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The Journal of the Association of British Clinical Diabetologists

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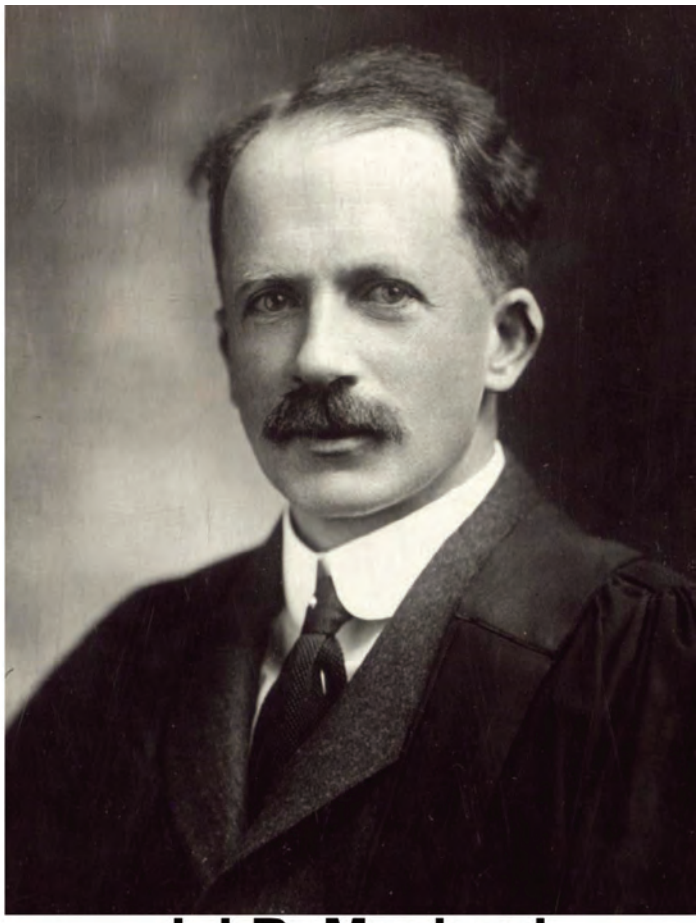
100 years of Insulin Anniversary Supplement

Sir Frederick Banting



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THE BRITISH JOURNAL OF Diabetes ABCD
The Journal of the Association of British Clinical Diabetologists

100 years of insulin anniversary supplement

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Preface

ROBERT EJ RYDER

Br J Diabetes 2022;**22**(Supp1):S1-S2

Key words: insulin centenary, Banting and Best, insulin, diabetes, Theresa May, Marjorie the dog

Following a timely reminder from Rury Holman, on 24 November 2020 I sent an email to the ABCD executive, past ABCD chairmen and several ABCD Trustees pointing out that January 11, 2022 would be 100 years to the day since insulin was first given to a human: "*On 11 January 1922, Leonard Thompson, a 14-year-old boy with diabetes, who lay dying at the Toronto General Hospital, was given the first injection of insulin. However, the extract was so impure that Thompson suffered a severe allergic reaction, and further injections were cancelled. Over the next 12 days, James Collip worked day and night to improve the ox-pancreas extract, and a second dose was injected on the 23 January. This was completely successful, not only in having no obvious side-effects, but in completely eliminating the glycosuria sign of diabetes*".[1]

We were in the midst of the COVID-19 pandemic at the time I sent the email, but I pointed out: "*by January 2022 we should all have been vaccinated to bits and COVID should hopefully be confined to history. I suggest ABCD at once books the Royal College of Physicians for an ABCD centenary meeting of this great occasion in the history of diabetes. If we can't get January 11 we could go for January 23 – not sure which of the two dates is the most important as the day of breakthrough. We should then set about advertising the date and promoting it as going to be the greatest ABCD meeting ever*"!

There was universal approval for this idea within ABCD. Throughout 2021, during the various lockdowns of the continuing COVID-19 pandemic (2020-2022), we were in the period 100 years since the momentous events recounted by the Toronto historian, Michael Bliss.[2] We were determined, after such a prolonged period without face-to-face meetings due to the COVID-19 pandemic, that this meeting should be face-to-face. After much consideration we decided that January 11th, 2022 would be the optimum date, being exactly 100 years to the day since that first injection of insulin into Leonard Thompson.[1]

We planned to have speakers covering all the 100 years of insulin, discussing the massive improvements in the care of people with diabetes that resulted from that initial spark. As we considered the subjects and the speakers the programme grew, and it became clear that the meeting was going to be a two-day event. We envisaged the event occurring at the Royal College of Physicians, with dinner in the evening. We were pleased that the former prime minister Lady Theresa May, herself a person with type 1 diabetes, agreed to be our guest at the dinner and to propose the toast to 'Banting, Best, Collip, MacCleod and Marjorie', with Marjorie representing the many dogs on whom Banting and Best tried their pancreatic extracts as they attempted to find a preparation that would work (Figure 1).[3] Lady May had done much for our cause through campaigning,[4] and the well-known picture of her openly wearing FreeStyle Libre (Figure 2).

Figure 1. The dogs who helped with the discovery of insulin[3]

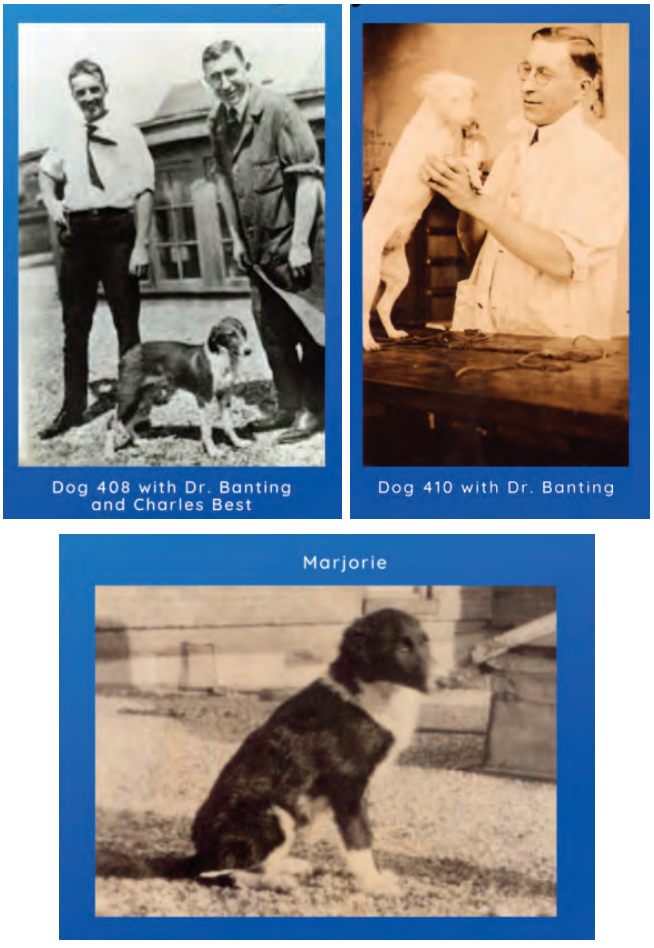

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Figure 2. Theresa May, the former Prime Minister, wearing FreeStyle Libre[4]

As 2021 progressed into the autumn, it did seem that the pandemic was subsiding to the extent that such a meeting could occur on January 11th and indeed the College and accommodation were booked, all the speakers signed up and everything was in place. Unfortunately, with just a month to go, in December 2021, the Omicron variant of Sars-Cov-2 emerged and with a new and rapidly spreading wave of infections, we realised that the event on January 11th had to be postponed. Another date some months later was sought when there was availability at the College and finally we settled on July 4th and 5th, 2022.

