The introduction of successful treatment of diabetes mellitus with insulin

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Introduction

The introduction of insulin for treating patients with diabetes mellitus must rate as Canada's earliest contribution to the welfare of humankind. The report by Banting and his colleagues[1] has been included in the James Lind Library because it provides an example of the kind of treatment effect that is so dramatic that there is no need for the very carefully controlled research which is needed to provide reliable evidence about the effects of most treatments.[2] What led to Banting's important study, and what evidence was published subsequently confirming that a major advance in treatment had been discovered?

Identifying and connecting excessive urination, sugar and the pancreas

Diabetes mellitus is one of the world's oldest known diseases. The Greek physician Aretaeus (81–138AD) appears to have been the first to describe the condition, which he named *diabetes*, from the Greek 'to pass through' or 'to siphon', so describing the excessive urination with which the condition is associated.[3] More than a millennium later, the British physician Thomas Willis noted the sweet taste of the urine of patients with diabetes, and used the Latin word for honey – *mellitus* – to distinguish between this condition and other causes of excessive urination. However, he attributed the sweetness to salts and acids, not to sugar.[4]

A century after Willis, Matthew Dobson, a Liverpool physician who graduated MD at Edinburgh, evaporated the urine of a diabetic patient and proved that its sweet taste was because it contained sugar, and observed an excess of sugar in the blood.[5] A decade after Willis, Thomas Cawley suggested a relationship between the pancreas and diabetes after observing stones and signs of tissue damage at the autopsy of a patient with diabetes,[6] but the significance of this clue was not appreciated for another hundred years. Concurrently, the Scots physician John Rollo attributed the abnormally high sugar production to stomach dysfunction. Using a urine glucose test devised by Dobson, Rollo developed the first effective treatment for diabetes: a diet high in what he called 'animal food' (fat and meat: 'plain blood puddings' and 'fat and rancid meat') and low in 'vegetable matter' (grains and breads) to manage the disease with foods their patients could absorb. This protein-rich, low-carbohydrate diet relieved the glycosuria of two diabetic patients.[7]

Another century passed before further advances were made at the end of the 19th century. In an institute in Strasbourg headed by an authority on diabetes, Bernhard Naunyn, Oscar Minkowski and Joseph Freiherr von Mering produced diabetes by removing the pancreas of a dog.[8] Serendipity is said to have played a role in this discovery. The urine of a polyuric depancreatised dog had been left uncleaned on the floor of the laboratory by a lazy attendant, and Minkowski checked it for glycosuria. This led to unsuccessful attempts to treat patients by feeding them pancreas in addition to the fat-rich, protein-poor, almost carbohydrate-free diet recommended by Naunyn.[9]

The introduction of pancreatic extracts

While Naunyn, Mering and Minkowski had focused on the pancreas as the seat of diabetes, Eugene Opie (1873–1971), a pathologist at Johns Hopkins University, Baltimore, made a further

important advance by establishing the association between diabetes and destruction of the islets of Langerhans,[10,11] and this observation stimulated research into the effects of administering pancreatic extracts. During the early 1900s in Aberdeen, Scotland, John Rennie and Thomas Fraser studied the effects in five patients with diabetes of giving an extract of "principal islets" (large islets forming separate globular aggregates made up mostly of endocrine pancreatic tissue present in some fishes (and snakes), but no convincing benefit was detected.[12] At around the same time, in Belgium, J De Meyer (1878–1934) discovered an internal secretion produced by the islets,[13,14] but his attempt to extract it from pancreatic tissue also failed.

