Insulin – a 100-year story

2021 marks the 100th anniversary of the discovery of insulin, the life-saving treatment needed by people with diabetes, writes **Prof Gerald Tomkin**

While diabetes mellitus has been known about since Egyptian times, it is still prevalent today. Despite new medications and advances in knowledge, the condition still shortens life span by about 10 years, although this figure is rapidly reducing due to earlier diagnosis and better treatment for high blood glucose, cholesterol and high blood pressure.

This year marks the 100th anniversary of the revolutionary discovery of insulin as a life-saving treatment for diabetes. It is hard for us to comprehend just what this discovery meant to people with diabetes in 1921.

Prior to this, obese patients who developed diabetes could treat the symptoms, including thirst, passing a lot of urine and tiredness, by weight reduction and exercise. The reason for improvements in their condition is now much better understood.

Today, we know that the hormone insulin, which is secreted by the islet cells in the pancreas, lowers blood glucose. A deficiency of insulin leads to a rising blood glucose and this is the cause of the thirst. The high blood glucose is no longer able to be contained by the kidney and is secreted in the urine. The high concentration of glucose in the urine pulls out glucose by osmosis, dragging water with it, therefore the higher the glucose in the blood and urine, the more water is pulled through the kidneys, which are filters.

The increased amount of water lost results in frequency of passing water, which is now full of glucose. The loss of water is recognised by the thirst mechanism, which gets switched on. As a result, the person with diabetes starts to drink continuously to make up for the loss of water in the urine. Sometimes the person tries to quench their thirst with copious amounts of sweetened drinks. This results in even further increases in blood glucose and even more thirst, until the whole system collapses. The person will lose consciousness, falling into a hyperosmolar coma, become very dehydrated and will die unless given intravenous fluids and then insulin.

The failure of the islets to secrete enough insulin leads to high blood glucose and that is the definition of diabetes. But how high must blood glucose be before the condition of diabetes is diagnosed? To decide this, it was felt a committee was needed and following this, many countries decided that they needed committees of their own.

The major criteria for the diagnosis of diabetes is harm, therefore if a blood glucose level of 6.5mmol/l is not associated with any of the complications of diabetes, then why label that patient diabetic? However, this approach presents a problem. In pregnancy, even very small increases in blood glucose in the mother may lead to a poor outcome. The foetus is very sensitive to the mother's raised glucose levels, which would not be considered a risk in the rest of the population. Very strict control of blood glucose in pregnancy leads to a normal outcome.

Minkowski, von Mering and the role of the pancreas

By 1921, it had already been discovered that if you removed the pancreas from dogs, they developed diabetes. This was discovered in 1889 by Oskar

Minkowski and Joseph von Mering when they performed their famous experiment in Strasbourg.

The discovery that the pancreas was the organ that held the secret of diabetes occurred by chance. Minkowski and von Mering were investigating the absorption of fat. Minkowski carried out a total pancreatectomy on a dog to examine fat absorption and found to his surprise that the dog developed diabetes. He carefully measured all parameters he could while the dog survived and realised that the pancreas contained an internal secretion that was necessary for survival. Minkowski went on to do a pancreatectomy and then attach a small part of the pancreas to the abdominal wall. No diabetes resulted until this remnant was removed, providing solid proof of the endocrine function of the pancreas. This was 10 years before the term 'hormone' had been introduced.

Minkowski's discovery that removal of the pancreas caused diabetes and therefore there must be some sort of regulator in the pancreas that regulated blood glucose, was game changing. This momentous discovery that diabetes was caused by a disease of the pancreas led to the discovery of insulin.

In 1921, Frederick Banting, a young surgeon at the University of Toronto, had an idea that if he ligated (tied up) the bile duct (the duct that secretes bile into the gut to help digestion), he might be able to extract an internal secretion, which would metabolise carbohydrate. He obtained reluctant support from professor of physiology, Prof John Macleod, who was an expert on carbohydrate metabolism. Macleod arranged for a laboratory to be made available in the summer of 1921 and assigned a student, Charles Best, to help Banting with the experiments. Macleod left them to it and went on holidays to Scotland.

Banting removed the pancreas from a dog named Marjorie, who then developed diabetes. They then gave her pancreatic extract and Marjorie lived for 70 days. This demonstrated how well the extract worked. With it, the dog lived despite her pancreatectomy, but without it, she died within a few days. This was an incredible discovery. If the extract could be given to humans, then people with diabetes could be saved from inevitable death.

Having made the discovery of an extract in the pancreas that would be called insulin, the problem was how to test it in humans. It had become clear that the pancreatic extract lowered blood glucose and stopped ketosis, the burning up of fat that was the usual cause of death in patients with diabetes before insulin. The problem was how to effectively and consistently purify the extract.

Collip and purification

James Collip, a chemist working on a sabbatical in Toronto, was employed to use his special skills to purify the extracts. He became a legend in his ability to extract hormones in his later years.

Leonard Thompson, a 14-year-old boy with a two-year history of diabetes, was being kept alive essentially by starvation. Weighing just 65lbs, he was dull and listless and smelled of acetone (ketosis).

On January 11, 1922, Banting and Best took their extract to Ward H of Toronto General Hospital, and the first ever injection of insulin was administered to Leonard Thompson by an intern. Leonard's blood glucose fell from 440 to 320, but he developed a sterile abscess and further injections were cancelled. Collip then worked tirelessly to purify the extract in a reproducible way. Leonard subsequently received an injection at 11am on January 23, a second dose that evening and then two injections the next day. His blood glucose became normal and the ketones disappeared.

It is hard to describe the impact this must have had and the astonishment the doctors, nurses and his parents must have felt when they witnessed such a seriously ill child coming back to full life and vigour.