In the end the event proved to be highly successful, with places in the auditorium at the College and at the dinner oversubscribed. We were delighted that Theresa May and her husband, Sir Philip, were able to join us (Figure3) and the toast did occur. We were also delighted, in the wake of such a successful event, that all the speakers agreed to write up their presentations for a special supplement of the British Journal of Diabetes. We are gratified that this was achieved during 2022, thanks in no small part to the combined efforts of Jen Atkinson and Helen Jones leading the BJD production department.

The programme of the actual event that took place on July 4-5, 2022 can be viewed online;[5] the contents pages of this supplement are slightly different, mostly because the authors of the supplement altered their titles slightly in many cases to suit the subjects' communication in written form. All the presentations (slides and recordings of the speakers) can also be viewed online.[6]

I would like to convey my sincere thanks to all the speakers who helped make it the greatest ABCD meeting ever, to Red Hot Irons for superb organisational support, to the attendees for coming and for their enthusiastic participation, to ABCD chair, Dr Dipesh Patel, for rescuing my wallet which I had left in the room-safe in Meliá White House Hotel, to Theresa and Philip May for joining us at the dinner, but most of all to Banting, Best, Collip, MacCleod … and Marjorie.

Conflict of interest REJR has received speaker fees, and/or consultancy fees and/or educational sponsorships from BioQuest, GI Dynamics and Novo Nordisk.

Funding None.

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Figure 3. Therese May and her husband, Sir Philip, at the dinner. **a**, left to right, Dr Bob Ryder (pages, S2, S23, S36, S82, S100), Dr Dipesh Patel (ABCD chair), Theresa and Philip May, Dr Barbara McGowan (page S62), Dr Umesh Dashora (ABCD Honorary Meeting Secretary), Prof Ken Shaw (page S13), Dr Vijay Jayagopal (ABCD Honorary Treasurer), Dr Richard Greenwood (Founder member of ABCD, first Honorary Secretary, former ABCD chair). **b**, left to right, Sir Philip May, Dr Alistair Lumb (DTN-UK Deputy Chair), Dr Emma Wilmot (pages S79, S82, S100), Theresa May, Prof Pratik Choudhary (page S69).

a

b

The discovery of insulin

K GEORGE MM ALBERTI,[1] CLIFF J BAILEY[2]

Br J Diabetes 2022;**22**(Supp1):S3-S5

Key words: pancreas, extracts, diabetes, insulin, history

Introduction

The discovery of insulin is a landmark of medical history: it introduced life-saving treatment for a previously fatal disease and brought hope to millions. The research studies of Banting and Best in Toronto during the summer of 1921 have been recounted many times over. So also have the later contributions of Collip and Macleod, leading to refinements of the pancreatic extracts and their successful administration to Leonard Thompson in January of 1922.[1] The award of the Nobel Prize and the commercialisation of insulin are also well rehearsed postscripts to the discovery story, but comparatively little consideration has been accorded to events of the late 1800s and early 1900s that led up to the work in Toronto: these events are focused upon here.

'Islands' of Langerhans

The discovery of insulin is conveniently traced from research by Paul Langerhans when he was a medical student in Berlin. In 1869 Langerhans submitted a thesis on the microscopic anatomy of the pancreas in which he described the 'islands' of tissue that now bear his name: their function was unknown.[2] Although Claude Bernard had noted more than a decade earlier that animals could not be kept alive after pancreatectomy,[3] the crucial link between the pancreas and diabetes had to wait for the work of Josef von Mering and Oskar Minkowski at the University of Strasbourg in 1889. While studying the role of the pancreas in fat digestion their technician observed the polyuria and glucosuria of a pancreatectomised dog. Minkowski and von Mering recognised these features to be typical of diabetes.[4] They pancreatectomised further dogs to confirm the findings, and Minkowski later reported partial reversal of the diabetes by subcutaneous implants of pieces of pancreas.[3,5]

Around the same time (1890-93) a French scientist, Edouard Hedon, also conducted experiments showing that subcutaneous auto-implants of pancreatic tissue could partially reverse the diabetes of pancreatectomised dogs and it was recalled that there had been reports (such as those of Etienne Lancereaux) that atrophy of the pancreas was often observed at autopsy of people with diabetes.[6,7] However, even though it was recognised that pancreatic duct ligation could cause pancreatic atrophy without destruction of the pancreatic islands and without glucosuria, the pancreatic islands were yet to be implicated in the prevention of diabetes.[8]

Extracts of pancreas

The possibility that the islands of Langerhans might produce an internal secretion that prevents glucosuria was suggested by Gustave Laguesse in 1893, fuelling the emerging concept of endocrine glands.[9] However, therapeutic studies for diabetes continued to focus on pancreas pieces and very crude extracts of pancreas: some short-term successes were reported with animal studies, but attempts to treat human diabetes with pieces of animal pancreas were unsuccessful.[7] For example, Patrick Watson-Williams in Bristol in 1894 implanted pieces of sheep pancreas under the skin of a 15-year-old boy who was severely ill with diabetes: the boy died several days later.

The question of an antidiabetic principle from the islands of Langerhans was revisited in 1901 when the American pathologist, Eugene Opie, described degenerated fibrotic islets in a patient with diabetes.[10] Similarly, interest was rekindled in 1906 when Wilhelm Heiberg reported fewer islands in pancreatic tissue from diabetes patients,[11] and in 1907 John Rennie and Thomas Fraser in Aberdeen reported that fish islet extracts slightly reduced glycosuria sometimes in five diabetes patients.[12] More encouraging progress came from Berlin, where Georg Zuelzer had been experimenting with injections of pancreas extracts into pancreatectomised dogs. In 1908 he obtained a pancreas extract (Acomatol) from a local pharmaceutical company and reported how injections of the extract kept a diabetes patient alive until supplies ran out: his own extracts were only temporarily helpful in this and other patients.[13] Sadly, he was unable to continue his work as his pharmaceutical sponsors felt that he would do better to concentrate on what is now recognised as type 2 diabetes.

Studies that stimulated Banting

Following the work of Zuelzer, several laboratories reported studies in diabetic animals, confirming that injections of pancreas extracts could reduce glycosuria and prolong survival.[11] Most notable of these were the studies of Ernest Scott (Chicago, 1911), John Murlin and Benjamin Kramer (New York, 1913), and Israel Kleiner (New York, 1919).[14-16] John Macleod, Professor of Physiology in Toronto, met Scott but he did not encourage him. Although no successful clinical studies emerged from these

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sources, the latter two are cited by Banting and Best in their seminal publication, indicating that they were key to Banting's rationale for selecting pancreatectomised dogs as the model in which to test his extracts.[17] Also stimulating Banting's thoughts on diabetes was a paper by Moses Barron from Minneapolis in 1920 which described a fibrotic pancreas with intact islets. This reminded Banting of animal studies of pancreatic duct ligation, and suggested to him that he "might obtain the internal secretion free from the external secretion".[18,19]

Parallel research

One of the most intriguing stories surrounding the discovery of insulin is the work of the French physiologist Eugène Gley. In Paris between 1900 and 1905 Gley prepared pancreas extracts and recorded that they reduced glycosuria and increased survival when injected into pancreatectomised dogs.[20] The next steps he did not publish but described in a sealed document which he deposited with the Société Française de Biologie in 1905, asking that it be opened only when he so requested.[11] In 1922, when the work of Banting and Best became known, Gley asked for the document to be opened: it appears that Gley had conducted studies around 1900 with extracts made from mainly islet tissue of pancreatic duct-ligated animals and had found these extracts to be particularly potent in preventing glycosuria in diabetic animals.[11]