In Berlin, Georg Ludwig Zuelzer extracted animal pancreas with alcohol and saline, and, after first experimenting on rabbits, he gave injections of the extract to a dying diabetic patient. Although there seemed to be an initial improvement (no biochemical measurements were made), the extract was used up within a few days and the patient relapsed and died. He carried out further experiments,[15] injecting five diabetic patients with pancreatic extract, but impurities caused fever. He spent a further three years trying to purify his extract. Zuelzer's method of extraction was subsequently developed by the pharmaceutical firm Hoechst and Zuelzer can justly be regarded as the first person to have achieved even partial success in finding a pancreatic extract with potential therapeutic value.[16]

Meanwhile, in Chicago, Ernest Scott (1877–1966) who was experimenting on dogs who had had their pancreas removed or tied off, was also searching for an effective pancreatic extract.[17] After his laboratory assistant had left him because of the constant presence of flies attracted to sticky puddles of urine in the laboratory, Scott realised that the dogs from whom the pancreas had been removed or destroyed had high levels of sugar in their urine. Further experiments showed that they also had high levels of glucose in the blood. Injection of isolated aqueous extracts made from excised pancreases temporarily reduced blood sugar levels and urinary output in the pancrectomised dogs (alcoholic extracts were ineffective). Scott subsequently left the laboratory, and the head of the laboratory, Anton Carlson, published his thesis for him. The thesis appeared in the *American Journal of Physiology* in 1912, apparently edited to largely discount Scott's discoveries.[17] Ten years later, Banting came upon Scott's little-known article and repeated his experiments more fully.

Israel Kleiner (1885–1966) carried out similar experiments on diabetic dogs in New York.[18] Injections of unfiltered water extracts of fresh pancreas diluted in 0.9% saline resulted in a marked decrease in blood sugar levels. He attributed the decrease in urinary sugar to a 'temporary toxic renal effect' (he had been expecting a compensating increase in glycosuria).

In experiments during the years leading up to World War I, in Bucharest, Romania, Nicola Paulesco demonstrated in dogs that pancreatic extracts (*pancreine*) caused hypoglycaemia. His method of extraction involved removing the pancreas under conditions as sterile as possible, mincing it, extracting with ice-cold water and then filtering it. Paulesco's detailed description of his experiments provided convincing proof of the hypoglycaemic properties of the pancreatic extracts he had isolated, but World War I delayed publication until 1921, when his research was reported in a series of short articles in a rather obscure French journal.[19] As a result, Paulesco's work passed almost unnoticed because, while he was still trying to solve the problems of purification and production of adequate quantities of *pancreine* for use in human diabetes, these difficulties had been overcome in the United States and Canada.[20]

In the USA, RT Woodyat had introduced fasting management of diabetes, a method much followed over succeeding years, and in 1917, Frederick Allen published an important clinical study entitled: 'Total dietary regulation in the treatment of diabetes'. He suggested ruthless starvation until glycosuria disappeared, followed by very gradual reintroduction of food until the limits of tolerance were reached. Prolongation of life was at the expense of great suffering by the malnourished patients. Elliot Joslin, who contributed greatly to the practical management of people with diabetes, adopted many of Allen's calorific and dietary restrictions.[21]

Banting and the Toronto team

Frederick G Banting, a Canadian, had attended Allen's lectures as a medical student. In November 1920, while a junior orthopaedic doctor at the

Western University, London, Ontario, while preparing for a lecture on the relation of the pancreas to diabetes, Banting came across an autopsy report about a rare case of pancreatic stones blocking the pancreatic duct, but leaving the islets unaffected.[22] He realized that, if the pancreatic duct were to be ligated and the digestive elements of the gland allowed to degenerate over several weeks, undamaged islets could be obtained from which the 'internal secretion' could be extracted. He submitted his idea to Prof JJR Macleod, the leading Toronto physiologist, who had contributed importantly to knowledge of carbohydrate metabolism and various forms of experimental diabetes.[23] Although Macleod was sceptical because of the rather discouraging results of previous workers, he invited Banting to Toronto and selected Charles H Best – a medical student working for his Master's thesis in physiology – to work with him.

Banting and Best commenced their investigations using procedures similar to those which had been employed previously by Scott and Paulesco. Degenerated pancreas with undamaged islets ground in Ringer's solution and injected into animals rendered diabetic by pancreatectomy resulted in a 40% decrease of blood glucose levels one hour later. After dog pancreas, they eventually went on to use fetal calf and adult beef pancreas, augmenting their supplies of extracts.