Alas, the fairy story of the discovery of insulin was tempered by the human condition. The happy pair who made the discovery, Banting and Best, were both very inexperienced. Banting was shy and had little experience of speaking in public and Best was still only a student. When they reported their first results at a meeting, their presentation was something of a disaster. Prof Macleod, who was chairing the meeting, intervened on their behalf trying to help. Banting thought that the professor was trying to steal the limelight and became consumed with jealousy, so much so that he hid himself in his room and started drinking heavily.

Collip was working away on purification. On the evening he realised that he had cracked it, he went to see Banting and Best in their laboratory and said he was not going to tell them how he did it. It is suggested that if Banting had been larger, there would have been a physical altercation.

Eventually, peace was brokered by Macleod and other senior figures in the hospital and university. They were worried that the discovery would go elsewhere and Toronto would lose out. Banting was bitter as he was excluded from the hospital because he did not have a job there. He was not allowed to administer the extract and did not have access to the data generated by the treatment in the beginning. However eventually, the hospital gave in and appointed him as a paid member of staff.

Macleod and manufacturing

Problems arose with manufacturing the extracts in large quantities, due to a lack of experience and poor equipment.

Realising that they did know how to manufacture on a large scale, Macleod sought the resources and expertise of Eli Lilly, whose researcher, George Clowes, had recognised the importance of this discovery from the start, but had not been put off by Banting's nervous and halting presentation. After a period of collaboration between Eli Lilly and Toronto researchers, insulin was finally effectively standardised and purified enough for widespread commercial use.

One person who was helped by the discovery early on was RD Lawrence, who had been diagnosed with diabetes

in 1920. In 1921, he had been sent to Switzerland for what was thought would be his last days, when he got a telegram about the discovery of insulin.

He returned to London and as a result of insulin, he went on to live a long and distinguished life as a diabetologist, dedicated to looking after people with diabetes in King's College Hospital. In 1935, he founded the British Diabetic Association with writer, HG Wells, who also had diabetes.

Nobel Prize

On October 25, 1923, an assembly of 19 professors voted by secret ballot to award the Nobel Award in Physiology or Medicine to Banting and Macleod. However, when Banting received this news he was furious and said he would not accept it.

He was later persuaded that he should accept it in the interest of science and Canada. Banting cabled Best who was giving a lecture in Harvard. The telegram read "I ascribe to Best equal share in the discovery", hurt that he was not so acknowledged by the Nobel trustees. Macleod in turn shared his prize with Collip.

Yalow, Berson and the radioimmunoassay

Following the discovery of insulin and its translation into therapy for many tens of thousands of patients with diabetes, there remained a problem in how to measure insulin and how to measure the concentration in each batch made. The best way at the time was to see how effective the sample was in lowering the blood glucose of an animal, such as a rabbit. Other methods were tried, but none were very specific or sensitive.

Then came Rosalyn Yalow, a woman who overcame many socioeconomic obstacles to eventually study nuclear physics and take a position in the Veterans Administration Hospital in New York's Bronx to develop the medical use of radioactive isotopes. She worked with Solomon Berson throughout the 1950s and together they discovered and developed the radioimmunoassay for the measurement of insulin, which was very sensitive and specific. This technique could also be used to measure many other hormones.

Among their many discoveries was that type 2 diabetes, then known as non-insulin dependent diabetes, was not a problem of no or little insulin, but rather of insulin resistance.

Pictured above is a historic packaging for insulin vials from 1945, a hospital pack by Schering AG, Berlin

There was much scepticism about their work. Their seminal paper was rejected by the prestigious journal, *Science*, and by the *Journal of Clinical Investigation*, although this was later accepted when they changed the title. The paper holds the record for being one of the most cited papers of that journal.

Their discovery revolutionised diabetes and endocrinology research. Yalow was subsequently awarded a Nobel Prize in 1977. Unfortunately, Berson had died prematurely some years before.

Significance of the insulin discovery

One-hundred years on and after a lifetime of looking after patients with diabetes, it is hard for me to comprehend what this discovery meant to people with diabetes. The joy of seeing a very dehydrated, vomiting, ill patient, whether a child or adult, come back to full life is still to me a miracle.

Diabetes is still a difficult condition to manage. Every meal has to be matched to the insulin and every exercise matched to the insulin requirements. There are no days off and anxiety may increase insulin needs. A short burst of exercise may increase blood glucose, but long exercise lowers it.

Too much insulin leads to coma and sometimes this can occur without warning. Diabetes can also place a huge pressure on the families of those with the condition.

One-hundred years ago, insulin was seen as a 'cure' – the patient survived. However, in later years, it became clear that some patients who initially did well developed complications of diabetes. High blood glucose after many years may damage the blood vessels, leading to blindness, neuropathy and kidney failure. Damage to the large blood vessels can lead to heart attacks, stroke and amputations.

However, there have also been wonderful improvements in management thanks to things like continuous glucose sensors, insulin pumps and semi-automated insulin delivery systems. These have made an enormous difference.

Thankfully, it is now rare to become blind because of revolutionary treatment by ophthalmologists. Furthermore, while high blood pressure and high cholesterol frequently accompany diabetes in middle age, treatments for both have increased life expectancy to normal or near normal.

And yet, diabetes can still be a huge burden, particularly in late adolescence and young adulthood, when acceptance of its imposition can prove difficult, adversely affecting its management.

Looking after someone with diabetes over many years is fascinating, instructive and humbling. You get to know so many things about your patients and their families. The honour of being trusted by a patient is hard to describe and each one has a different journey.

While there are still unknowns, we know so much more about treating patients with diabetes now. And while the prevention of diabetes is still a hurdle to be jumped, progress is slowly being made.

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