Another important piece of parallel research with pancreatic extracts was undertaken by physiologist Nicolae Paulesco in Bucharest. In 1916, Paulesco prepared and injected pancreatic extracts into pancreatectomised dogs and noted the reduction in blood sugar. The work was interrupted by World War I and was not published until August 1921; it had not proceeded as far as clinical studies.[21]

Successful clinical outcome

As the histological studies of Langerhans became subsumed into the initial concepts of endocrinology the nomenclature evolved and in 1909 the Belgian physiologist Jean De Meyer suggested the name 'insuline' for the putative antidiabetic internal secretion of the islands.[22] The same name ('insulin') was independently proposed by English physiologist Edward Sharpey–Schäfer in 1916, but it was not until well into the 1920s that reasonably purified preparations became available. Even the refined pancreatic extracts prepared for clinical use by Collip in early 1922 were still the consistency of a sludge and probably the source of infections that accompanied the initial injections.[1,23] Further purification on a large scale was vital to the possible clinical usefulness of pancreatic extracts. Collip and Macleod formed a close association with Eli Lilly (and in particular with George Clowes) who were able to purify the extract further and also to assist Connaught Laboratories in Toronto to produce clinically useful extracts.

The question of who deserved the Nobel Prize remains a matter for debate, and more credit should perhaps have been given to Paulesco, whose critical paper was mistranslated by Best and therefore was not quoted in the seminal paper by Banting and Best. That said, we acknowledge with grateful thanks the contributions of all concerned in the pre-insulin research that provided the foundation for the achievements of the group in Toronto during 1921 and early 1922. We have seen how so many came so close to preparing a clinically effective pancreatic extract but did not achieve a successful clinical outcome. This awaited the enthusiasm and concerted efforts of Frederick Banting, the diligent assistance of Charles Best, the guidance and facilities provided by John Macleod, the biochemical expertise of James Collip, the support of Eli Lilly and the desperation of the mother of a 13-year-old son in diabetic coma with no more than days to live.

Key messages

- Discovery of insulin was one of most important developments in medicine of last 150 years.
- It took decades for the initial suggestions of the role of the islets of Langerhans in diabetes to be translated into treatment for humans
- No single person or group was responsible for identifying the source of insulin, its extraction and therapeutic significance

Conflict of interest None.
Funding None.

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The Life of RD Lawrence (1892-1968) - pioneering doctor and survivor of diabetes

HUGO LAWRENCE

Br J Diabetes 2022;**22**(Supp1):S6-S8

Key words: Survivor, pioneer, founder

Without the discovery of insulin, I would not be here today. My children would not have been born, indeed my father would never have come into existence and met my mother. I am only here because of the pioneering work of those many doctors that discovered the cause of diabetes and worked so hard to find its treatment in the form of insulin. How many millions of us are there who can trace our ancestry back to a person with T1DM? Four generations of Lawrence survivors now have those pioneers to thank for our lives. What adds to the tension of our story is the 'just in the nick of time' element and the manner in which my grandfather, RD Lawrence (RDL), was saved from his descent into death.

The real reason why so many of us remember him during this celebration of 100 years since the discovery of insulin is the work RDL went on to do following his medical resurrection, founding the British Diabetic Association and writing The Diabetic Life. My grandfather set the cornerstone for patient-centered Diabetes care in this country. The British Diabetic Association (now Diabetes UK) pioneered the patient-centered approach to managing care which we now see as standard across a huge range of medical conditions and illnesses.

My talk at the meeting followed on from Professor Alberti's presentation. He had traced the team of doctors responsible for the discovery of insulin, crediting previously overlooked work and highlighting some of the tensions and disagreements between the personnel. The story I told was based on my mother's biography of RDL, *Diabetes, Insulin and the Life of RD Lawrence* (Jane Lawrence 2012) and the slideshow that accompanies it. Some photos from the slideshow are included here. Sadly, she was not able to present but she was delighted with the report my son, Joseph and I brought back from the event, and she was also able to listen to the whole talk which the technical team at the Royal Society of Physicians had kindly recorded. To highlight the health aspect, I delivered the talk in sports kit as the House I am head of was competing in Sports Day later that afternoon and I needed to rush back to school to cheer them on!

Hugo Lawrence (born 1967) is the grandson of RD Lawrence

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4 generations of Lawrences: Hugo Lawrence presenting Jane Lawrence's research on R.D.Lawrence. Photo by Joseph Lawrence

Looking at his early life RDL (1892-1968) appears to have been a bit of a maverick but firmly rooted in his well-to-do Scottish family and with friends from Aberdeen Grammar School, the Gordon Highlanders and Aberdeen University. A gifted sportsman and angler, he was described as 'the most energetic man alive, high spirited and bubbling over with joie de vivre'. He was unable to enlist in the First World War due to an appendectomy and was devastated to lose most of his friends during the conflict as he convalesced, fighting the infections that failed to settle. He was posted to India for a spell and on his return in 1919, he started work at King's College Hospital with the ambition of becoming a surgeon. Tests following a further infection, caused by a chip of bone in the

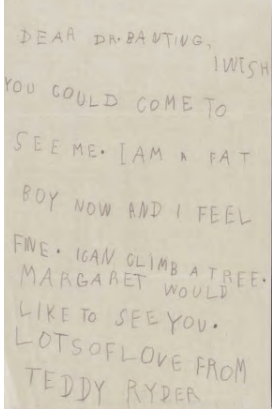
RDL at King's College Hospital in 1921, nine months after his diagnosis with diabetes. He is seated in the front row, third from the left, wearing spats.

RDL and Dino Spranger

eye received during a post mortem, revealed diabetes. In 1919 this was a death sentence with a waiting time of three years and starvation as the most effective form of treatment.

He switched his studies to biochemistry and presented his thesis on diastase in the blood and urine in diabetes mellitus before heading off to Florence in 1922, to die in the warmth and beauty of Italy with his friend Dino Spranger, sparing his family the agony.

Meanwhile, on the other side of the world, the breakthrough happened in the lab of Collip, Banting and Best. We heard the story of the treatment of 14-year-old Leonard Thompson, the first patient to receive insulin, on the children's ward and the resultant raising of the near dead, of the entire ward of children. We imagined the joy and disbelief of the parents as they saw their children come back to life. We heard from Teddy Ryder whose thin and emaciated body was restored to health. He wrote to Dr Banting, 'I'm a fat boy now and I feel fine'.

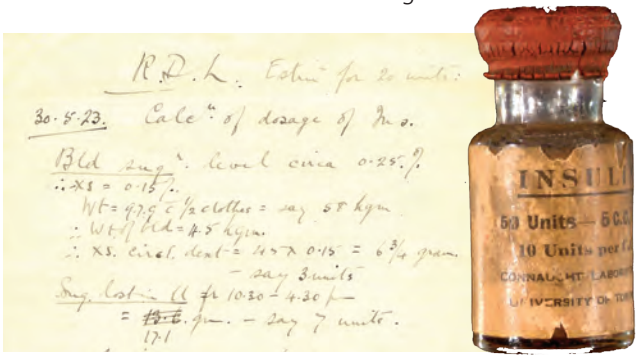


Teddy Ryder's letter to Dr Banting; and his appearance before and after receiving insulin in 1922.

