A History of Diabetes Since the Discovery of Insulin – A Family Perspective

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My father, Russ Macaulay, has been diabetic for 72 years of his 75 years of life. His story provides a meaningful glimpse into the life of a diabetic since the discovery of insulin in 1922 by Banting, Best, Collip and Macleod. The remarkable success of insulin therapy for the treatment of diabetes is true testament to the value of basic and clinical research (see 1,2 for review). There are very few examples in science where the benefits of treatment have been so rewarding. Type 1 diabetes is primarily a juvenile onset disease resulting from autoimmune destruction of the pancreatic beta cells that produce insulin. Prior to insulin therapy, patients relied primarily on dietary treatment, the most popular at the time of the discovery of insulin being controlled fasting and restricting carbohydrate while feeding a diet high in protein and fat. In some cases this led to claims that patients could win themselves a few extra years of life, but eventually they wasted away as lipolysis accelerated and free fatty acids taken up by the liver became substrates for ketone formation, leading to acidosis, coma and death.

A variety of extracts were tried as therapeutics, particularly plant extracts, but with little or no success. Can you imagine the excitement of delivering the pancreatic insulin extract to emaciated, wasted children and seeing them return to health over a period of a few months? Not in their wildest dreams would researchers have believed that the development of this treatment would allow diabetics such as my father to live a normal and productive life, to work, play sport at a high level, and enjoy parenthood and grandparenthood. My father lives fully independently to this day, having outlived my mother – she unfortunately died of cancer several years ago.

CSL started production of insulin in Australia in 1923 after trials in late 1922, although it was also supplied from overseas. My father was treated on Burroughs Wellcome insulin from the UK during his early years. Treatment with insulin in the first few years after its discovery was fraught with danger and was not met with universal support. Some argued that it was too potent for general treatment. Ironically, an editorial in the *Medical Journal of Australia* at the time suggested that "hundreds of diabetics would be hastened to their graves" by their treatment with insulin (3). Indeed, potency of insulin in the early years of treatment was variable. Diabetic acidosis was an often a fatal complication in the first four years of the introduction of insulin, with mortality in the range of 50-80%. Hypoglycemic episodes were also common.

Monitoring urinary sugar became a crucial aspect of diabetic care, balancing diet with insulin therapy. My father's sister has told me that during the early years of his treatment, and the depression years, the cost and availability of insulin meant that dietary restriction was an important aspect of care as this reduced the amount of insulin required. My father was maintained on a restricted, low carbohydrate diet during this phase where every food portion was weighed. Bread was forbidden but a few dry biscuits were allowable. Not surprisingly, he was thin and physically wasted as physicians and researchers grappled with treatments. Issues of diet, especially increasing carbohydrate intake, had to be balanced with cost and availability of insulin. It was only when he was 14 or so and seen at the clinic at St Vincent's Hospital in Melbourne that his diet was significantly changed and he was encouraged to eat more and to supplement this with more insulin. The effects of this treatment of course meant that he gained weight and was able to reach his full physical potential.

Russ Macaulay receiving his 70 year Kellion Award (for having lived with Type I diabetes treatment for so long) from Gordon Bungan (Diabetes Australia) and Dame Elizabeth Murdoch.

Biotechnology has had a huge input into patient care for my father and other diabetics. Several factors have had major impacts in the treatment of diabetics. First, significant

Russ Macaulay with his grandchildren, Christmas 2001.

developments occurred in the formulations of the hormone itself.'"Regular" short acting insulin was the only formulation available during the early years. This was delivered via a large-gauge needle just before meals. Initially this was of varying potency and purity, as scientists grappled with extraction procedures. A leader in this field was Brailsford Robertson, who became the first chief of the CSIRO Division I currently work in. In the late 1930s protamine zinc insulin was introduced into patient care.

This formulation was slow acting as it released active insulin from a complex over a period of hours. This was a major achievement as it meant diabetics could be managed with one injection a day of a mixture of the regular and protamine zinc insulins. A relatively recent development in hormone therapy itself was the introduction of recombinant human insulin into patient care. Although this was met initially with trepidation over potency issues and hypoglycemic blindness, these have not proved to be major issues in patient care.

Developments in insulin delivery systems have also had a major influence on patient care. Initially glass syringes were used and needles were reused over and over again until they were too blunt to force through the skin. Syringes and needles had to be sterilised before each use by boiling and storing in methylated spirits. The advent of disposable needles and syringes was a huge bonus both for convenience and, importantly, also patient care. My father's skin had become so tough through the early years of insulin injection that it was difficult to actually force the needle through his skin. He had been injected in every possible site thousands of times during the course of his treatment.

A further advance was the introduction of the insulin pen, a syringe that outwardly looks similar to a pen, which delivers a measured quantity of insulin. This enabled diabetics with visual impairment (a common complication) to accurately deliver their insulin, and for diabetics in general to deliver insulin in different social situations. Thus, diabetics can now deliver their insulin in a restaurant, at the football or in the comfort of their home. The importance of this development cannot be overstated because it has made it feasible for diabetics to tightly control their blood sugar throughout the day and so avoid the complications of the disease. A significant additional option for some diabetics, though not my father, has been the introduction of the insulin pump that delivers small, measured doses of insulin throughout the day.

Sugar monitoring has had a major impact on patient management. Tightly regulating blood sugar levels was shown by the Diabetic Control and Complications Trial (DCCT) in the USA to be a significant, if not the major, factor in reducing the risk of diabetic complications. These complications are the major factors underlying the morbidity of the disease and include diabetic retinopathy leading to blindness, nephropathy and the need for dialysis, and microvascular complications, requiring in limb amputation. The link between urinary sugar and diabetes was recognised more than a thousand years ago by the early Egyptians. Urinary sugar formed the basis of early current day testing and management of diabetes, although even in the 1700s raised blood sugar in diabetics was recognised as being linked with urinary sugar output.

Urinary sugar testing in the early years of insulin therapy was difficult for both patient and physician alike, requiring the complexity of boiling urine to perform complicated Fehling's or Benedict's tests – relatively simple for biochemists, but not so for diabetics.

The development of paper indicator strips to measure urinary sugar (similar to the commonly used pH strips found in most biochemistry laboratories) was a major breakthrough for self-monitoring. However, the strips clearly did not provide an accurate measure of blood sugar level at the measurement time; rather, the value indicated was a reflection of a history of the time interval since the diabetic last visited the toilet. This was a particular arguing point in my family during this period with my father relying on these tests only to find that hypoglycaemic episodes ensued. The current portable blood sugar monitoring tests enable realistic testing to be carried out and so allow the tight control needed to avoid hypoglycaemic episodes and the complications arising from the disease.

We, as a family, are grateful for the advances in diabetes care that have resulted from research over the last century. Furthermore, I feel privileged to have been able to work in the field of insulin action for much of my career. I believe the future looks bright for diabetics. Further advances may come from implantable pancreas (be it from stem cells, human or animal islets or artificial means), oral insulins, continuous glucose monitoring devices, or increasing insulin sensitivity through understanding hormone action. I feel confident that future treatments will provide even better patient care and enable other diabetics to more comfortably experience the fulfilling life my father has been afforded.

References

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