A few months later, JB Collip, Professor of Biochemistry, arrived in Toronto for a Rockefeller Travelling Fellowship and joined the research group. With his help, using fractional precipitation with different concentrations of alcohol and other procedures, extracts of islets were obtained which could be safely injected into humans. This potent, effective and non-toxic material, named '*isletin*' (later called by Macleod '*insulin*' from its Latin root), was used in the first effective clinical studies.

Banting and Best presented their first findings in dogs in November 1921 before the Physiological Journal Club of the University of Toronto, and in December the same year before the American Physiology Society. On February 1922, they published their first paper on 'The Internal Secretion of the Pancreas', demonstrating that insulin could abolish ketosis and stimulate glycogen formation in the livers of diabetic dogs.[24] These conclusions were virtually identical with those of Paulesco (*isletin* being identical to *pancreine*), although Banting and Best carried out their research completely unaware of the Romanian's success.

Their major clinical publication, 'Pancreatic extracts in the treatment of diabetes mellitus', came in March 1922, in the *Journal of the Canadian Medical Association*. They reviewed the previous literature critically and described in detail previous attempts to treat diabetes with pancreatic extracts (including Paulesco's experiments). They also presented the results of insulin treatment of diabetic patients in Toronto General Hospital by WR Campbell and AA Fletcher, under the supervision of Professor D Graham. Their data demonstrated that insulin reduced blood sugar to normal values, abolished glycosuria and acetone bodies in the urine and produced general clinical improvement in human patients with severe diabetes:[1]

> *'… All the patients were improved clinically. It is difficult to put in words what is meant by clinical improvement. Those who have been treating diabetes will have recognized as early signs of improvement a certain change in the skin, the appearance of the eyes, the behaviour of the patient, his mental and psychic activity, and the physical evidences, as well as his testimony, of increased vigor and desire to use his muscles … This is the nature of the improvement seen clinically as a result of the administration of these extracts …'*

In the paper they also presented the case report of Leonard Thomson, a 14-year-old boy who was treated with pancreatic extracts with immediate and dramatic success:

> *'… The acetone bodies disappeared from the urine. The boy became brighter, more active, looked better and said he felt stronger …'*

In 1923, the award of the Nobel Prize for Medicine and Physiology was given jointly to Banting and Macleod. This led to criticism that the Nobel Award Committee had not included Best in the award, but it has been suggested that it was not technically possible to do so because no-one had nominated him.[25] Banting, who resented the inclusion of Macleod, expressed his dissatisfaction by sharing one half of his prize with Best. Macleod thereupon shared his prize with Collip. It was extremely unusual for a medical discovery to be honoured in this way so soon after it had been made, and this reflected the significance of this medical treatment. It should be noted that the

nomination was followed by protests from both Georg Zuelzer and Nicholas Paulesco, who claimed priority. Paulesco made representations to the French Academy of Medicine, but it was too late since, according to the rules of the Nobel Award Committee, an award once made cannot be reviewed. On a more positive note, had it not been for the discovery of insulin, George Minot would almost certainly not have survived to do the research on pernicious anaemia[26] which led him and William Murphy to be the first American recipients of the Nobel Prize.[27]

Producing, standardizing and distributing insulin

The demonstration by the Canadian group that it was possible to extract insulin from beef pancreas laid the foundation for large-scale insulin production by the pharmaceutical industry. Banting and Best patented their process and gifted their patent rights to Toronto University, which set up an Insulin Committee to advise on matters of administration. Early insulin preparations were in powder or tablet form and had to be dissolved in boiled water by patients themselves, and this resulted in sterile abscesses. In May 1922, Macleod agreed to co-operate with the Eli Lilly company and, with the help of chemical engineers, pure and potent sterile acid bovine insulin solutions became available. Early commercial insulin production developed by Eli Lilly led to the availability of insulin for clinical care throughout the world within 2 years.

