Two types of diabetes: Case Study

While diabetes has been recognised as a severe disease since ancient times, it was only during the mid-20th century that NHMRC-funded researchers at the Baker Heart and Diabetes Institute conclusively demonstrated that there are two major types of diabetes – type 2 (T2D) and type 1 (T1D) – based upon whether a person can or cannot produce their own insulin. This finding enabled future generations of researchers and clinicians to address each type separately, leading to improved treatments and health advice for those living with diabetes.

Origin

Diabetes mellitus is a disease associated with high levels of blood sugar, a condition that if untreated can be fatal. It can also lead to serious health problems including cardiovascular disease, nerve damage, kidney damage, eye damage and hearing impairment.

Diabetes was medically described as early as the 5th century BC, in India,[1] and by 1866 at least two distinct forms of the disease were recognised, requiring distinct courses of treatment.[2]

In 1889, researchers discovered that the pancreas produced a substance (insulin) that helped to prevent diabetes and in 1921 insulin itself was chemically isolated. Production of insulin commenced soon after, including (in 1922) by Australia's Commonwealth Serum Laboratories.[3]

In 1930, NHMRC's precursor body, the Federal Health Council, received a report from one of its members – Dr E Robertson, Chair of the Health Commission, Victoria – on "action taken in Victoria to place the treatment by insulin and the provision of insulin for diabetics on a proper basis."

This action was to occur within a broader "Scheme for the reduction of the diabetic mortality in the State of Victoria", which was developed by Dr WJ Penfold of the Baker Medical Research Institute. The scheme comprised a number of steps, including determining which patients with high levels of blood sugar "were true diabetics."

Further understanding of this distinction between "true" and other diabetes was provided in 1936 by the finding that people with diabetes could be divided into insulin-resistant and insulin-sensitive types.[4] However, to prove or disprove definitively that these two types related to insulin production it was necessary to estimate the plasma insulin level in those with diabetes.[5] In the 1930s, no method for doing so existed.

Grants and Investment

NHMRC began funding medical research in 1938 and, commencing in 1939, researchers at the Baker Institute – which was established in 1926 as the biochemistry laboratory of The Alfred Hospital in Melbourne – received a succession of grants to support research on carbohydrate metabolism and diabetes. These topics had become highly significant once insulin started to become available.

The grants supported the work of a number of researchers including Charlotte Anderson, Joseph Bornstein, Arnold Ennor, GJ Lincoln, Shirley Richardson, Noel Rome and Phyliss Trewhella.

Insulin

Insulin is a small protein molecule and a hormone: a chemical messenger within the body. Cells in the pancreas (beta cells) produce insulin in response to raised blood sugar levels.

In turn, insulin causes the cell membranes of muscle cells to draw in glucose, providing them with energy.

If the body has sufficient energy, insulin signals the liver and muscle cells to store glucose as glycogen and it signals the liver and the body's adipose (fat) tissues to convert glucose into triglycerides (a type of fat).

Circulating insulin also promotes protein synthesis inside body cells.

CSL and insulin

A Federal Serum Institute (later known as the Commonwealth Serum Laboratories and now CSL Ltd) was founded by the Australian Government in 1916. CSL established insulin production late in 1922 and treatment with this insulin was initiated in 1923. At this time, CSL was one of only four laboratories world wide to produce insulin, and it remains the sole manufacturer of insulin in Australia today.[3]

Research

Anderson commenced research at the Institute in 1936 by investigating the effect of the pituitary gland upon diabetes. Her work indicated that extracts of the gland reduced the effectiveness of insulin in lowering blood sugar because they also increased the transformation of glycogen (stored in the liver and elsewhere) into glucose.[6,7]

Ennor recommenced work at the Institute in 1939 following completion of a Masters thesis on the effects of the adrenal gland on carbohydrate metabolism.[8] Informed by Anderson's work, he began the search for an 'anti-diabetogenic' hormone whose production was stimulated by exposure to the pituitary gland extracts.[9] His work also examined the effect of pituitary gland extracts on levels of the antioxidant glutathione in the liver.[10]

