly potent, and could be administered subcutaneously to humans.

Case report: 1st human trial

Once the active principle of the pancreatic extract was isolated, it was injected into seven people with diabetes, all in-patients at Toronto General Hospital. The investigators monitored their blood sugar, urinary sugar, acetone bodies and respiratory quotient, as well as completing routine clinical examination. They then determined the effect of administrating the pancreatic extracts on these measures. *Figures 1* and *2* are taken from the paper and demonstrate the effect of injecting the pancreatic extract on both urinary ketones and blood sugar in the first recipient: a boy of 14 years admitted to the hospital with a 3-year history of progressive symptoms of juvenile-onset diabetes culminating in ketoacidosis.

Despite overall success (with improvement in symptoms, clinical signs and laboratory values), the spectre of allergic reaction continued to rear its head over these early experiments, particularly for the first recipient. It would require substantial work beyond this first trial to isolate the responsible substance in its pure form.

Why it still shines today

This is the seminal paper in the discovery of insulin, and its later purification and mass production. The cautious excitement of the authors is palpable. This was a heady time for diabetes research, and the paper was clearly prioritised for "fast-track" publication: the first human recipient received the pancreatic extract on 11 January 1922, the report was submitted 6 weeks later, and it appeared in print in the March 1922 issue of the *Canadian Medical Association Journal*. Just 2 years after the experiments in Macleod's laboratory, Banting and Macleod were awarded the Nobel Prize for Medicine in 1923 for their discovery. Banting, still only 32 years of age, chose to share his prize with Best, and Macleod shared his with Collip.

This is a classical study that demonstrates other principles influencing medical progress: Banting and Best seem to have capitalised on the freedom to think laterally in MacLeod's laboratory during the summer of 1921. Banting's surgical background enabled him to recognise the value of tying off the arterial supply to a dog's pancreas and the effect this would have in preserving the endocrine function. Who would have guessed that a surgeon would find the cure for type 1 diabetes?

The story continued to unfold through 1922 as the substance was confirmed to be associated with the islets on Langerhans and initially termed "isletin". A *BMJ* paper by MacLeod (1922) published later the same year explains that the newer term "insulin" had been coined by the English physiologist Edward Sharpey-Schafer (who also suggested the term "endocrinology"). The term "isletin" had only a brief appearance in the medical literature as it was soon replaced by "insulin".

In contrast to the modern approach to pharmaceutical discovery, in which the detailed chemical structure of multiple candidate molecules are conceived before they exist in reality, these experiments involved a substance whose chemical structure was unknown and whose exact cellular origin was still only a suspicion. But within a year of that first human injection, Eli Lilly had a product available for people with diabetes (Iletin), at least in the US. It was not long before mass production to a global market would follow.

A year after the article by Banting et al, a review article by Henry F Moore (1923) entitled *"Insulin" and Diabetes: The present position* was published. It gives an interesting account of the status of insulin (still new enough to justify inverted commas in the title) in the management of diabetes at that time. There is caution (which was also expressed by Banting and colleagues in their report) that the availability of this new treatment might downplay the importance of the dietetic approach, at that time, the mainstay of diabetes management. This concern is still relevant in modern diabetes care, where the much wider availability of drug therapies may similarly deprioritise lifestyle change as a fundamental basis for blood glucose and cardiovascular risk factor control. The review by Moore (1923) also noted hypoglycaemia as a hazard of the new treatment, still an issue today, and the need for frequent blood glucose monitoring to reduce this risk.

Clinicians at the time considered the place of insulin to be in fairly acute situations, such as the ketoacidosis scenario of the first recipient, where the transitory effects of a substance that required injection rather than oral administration would be appropriate. The history of insulin therapy since 1922 has seen improvements not only to purification techniques, to the production of genetically engineered human insulin and to the advent of insulin analogues, but also to the technology of injecting and self-monitoring devices that make all the difference to the quality of life of people with diabetes. These developments have amplified the impact of the research described in this paper in a way that these authors could not have imagined.

Macleod JJ (1922) Insulin and diabetes: A general statement of the physiological and therapeutic effects of insulin. *Br Med J* **2**: 833–5

Moore HF (1923) "Insulin" and diabetes: The present position. *Lancet* **201**: 715–7

Paulescu N (1921) Action of the pancreatic extract injected in the blood of a diabetic animal. *Comp Rend de Soc de Biol* **27**: 555–9

Von Mering J, Minkowski O (1889) Diabetes mellitus after pancreas extirpation. *Arch Fur Exper Path Pharmakol* **26**: 3711