One of the first people in the UK to benefit from the discovery of insulin was the Treasurer of the Royal College of Physicians of Edinburgh, Sir Norman Purvis Walker. He was suffering from diabetes, and by 1922 he was critically ill. Some insulin was sent over for him from Canada before it was generally available. When Walker received the insulin the effect was immediate.

> *'… This saved his life. The transformation was nothing short of marvellous and in a few weeks he had put on several stones in weight and looked as he had done before his illness …'*[28]

Walker went on to be awarded a knighthood in 1923 and to become both President of the College and of the General Medical Council.

The first 'home-made' insulin in the UK was produced in Edinburgh by JC Meakins and used in the Diabetic and Dietetic Department opened in the Edinburgh Royal Infirmary – the first department of its kind to be established in the UK. Commercial supplies became available in 1923. On Macleod's advice, the Toronto authorities granted the UK patent to the Medical Research Council, through Sir Henry Dale.

Sir Derrick Dunlop, Professor of Therapeutics and Clinical Medicine in Edinburgh, described at that time how he had '… never seen anything in medicine more heart-warming or rewarding than to watch those diabetic patients raise them themselves step by step out of the valley of the shadow …'.

As he remarked, insulin therapy was also unique in that it gave maximum relief with minimum toxicity.[29]

The production and packing of insulin in standardized units was the result of the impressive working of transdisciplinary and transnational networks. It is generally considered to have been a process conducted by physiologists under the direction of Sir Henry Dale, whose political leadership was paramount for the international phase of the standardization. However, many contributed – physiologists, clinicians and pharmacists – leading to the earliest administration to patients in Canada and the United States. During the first phase, both the US private drug company Eli Lilly and a public Canadian company, contributed actively to the standardisation.[30] New modes of standardization were developed which led to wider reforms. Without the regulation and standardization of its effects no biological dosage and commercial use would have been possible.

The discovery of insulin for the treatment of diabetes mellitus was immediately received with worldwide relief. Finding an agent for the treatment of a disease so frequently fatal, seemed like a miracle, dramatically increasing the life expectancy of diabetic patients. Between 1914 and 1922 (the era of starvation therapy) the life expectancy of someone with diabetes had been 6.1 years from diagnosis. By 1950 to 1957, it had increased to 18.2 years. In young diabetics (< 30 years old at onset), a life expectancy before the first world war of only 1.3 years from diagnosis had increased to 2.9 years with the introduction of starvation therapy and, by 1957 – 35 years after the introduction of insulin – to 26.4 years.

Much controversy was provoked by the fascinating discovery of insulin. The achievements by the Toronto team were, undoubtedly, the culmination of the work of many other people, in many countries, over many years.

Recognition that insulin does not cure diabetes

Nevertheless, the discovery of insulin did not provide the world with a cure for diabetes mellitus. Complications such as retinopathy, nephropathy, neuropathy, and coronary and peripheral angiopathy continued to occur and raised the question whether '… they are to be regarded fatalistically as something inherent in the diabetic process … or can they be postponed by care and trouble directed to the control of the metabolic disturbance?'[29]

Evidence from the 10-year prospective DCCT (Diabetes Control and Complications Trial) study gave the answer, suggesting that 'intensive' treatment which reduces hyperglycemia will unequivocally delay the onset and/or reduce the progression of microvascular complications.[31] The question now is not why or whether to maintain good glycaemic control, but how.

In the early 1980s, knowledge of the basic amino acid structure of insulin and species differences, along with recombinant DNA technology and genetic engineering, led eventually to the ability to produce 'human insulin' and, more recently, insulin analogues and continuous subcutaneous insulin infusion therapies to enable closer mimicking of physiological insulin secretion.

With the development of effective treatment with insulin, prevention of complications and prevention of diabetes moved from being inconceivable to realistically attainable future goals. The challenge today is not just achievement and maintenance of normal glucose levels in the blood, however, but doing so in the context of a child's or adolescent's normal physical and emotional growth, and an adult's normal lifestyle.

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