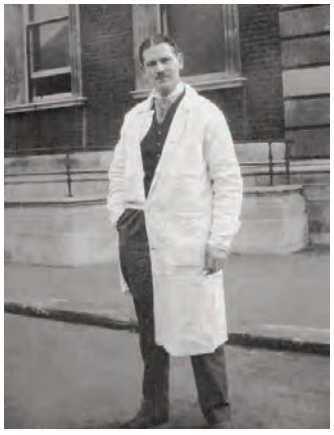
Telegram from Dr Harrison; RDL on the way home from Italy

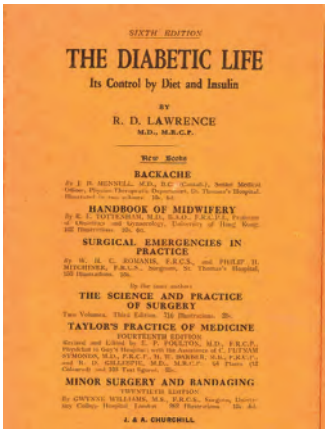
RDL had been managing his condition through diet for two years by this time and, despite the breakthrough of insulin in Canada, it was more than a year later when he received a telegram from one of his colleagues telling him to come home urgently as some insulin had finally arrived back home.

He found an Italian taxi driver who wanted to visit his son in England and they drove from Florence to London, with RDL having to take the wheel through Paris as the taxi driver was too frightened! Few if any of the roads were tarmacked and the cross-channel ferry used a winch to load the cars. He arrived 'more dead than alive but no pre-coma.' On 31st May 1923 Dr George Harrison and Dr RD Lawrence 'went to the fridge, took out a bottle of insulin, and we discussed in our ignorance what the dose should be. It was all experimental, for I didn't know a thing about it; and neither did he for he had only treated about three people. So we decided to have 20 units – a nice round figure.'



He was restored to health with marvellous speed and began a career in which he shaped the clinical management of diabetes for over 40 years. He was the first to identify T2DM. He went from facing diabetic death to writing The Diabetic Life, teaching patients how to manage their condition. He had a 'demon passion for work and seldom did a day go by in which he did not perform an experiment on himself'.





In 1928 he married his wife Anna, of whom he said, 'I might so easily have gone through life without finding you'. They had three children and lived happily together in London.

Wedding of RDL to Anna Batson; RDL with his sons; his wife Anna.

He treated HG Wells, and together they founded the British Diabetic Association with the objective of supporting patients and reducing the stigma of the disease. They promoted a patient-centered approach and encouraged patients to take an active role in managing their condition. He wrote: 'Diabetes is not an illness any more than having flat feet is an illness. It is a permanent condition that has to be accepted and organized. If anyone from the diabetic establishment tries to persuade you that you have an illness, close your ears and go elsewhere for help and guidance.'

RDL and HG Wells on the cover of the 70th Anniversary Edition of 'Balance' the Diabetes UK Magazine (Formerly British Diabetic Association)

RDL working with 'These special children'

This was an era when negative labels abounded and people were defined by their disability with awful names such as spastic, mongol, incurable, remedial. He preferred 'people with diabetes' rather than diabetic and campaigned for children with diabetes, calling them 'these special children'.

Professor Harry Keen said of him: 'This was our founder. This was an internationally great figure. This was a physician of the old school who ushered in the new school. This was a physician-philosopher, a physician-liberator, a 'can do' physician. He pioneered bi-directional education in diabetes, developing the concept of the patient not as a consumer but as an essential co-producer of health care. His Diabetic Association was a major first step in the 'emancipation of the patient' – not just the patient with diabetes.'

He was made Honorary President of the International Diabetic Foundation and presented with a silver writing block inscribed with the words:

Thank you for teaching us how to live in joy and happiness

Participating in ABCD's 100 Years of Insulin conference was a proud moment for me and my family. Thank you for the opportunity to come and tell the story of my grandfather.

Joseph Lawrence (2007) and Hugo Lawrence (1967)

Key messages

- Hope
- Gratitude
- Diligence

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For Information

Material for this talk was taken from *Diabetes, Insulin and the Life of RD Lawrence*' by Jane Lawrence, published 2012.

From muck to molecule: insulin discovery over 50 years

PHILIP HOME

Abstract

A pancreatic extract which was successful in lowering glucose in diabetes was developed and commercialized with leadership from the University of Toronto in 1921-1922. The active principle remained unknown, though it was assumed to be the 'insulin' (or 'isletin' or 'insuline') identified microscopically in the islets of Langerhans from work in the previous 50 years. Within four years the active principle was crystallized by Abel and co-workers, and convincing proof given that it was a peptide. Determining the amino acid sequence of this relatively small protein proved a 30-year task for science, due to the confounding effects of two short chains united by di-sulphide bridges. Even then it was a mystery how the sequence related to insulin activity.

That remained the case when the early X-ray diffraction work in the 1930s by Crowfoot (Hodgkin) matured in 1969 with the determination of the 3-dimensional structure of the insulin hexamer. Meanwhile 25 years of work, much in industry, invented useful extended-acting insulin preparations and, over an even longer time course, insulin preparations of high enough purity to be non-immunogenic in clinical practice. In the 1960s and 1970s work on radioimmunoassay and on glucose clamps provided tools that would prove critical to the further development of insulin as a medication over its second 50 years.

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Key words: diabetes, insulin, discovery

The pancreatic extract

A legal assignment signed on 19 December 1922 by Frederick G Banting MD, Charles Hubert Best and James Bertram Collip, and effected 01 January 1923, specifically concerns an 'Extract obtainable from the mammalian pancreas or the related glands of fishes', detailed wording indicating that the assigners 'invented an extract'.[1] There is no mention of insulin. Indeed, while the extract prepared from slaughterhouse beef pancreas by Collip produced the first clear lowering of blood and urine reducing sugars on 23 January 1922 (following very unclear results from Banting and Best's extract on 11 January of that year),[2] there was no evidence of what the active principle was, and indeed no prior evidence of what those pancreatic β-cell granules which disappeared in diabetes might be.[3-6]

The concentration of the active principle was also unknown, and is difficult to establish in retrospect. Collip seems to have been producing 2-4 cc injection aliquots soon after the first successful injection,[2] so perhaps purity was as low as 10% of all extracted matter. Thus, insulin had not been isolated, and certainly not 'discovered'. The assignment transferred the rights to the extract to the University of Toronto, and was formally supervised by JJR Macleod, who himself was already a tenured member of the University. The assignment followed heated and close to violent exchanges over the previous months, notably between Banting and Collip, the latter indicating at one stage that he intended to patent his process.[2] Banting believed strongly that preparations containing insulin would need to be made available quickly and at lowest possible cost across the world and, aided by advice on patents and agreements from George Clowes of Ely Lilly, the assignment allowed the University to freely license the process.[2]

Clowes, like Macleod of British extraction, was himself an active researcher with his own laboratories far from the headquarters of the company for which he was research director. Clowes and Macleod knew each other: they had met well before Banting's proposal to Macleod was made, and could well have implanted in Macleod's mind the idea (see article by Alberti and Bailey in this supplement) of a pancreatic extract.[7] The relationship with Clowes became important, as it was with Lilly that Toronto partnered in translating the laboratory process to commercial production, notably harnessing the skills and knowledge of the production chemist George Walden, who set on its way the path from pancreatic extract to isolation and definition of insulin.