Informed by the work of Anderson, Ennor, and other researchers at the Institute, Bornstein began working with Trewhella in 1947 on how to measure the concentration of insulin in human blood plasma.[11] Their approach was to create a type of rat that was unable to produce its own insulin or the pituitary and adrenal hormones that had previously been found to influence blood glucose (BG) levels and insulin uptake.[12] These rats were difficult to work with[13] because they tended to experience hypoglycemia (low BG levels)[14] but they were also extremely sensitive to insulin and would experience a measurable reduction in BG after receiving only 2 nanograms of insulin.[13,15]

After being injected with both glucose and insulin, periodic measurement of BG levels in the rats would indicate how much insulin they had received. The more they had received the more their BG levels would fall.[14] If such a rat was injected with human blood plasma, and if that plasma contained insulin, then this could be measured by changes in the rat's own BG levels.

Results and Translation

In 1949, Bornstein and Trewhella used their technique in a study of 19 diabetic patients and found that "in the majority no insulin could be detected in their plasma. The minority had, however, normal insulin concentrations in the plasma, suggesting that some mechanism operates which either creates a demand for more insulin than the body can secrete or prevents insulin from operating normally."[13] In 1950, they reported testing 17 patients of the Alfred Hospital diabetic clinic. These patients were found to fall into two groups and they concluded "... at least two forms of diabetes mellitus exist."[16]

Supported by an NHMRC fellowship,[17] Bornstein travelled to the UK in 1950 to trial the technique with Robert Lawrence, a world leader in diabetes research. They investigated the plasma insulin content of patients who, on clinical grounds, appeared to be diabetic due either to a lack of insulin or to factors other than lack of insulin, and confirmed that the first group had no measurable insulin while the second group did.[18] They concluded that they had proved "that two clinical types of diabetes differ also in plasma insulin content."[13]

From Bornstein and Lawrence's 1951 paper

"From these analyses of plasma insulin related to clinical cases we consider that two main types of human diabetes exist and can be distinguished.

The first is severe and is characterized by weight loss and ketosis as well as hyperglycaemia; it occurs at any age, but mainly in the young, and their plasma contains no available insulin .... They require insulin treatment to live.

The second type ... is distinguished by the absence of ketosis and loss of weight. Their plasma contains available insulin, roughly 70% of normal controls .... Their diabetic state is easily controlled by diet alone, especially when obesity is thereby reduced."[13]

Health Outcomes and Impact

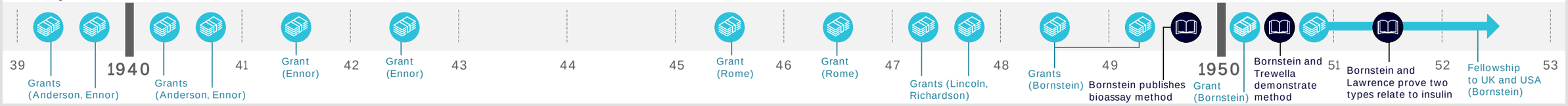
The ability to distinguish T1D and T2D was globally significant because the two types are essentially separate diseases: they have different underlying molecular mechanisms and require different types of treatment.

Since insulin was first isolated, health and medical research has led to continual innovation in the treatment of diabetes and technologies have significantly improved a patient's ability to deliver the right amount of insulin. The most notable innovations include genetically-engineered synthetic 'human' insulin, insulin pumps, advances in glucose monitoring and the capacity for these technologies to interact. These new technologies have provided patients with enhanced flexibility in how and when they receive insulin and the ability to improve glucose levels, leading to better quality of life.

Recognising these benefits, the uptake of advanced technologies in Australians with T1D has increased. In 2018–19, 41% of children and 26% of adults attending hospital diabetes clinics managed their T1D with insulin pumps and 55% of children and 13% of adults newly commenced continuous glucose monitoring (CGM).[19]

Diabetes remains a significant public health issue in Australia with an estimated 1.2 million Australians (or almost 5% of the total population) living with diabetes in 2017-18. However, the prevalence of T1D diabetes is much lower than that of T2D (0.3% versus 2.2% of the total burden of disease).