Purifying, crystallizing, and identifying insulin

Walden knew how important the quality of reagents was in obtaining consistency in handling biological materials, and quickly established a reproducible process that overcame the erratic performance of the methods of Banting and Best, and of Collip.[2] At one point Lilly were supplying their insulin preparation to Toronto hospitals, when the local researchers' methods unaccountably failed. Walden also set in motion the movement to successful isolation of insulin itself by the introduction of isoelectric precipitation, which produced an amorphous, non-crystalline precipitate of insulin which was perhaps 60-70% insulin. In Toronto the University was closely linked with Connaught Laboratories (early insulin formulations for injection had both institutions named on the label), and Connaught had its own

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Table 1 Steps in the discovery of insulin

Year	New knowledge	Researcher	Note
1877	Pancreatic origin of diabetes	Lancereaux[4]	Cawley speculated on the relationship of the pancreas to diabetes, 1788 Confirmed by pancreas removal, von Mering and Minkowski, 1889
1901	Islets of Langerhans source of anti-diabetic substance	Opie[6]	Islet morphology described by Langerhans, 1869
1914-1921	Diverse demonstrations of a glucose-lowering pancreatic extract in animals	Notably Zeulzer, Paulesco, Banting and Best	See article by Alberti and Bailey in this issue[7]
1922	Clinically useful pancreatic extract and commercialization	Banting, Best, Collip, Macleod, Walden[1,2]	Quickly licensed globally
1926	Insulin crystals	Abel[9]	
1928	Insulin a protein	Abel and colleagues[10]	Atomic composition, amino acids detected
1935	Insulin crystals have structure	Crowfoot (Hodgkin)[13-15]	Purely qualitative in 1935, data-loaded in 1938, 1939
1956	Amino acid sequence; di-peptide chain	Sanger[17]	Defines the insulin monomer, 2-dimensionally
1969	3-D structure of the insulin hexamer	Blundell, Dodson, and Hodgkin[15]	Insulin has other conformations

laboratories investigating biological products (including protamine, Canada being a good source of salmon and trout).

It had been known for some time that whatever the active principle (named 'insuline' or 'isletin') might be it was in the pancreas (Table 1), and it was inactivated by oral ingestion. Though that might be due to chemical instability, destruction by digestion would imply a protein (or fat or carbohydrate or adduct of two of these). Later, a number of very early clinical attempts at oral administration of commercial insulin preparations failed.[8]

John Abel and colleagues in 1926 were able to use redissolved amorphous precipitate to produce 'highly refractive' insulin crystals, which when redissolved proved very potent at lowering blood sugar levels in rabbits.[9] He noted the substance contained sulphur, and given the potency described it as a 'hormone'. A positive ('beautiful') biuret reaction identifies the presence of nitrogen, strongly suggesting a protein; this was supported by a positive Millon's reaction (detecting the phenolic ring of tyrosine) and ninhydrin test (detecting lysine amine side chains). Crystals are only formed with higher purity, likely here over 90%, and so this paper marks the first isolation of the insulin molecule, the true 'discovery' of insulin (Table 1).

Cameron, writing only two years later, summarizes the further work from Abel's laboratory, including insulin's molecular content $C_{90}H_{150}0_{34}N_{22}S_2$ (or multiple thereof), and the presence of disulphide bonds and various amino acids.[10] The complexity compared to 'adrenine' (epinephrine) and thyroxine is noted, and the general properties are said to be those of a 'proteose' (a polypeptide). In discovery terms this is rather like finding a new vertebrate fossil, being aware it has bones (and thus muscle and blood and a nervous system) but not having any idea of what the animal might have looked like.

Understanding insulin

Insulin action is still not fully understood, partly because it is a very flexible molecule when in solution, and indeed changes shape on receptor interaction.[11] But understanding of the importance of zinc in insulin crystallization, notably by David Scott in Toronto in the early 1930s,[12] allowed the production of more substantial crystals that could be subject to novel techniques of investigation. Crystals from the Boots Pure Drug Company, a sub-licensee of the rights to insulin production in the UK, were the source of the self-described most wonderful moment in one lady's academic life, when Dorothy Crowfoot (later Hodgkin) in Oxford in 1934, using early, low-power, X-ray crystallography, determined asymmetries in the diffraction pattern, meaning that insulin had structure.[13] A curious anecdote here is that another hero of insulin development, Hans Christian Hagedorn, a few months later found no diffraction pattern in insulin crystals, seemingly unaware of Crowfoot's publication in Nature that year (1935). Crowfoot's work advanced rapidly so that by 1939 she could describe different types of insulin crystal in some detail, including a molecular weight and the insight that the molecule had a substructure of perhaps three or six parts.[14,15]

Full elucidation of the hexameric structure had to wait until 1969, and members of the Zoology Department in Oxford still remember the celebrations around Hodgkin's team that summer when the latest X-ray diffraction patterns were finally interpreted.[16]

That was of course aided by understanding of the amino acid sequence of insulin. As noted above, many amino acids were identified in Abel's laboratories in the late 1920s, but the two-peptide chain sequence of insulin, united by cystine bonds, and the difficulties of determining sequence rather than content, defied chemists until the work of Frederick Sanger in the early 1950s.[17] Even then, the Nobel Prize-winning work took some five years. As with Hodgkin's work there was a limit to the understanding, rather than knowledge, of insulin gained. Asked at a lecture at Manchester University in 1965 what insight the 2-D structure gave into the mechanism of action of insulin, Sanger replied in one word: 'None'. (I was a schoolboy in the audience – the question was asked by my biology teacher.)

Inventing clinically useful insulin preparations

The first 50 years after the invention of the pancreatic extract is marked in retrospect by two major developments in the nature and quality of insulin preparations, and two scene-setting advances in clinical science that would be applied to great effect subsequently.

Purification

As noted above, rapid advances were made in Toronto and by Walden at Eli Lilly in reducing the mainly protein impurities in the early extracts. Isoelectric precipitation and then recrystallization were key advances, and became the standard methods into

the 1960s. But that decade saw advances in chromatographic techniques applied on a commercial scale, initially gel filtration and then ion-exchange chromatography.[18,19] The so-called monocomponent and rarely immunogenic animal insulins essentially abolished the immune problems of injection-site lipodystrophy, immunological insulin resistance and neonatal hypoglycaemia, at least in those patients/mothers who had never been exposed to earlier insulin preparations.

These advances proved their worth beyond the first 50 years, when the introduction of fermentation-manufactured (bacteria, yeasts) insulins produced a new imperative for purification by chromatography, one that has not failed to date.

Extended-acting insulins

It became clear, in the first year of insulin use, that a single subcutaneous injection of the unmodified extract would not control glucose and ketones for 24 hours. While two injections were widely used, it can be speculated that this was only possible because of the retarding properties of the impure preparations and insulin antibodies. Anecdotal reports are of physicians with diabetes, such as Robin Lawrence, giving themselves up to seven injections a day. Accordingly, the hunt was on for extended-acting preparations, though with limited understanding of insulin physiology this was seen as being aimed at a once-daily preparation.

Clinically useful extended-acting preparations took 25-30 years to develop, though the scene-setting begins with Scott and Hagedorn's work in the 1930s on interactions with zinc and protamine.[20,21] Other approaches which were tried included gum arabic, oils, tannin, lecithin, adrenaline, vasopressin, cholesterol and diverse proteins, and while some could prolong action, their erratic effects prevented standardization. Although DA Scott worked at Connaught Laboratories, and Connaught were already manufacturers of protamine preparations, he attributes the idea of combination with protamine to Hagedorn. It took more than a further decade to establish the right conditions for the preparation of neutral protamine crystals, major challenges being the zinc content, optimal pH, the precise ratio of insulin:protamine, and the critical role of phenol and its derivatives.[22]

Rivalry in north Copenhagen was strong, however, between the Nordisk Insulinlaboratorium and Novo Terapeutisk Laboratorium, both having been licensed insulin manufacturers since 1923. Knud Hallas-Møller, who joined the latter in 1937, built on the experience of zinc concentrations on solubility to devise the insulin-zinc suspension series of insulin preparations, semilente, lente and ultralente.[23] Lente had a very similar profile of effect as NPH insulin,[19] and was a mainstay of twice- daily insulin therapy (together with unmodified insulin) in many clinical services. It only dropped out of use because of its unsuitability for use in fine-needle pen-injectors, and the less effective profile of the necessary preservative, methyl parahydroxybenzoate.

Methodological advances

Radioimmunoassay was developed in the 1960s by Solomon Berson and Rosalyn Yalow, the latter gaining a Nobel Prize (Berson meanwhile had died), and was rapidly applied to insulin pharmacokinetics. Notable here was a paper from Robert Turner, somewhat misleadingly called 'Measurement of the insulin delivery rate in man', misleading because insulin secretion rate was not calculated. The paper did, however, show that insulin half time in plasma was very short,[24] making a nonsense of clinical practice for the management of diabetic ketoacidosis (DKA) at the time, in which as much as 100 U of insulin was given initially intravenously. The paper records a similar unpublished observation from Peter Sonksen. Together with other understandings of insulin-dose response curves this led to the low-dose insulin regimens for DKA introduced by George Alberti and colleagues in 1971.[25]

Like radioimmunoassay, insulin glucose clamps only really became methodologically important in the development of the new insulins and analogues beyond the scope of the present paper. Clamps were developed in the 1960s to study insulin resistance,[26] and were only 'reversed' to study insulin action in the 1980s, becoming an essential part of the measurement of insulin pharmacodynamic profiles.[27,28]

Key messages

- Banting and Best produced a useful pancreatic extract in 1922, but had no knowledge of the active principle it contained
- Abel and colleagues crystallized insulin, and showed it to be a peptide in the late 1920's, but it took science 30 years to provide the amino acid sequence, and >45 years to define the 3-D shape
- Activity in industry improved purification, taking 50 years to provide truly pure insulin preparations, but also developing useful extended-acting insulins after 25 to 30 years

Conclusion

Fifty years is a long period in the development of any medication, and while the isolation and identification of insulin occurred fairly quickly once reliable methods had become available for pancreatic extraction, defining its amino acid sequence took more than 30 years and the 3-dimensional structure 48 years. Nevertheless, in that time insulin has contributed to or generated six Nobel Prizes. The major clinical advances in purification and prolongation of action for subcutaneous administration in those times grew out of lengthy work by the pharmaceutical industry, though founded in the early studies of insulin chemistry. Insulin has also benefitted and stimulated methodological advances in laboratory science, which in turn have been harnessed for development of more recent insulin products.

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Insulin: a momentous transformation of diabetes care from the 1970s to the millennium

KEN SHAW

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Key words: Insulin, longevity, diabetes care, glycaemic control, 'designer' insulins, self blood glucose monitoring, diabetes education

Introduction

The last three decades of the 20th century witnessed a spectacular and remarkable progression in the delivery of diabetes care. In the 1970s diabetes provision was almost entirely hospital-based but by the millennium the exponential explosion of diabetes numbers necessitated a complete restructuring of diabetes services with a substantial switch to primary care, while hospital diabetes centres focused on more specific specialist and complicated subgroups. This period of time saw a radical transformation of diabetes management from an historical empirical, rigid conformity, overtly didactic and prescriptive in nature, to the guiding principle of a much more patient-centered and flexible approach. In this time, we witnessed dramatic developments with insulin and its usage – new insulins, new delivery devices – and once the importance of good diabetes control was fully accepted and the rational evidence base established, the monitoring of such metamorphosed from indirect and generally inadequate urinalysis to the increasingly sophisticated measurement of blood glucose, both immediate and long-term. With these transformative developments, education for healthcare professionals, and for people living with diabetes, became a prime priority to be integrated into the singularly rewarding domain of diabetes care.

The prospect of longevity

Described as Banting's "prize" patient, Elizabeth Hughes became the first American to benefit from the recent discovery of insulin – acclaimed in her own words as "unspeakably wonderful". Elizabeth, only 11 years of age, had been diagnosed in 1918 with diabetes and subjected to the then punitive, calorie-restricted diet recommended by the obsessional New York physician, Frederick Allen. To his credit, when Allen realised the successful outcomes of insulin administration being reported from Toronto, he contacted Banting on behalf of Elizabeth, by which time three years later she was recorded as in a "pitiful state, weighing 45 lbs, extremely emaciated and scarcely able to walk". Insulin treatment was commenced immediately in August 1922, with rapid restoration of her health and a relief to be "awakened from the nightmare of the 'starvation diet'". Keeping her medical history secret, Elizabeth lived her life in relative obscurity until in 1980 the Canadian historian Michael Bliss was privileged and delighted to make contact with her, finding her 'perfectly alert mentally, and with none of the debilities that may result from long-term diabetes".[1] Elizabeth Hughes (1907-1981) survived for almost 60 years on insulin.

By the 17th edition (1965) of his book *The Diabetic Life*, Dr RD Lawrence was able to comment that "thousands of insulin cases have been on insulin continuously for 40 years or longer, with the ultimate expectation of life seemingly nearly (sic) normal in many cases". However, even in the early 1990s prolonged survival with insulin-dependent diabetes of more than 50 years from diagnosis was considered unusual, a select group "remarkably fit and relatively free of complications".[2] This milestone has been recognised by the British Diabetic Association with the award of the Alan Nabarro medal; 446 had been so honoured in the UK by December 1990.[3] Alan Nabarro (1914-1977), himself diagnosed with diabetes aged 7 years, was one of the first patients to receive insulin, living a full life for a further 55 years and dedicated to the cause of diabetes.

In due course, 60-year RD Lawrence medals were awarded. One of my own 'prize' patients, on developing acute diabetes at the age of 11 years, had spent six weeks in the Royal Portsmouth Hospital while insulin was initiated. "48,000 jabs later", she was thrilled to receive the RDL medal, and an invitation to attend the commemorative service at Westminster Abbey, celebrating the same 60-year anniversary of the foundation of the then British Diabetic Association.

Clinical uncertainties

Insulin was indeed truly wonderful – life-changing both immediately and for the years ahead. Yet, despite such optimism, Lawrence became aware that "some longstanding cases develop mysterious complications". Although the first cases of diabetic retinopathy (1855) and nephropathy (1859) had been described during the previous century, such was the striking increase of these conditions, that it was seriously mooted whether insulin itself might be the causative factor. Furthermore, observations that intensified insulin treatment, such as the Kroc Collaborative

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(1984) and Oslo (1985) studies, might transiently worsen established retinopathy appeared to support this concept.[4,5] Fortunately, with longer-term observation and evidence eventually emerging to the contrary, it was realised that the progression of the early stages of late diabetic complications might be prevented through tighter insulin administration.

Both these studies concluded that achieving near-normoglycaemia was the important factor in lessening complication progression, but evidential proof had yet to be established, with the definitive Diabetes Control & Complications Trial (DCCT) report still 20 years ahead. It was not unusual in the 1970s to hear from those who were unconvinced and accepted a 'laissez-faire' approach to management. Nonetheless, some progress was being made. Jean Pirart, a Belgian physician, reported an unprecedented observational study of 4,400 patients between 1947-1973.[6] Based predominantly on urine analyses and occasional blood sugar measurements, he categorised diabetes control as being good, fair or poor, and was able to correlate the development of complications such as peripheral neuropathy with long duration of diabetes and poor glycaemic control.