In 2015 in Australia, 4.7% of the total burden of disease was attributed to high blood plasma glucose levels (which includes diabetes and pre-diabetes). In 2015–16, an estimated 2.3% ($2.7 billion) of total disease expenditure in the Australian health system was attributed to diabetes.[20]



Note: NHMRC grants are dated by their start year

Dr Charlotte Anderson AM

Charlotte Morrison Anderson (1915 2002) worked at the Baker Institute from 1936 to 1941, then as registrar and research fellow at the Royal Children's Hospital, Melbourne, where she made major contributions to the treatment of cystic fibrosis, coeliac disease and sugar intolerance.

In 1968, she became the first female Professor of Paediatrics in the United Kingdom, at the University of Birmingham Medical School, a position she held until she retired in 1980.

In 1997, Anderson was appointed a Member of the Order of Australia for her service to medicine.

Sir Arnold Ennor CBE

Arnold Hughes Ennor (1912 1977) worked from 1938 to 1943 at the Baker Institute and during 1946 1947 in the Department of Biochemistry at Oxford University. He returned to Melbourne in 1948 to be Senior Biochemist at CSL but was then appointed to the Foundation Chair of Bio chemistry in the newly formed John Curtin School of Medical Research at The Australian National University, a role in which he remained for nearly two decades. He was Permanent Head of the Australian Government Department of Education and Science and then of the Department of Science (1967 1977). He was appointed CBE in 1963 and a Knight Bachelor in 1965.

Prof Joseph Bornstein

Joseph Bornstein was a biochemist who was closely associated with The Alfred Hospital as a student. He joined the Baker Institute in 1947 then worked in The Alfred Hospital Metabolic and Diabetic Unit from its establishment in 1955 until 1961.

Bornstein was then appointed Professor of Medical Biochemistry at Monash University and the Foundation Professor of Monash s new Department of Biochemistry.

Dr William Penfold

Dr William James Penfold (1875 1941) was recruited from the Lister Institute in London to be CSL's founding director in 1916, where he remained until he left to direct the newly formed Baker Institute in 1926, retiring in 1938.

Phyllis Trewhella B.Sc.

Phyllis Trewhella studied science at The University of Melbourne. She worked at the Baker Institute from 1949 to 1951, then worked as a teaching laboratory demonstrator at the Pharmacy College in Melbourne.

Types of diabetes

T1D often commences during childhood or young adulthood but can actually begin at any stage of life. It results from an autoimmune reaction that destroys the insulin producing beta cells in the pancreas. Treatment for T1D involves the regular injection of insulin to manage raised blood sugar levels (hyperglycemia).

Such injections are necessary multiple times per day, with dosages adjusted to account for food intake, blood glucose levels and physical activity. Prolonged lack of insulin can result in diabetic ketoacidosis which, if untreated, can rapidly progress to loss of consciousness, coma and death.

T2D diabetes is characterised by a combination of insulin resistance (an impairment of the body's response to insulin) and a reduction in the amount of insulin that is produced. A person may have a strong genetic disposition towards T2D and their risk is greatly increased if they are overweight and inactive.

Those living with T2D can improve their blood glucose levels with regular exercise and by following a healthy diet, as well as by using a range of medications including insulin.

Gestational diabetes occurs during pregnancy and usually disappears after the baby's birth.

Australian Government
National Health and Medical Research Council

NHMRC

References

This case study was developed in partnership with the Baker Heart and Diabetes Institute.

The information and images from which impact case studies are produced may be obtained from a number of sources including our case study partner, NHMRC's internal records and publicly available materials.

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- Best practice methodology in the use of animals for scientific purposes (2017).
- Principles and guidelines on the care and use of non-human primates for scientific purposes (2016)
- A guide to the care and use of Australian native mammals in research and teaching (2014).

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