In the 1970s most patients needing insulin would be on a single injection a day, at least for the first 10 years from diagnosis. For Portsmouth this strategy included children as well. The suggestion that this was not good enough led to a modicum of castigation from well intentioned but protective parents. "Why inflict more injections than necessary – surely once daily is sufficient?" Yet the evidence was slowly growing, with studies such as those of Georges Tchobrousky and colleagues at the renowned diabetes centre of excellence within the Hôtel-Dieu de Paris Hospital.[7] Forty-two patients with early-stage diabetic retinopathy were assigned to an insulin regimen of either single or multiple daily injections, with microaneurysm (MA) formation quantitated by fluorescein angiography. After a mean duration of three years, progression in the number of MAs was significantly less in the multiple- than the single-injection group. So the perception that good control of diabetes was important in lessening risk of developing future diabetes-related complications became established as did the realisation that more careful consideration of insulin administration was essential in achieving such – predating and paving the way for the DCCT (1982-93).

Practical problems with insulin

The life-changing benefits of insulin have been immense clearly, but its administration has never been straightforward, rather fraught with many difficulties. Subcutaneous injection, not the most physiological point of systemic entry, could lead to local irritant reaction in the short term and more substantial skin changes with longer usage. Injecting into favoured cutaneous sites, usually identified areas of least sensitivity, often resulted in local and disfiguring structural changes. These changes are not simply cosmetic: changes of both lipo-atrophy, an immune-mediated inflammatory response, and lipo-hypertrophy, arising from the anabolic effect of insulin, could adversely affect absorption of insulin and lead to a significant inconsistency of effect. Even in the absence of local injection site changes, the synchronisation and timing of the insulin injection and the desired impact on both basal and post-prandial blood glucose levels could be frustrating. Never the best place for establishing optimal diabetes control appropriate for the outside world, the hospital diabetes ward with its inevitably irregular meal times would frequently be entirely dissociated from when the insulin injection was given or withheld. No wonder hypoglycaemia could be so prevalent on the wards. The relationship and timing between injections and eating was very much a learning curve in those early days.

The pursuit of purer insulins

It was recognised that the insulin we were giving was mixed with other impurities, including proinsulin and pancreatic polypeptide, and that such impurities could result in a degree of adverse antibody formation. Purifying through recrystallisation towards monocomponent insulin and altering the pH to neutral resulted in more stable insulin with faster absorption and the benefit of reduced dosage. For most of these early days, insulin was primarily of beef extraction. Then, as a fortuitous biproduct of the Danish bacon industry, porcine insulin became the more popular replacement. In the 1980s it was said that 15,000 pigs were needed to supply sufficient insulin for 750 patients for one year. Soon this was to be considered not enough to meet increasing demand as the number of people with diabetes rose worldwide. It is salutary to realise as humans that our insulin molecule differs from that of pigs by one single amino acid, and that by clever enzymatic conversion of the B-chain30alanine to threonine, semi-synthetic human insulin was produced. However, the major breakthrough towards human insulin came with the development of recombinant DNA technology, inserting the human insulin gene into the genetic material (plasmid) of bacterial DNA. Human insulin synthesised by this innovative technology was confirmed by the much respected doyen of diabetes, Professor Harry Keen and his team, among others, to be essentially safe and effective in man, with the caveat that its dose-response relationship may differ from that of porcine insulin.[8]

However, the transition to human insulin was not entirely straightforward. Commenting in a *British Medical Journal* editorial (21st October 1989), John Pickup observed that by 1989 at least three quarters of the approximately 200,000 people with insulin-dependent diabetes (Type 1) were taking human insulin, a substantial change in clinical practice but nonetheless not without certain concerns. As a result of adverse event reporting, it was noted that the Committee on Safety of Medicines and the British Diabetic Association were urgently investigating reports of loss of normal warning of hypoglycaemia, predominantly in those transferring from animal to human insulin.[9] The BDA estimated that 24% of individuals switched to human insulin were encountering problems with hypoglycaemia and that 15% were reporting worryingly few warning symptoms.[10] Although perception of impending hypoglycaemia tends to become more subtle with longer duration, people reporting problems were convinced of a specific, seemingly abrupt reaction on changing to human insulin. Dose reduction helped in

most cases, but many lacking confidence requested return to animal insulin. This problem appeared largely to affect those already established on long-term insulin and overall has ceased to be an issue in subsequent years.

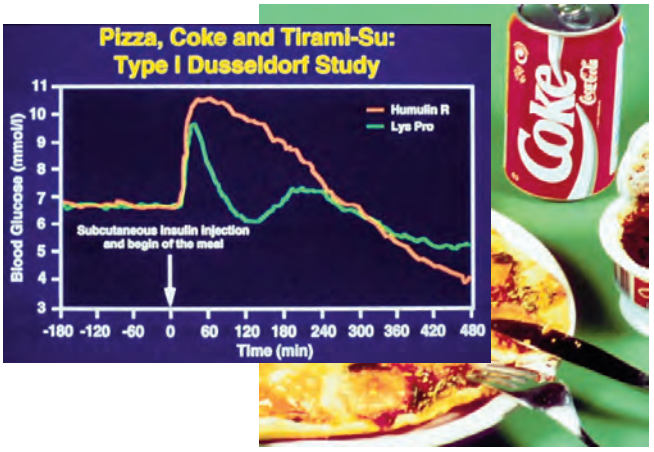
It was not just the type of insulin that was causing uncertainties in the 1980s. We also had to confront a change in insulin strength as a result of increasing confusion over marks on the syringe and units of insulin prescribed. Misunderstanding of these was leading to mishaps and the potential hazard of wrong dose administration. Change to a single U100 strength insulin was therefore carried out over a 2-year period from 1983. It proved to be a major exercise, deploying a considerable amount of nurse specialist time. Complicating the transition even further was the urgent need to move to the use of plastic syringes following difficulties engraving the necessary U100 marks on glass – apart from the evident preference for plastic. The DHSS were not initially sympathetic to such a widespread change, but after a vigorous campaign, championed by Sir Michael Hirst of the BDA and Edwina Currie at debate in Parliament, the transition to plastic syringes was finally accepted. To facilitate the economic cause, many of us argued that multiple syringe usage could be practiced safely but single use and subsequent disposal eventually prevailed.

In due course, disposable plastic syringes were to be replaced by pen delivery devices, providing easier, more convenient and an increasingly popular means of insulin administration. The first insulin pen, the NovoPen, was introduced by NovoNordisk in 1985. With further refinement and technological innovation, pens offered more flexibility and an all-round quality improvement in the daily discipline of insulin injection compared to syringes. Meanwhile, parallel development of insulin pumps allowing continuous subcutaneous infusion (CSII) offered yet more options, with the first commercially available insulin pump ensuing in 1979. Although modern pump technology is now highly sophisticated and clearly superior in terms of achieving better glycaemic and metabolic control, economic considerations limited a wider introduction of pump usage at this time.

Advent of designer insulins

The late 1990s was a fascinating period of insulin innovation, as pharmaceutical companies introduced us to new concepts of insulin pharmacokinetics – fast absorption; slow absorption; quicker action; longer duration; sharper peak activity; flatter profile. The world of insulin analogues had arrived. The first short-acting insulins, Lispro (Eli Lilly) introduced in 1996, followed by Aspart (NovoNordisk) in 2000, meant insulin could be injected much closer to mealtimes, and purportedly with a more physiological profile, earlier peak and shorter duration of action, aspiring to reduced risk of hypoglycaemia. Illustrating the practical postprandial benefits of their fast-acting insulin Lispro (Humalog), Eli Lilly presented all of us prospective prescribers with the now iconic teaching slide of Michael Berger's renowned Düsseldorf Study,[11] in which 10 patients with T1DM were given a carbohydrate-laden (total 140 g) meal comprising pizza, a cola drink and a rich dessert of tiramisu (Figure 1). After pre-meal injection of insulin Lispro, blood glucose excursions after this meal were significantly lessened, with a 78% reduction under the blood glucose curve in comparison to human regular insulin.

Figure 1. Dusseldorf Carbohydrate rich diet study (1996)

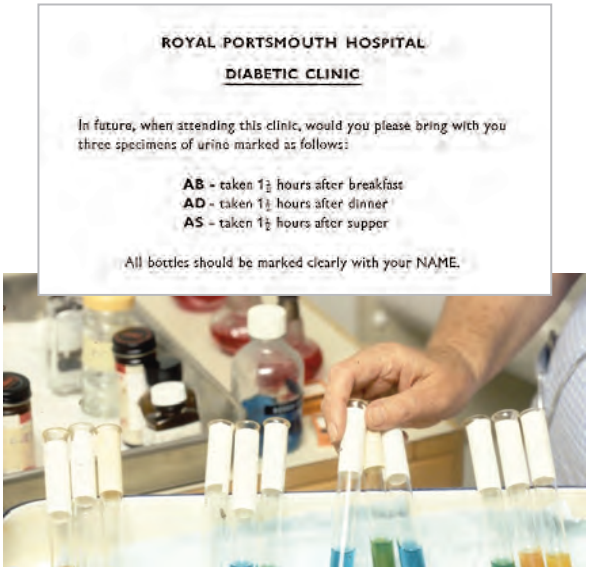


A decade later we had insulins of prolonged absorption with minimal peak activity, which were therefore suitable as alternatives for basal glycaemic control. Pharmaceutical ingenuity was indeed impressive. Insulin Glargine's prolonged action (Lantus/Sanofi)) was achieved by inducing microprecipitate formation at the site of injection, whilst a 14-C fatty acid chain attachment to the insulin molecule produced a comparable effect with detemir (Levemir/NovoNordisk). We soon became spoilt for choice, as these new "designer" insulins offered various therapeutic options and opportunities for more individualised diabetes management. The insulin we use today has evolved substantially from that developed by Banting and Best. Although they are not perfect, these newer insulins mimic natural physiological conditions more closely and in general are much safer than the older agents. Yet insulin even now has to be injected; we still await the ultimate goal of a safe and effective oral preparation.

Diabetes monitoring transforms

The standard hospital diabetes clinic in the early to mid 1970s – and almost everyone with diagnosed diabetes would be referred to the hospital ("glycosuria; please see and advise") – relied on urine glucose testing (Benedict's Solution/Clinitest) as a guide to the degree of acceptable diabetes control. Those attending my predecessor's clinic were requested to bring along three specimens of urine from the preceding day, passed 90 minutes after each of the three main meals (Figure 2). Urine-filled test tubes, exhibiting all colours of the rainbow, would be placed prominently between the dutiful patient and the dictating consultant, often providing the sole focus of the consultation concerned ("1. Yellow, 2. Yellow, 3. Green": "not keeping to diet; test urine more often; see in 2 months"!). Keeping a trace of glycosuria to lessen risk of hypoglycaemia meant blood sugars were almost certainly running too high. A step in the right direction came

Figure 2. Clinic urinalysis in the 1970s



when in 1970 the somewhat cumbersome Ames "Eyetone" colorimeter became available and clinics were able to include a spot blood glucose measurement – though this is still a poor indicator of overall diabetes control, more often reflecting clinic circumstances than the real world.

However, the rapid technological development of glucose reflectance meters in the later 1970s led to arguably one of the most significant milestones in diabetes care – the notion that people with diabetes themselves could derive more personal awareness of their individual ambient glucose status, introducing the novel concept of self-monitoring and self-management. In 1978 the *Lancet* published two groundbreaking papers which outlined the considerable benefits of self-monitoring of blood glucose (SMBG). Robert Tattersall and colleagues (Nottingham) reported better motivation, greater understanding of diabetes and a sustained improvement in control when patients, using the "Reflomat" (Boehringer Mannheim) reflectance meter, were able to measure their own blood glucose profile.[12] Likewise, Peter Sonksen and co-researchers (St Thomas' Hospital) observed hitherto unobtainable similar improvement in diabetes control with less frequent hypoglycaemic episodes. With use of the 'Eyetone' (Ames) meter, adjustment of insulin dosage was found to be both easier and more predictable than with urine glucose analysis.[13] The widespread subsequent introduction of SMBG did indeed prove a popular quantum leap forward in terms of practical day-to-day diabetes management, progressively improving and culminating in the remarkable state of the art technology seen today.

Despite the reams of diligently recorded blood glucose tests presented for inspection and deliberation on each clinic attendance, cautious consultants were to welcome a further scientific advance with the knowledge that measurement of glycated haemoglobin (HbA_{1c}) concentration in the blood correlated closely with glucose regulation over the red cell lifetime span of approximately 120 days. As a result of their studies, Anthony Cerami and colleagues (Rockefeller University) commented that "periodic monitoring of HbA_{1c} levels might provide a useful way of documenting the degree of control of glucose metabolism in diabetic patients".[14] Useful indeed! So much so that the HbA_{1c} became the gold standard index of overall glycaemic control for the next five decades, both in clinical practice and in landmark clinical research trials such as the DCCT. HbA_{1c} measurement has provided a very practical and convenient monitoring assessment, and it has served us well.

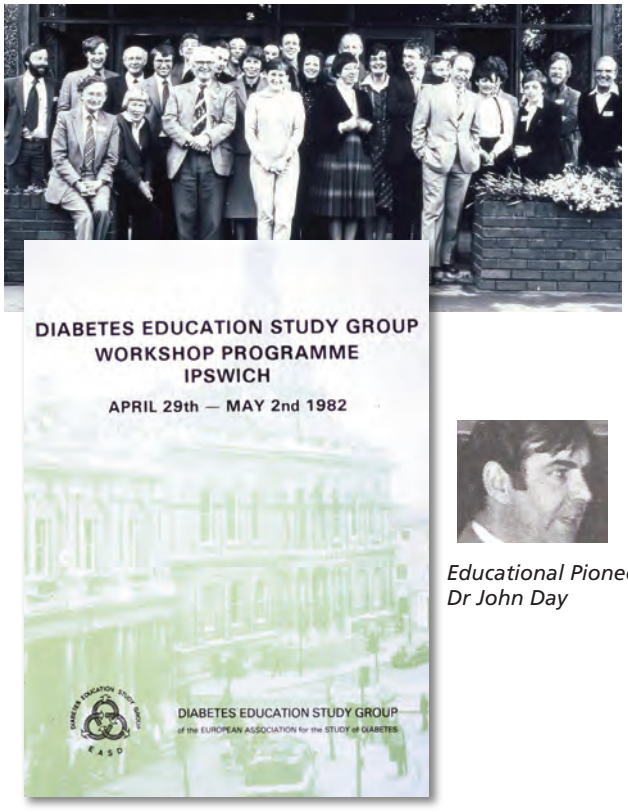
The HbA_{1c} reflects mean glycaemic exposure though it does not identify individual diurnal glucose variability – but it has been the best available measure during this period. Measuring whole glucose excursion – percentage time within 'target' range - has only become feasible in recent times with the wider implementation of continuous blood glucose monitoring devices. Having been immersed in diabetes for a professional lifetime of more than 50 years, one cannot but be astonished by the stunning progressive technological developments that have occurred over this period.

Education

Finally, any review of the period from the1970s to the millennium has to make reference to the educational priorities and initiatives that arose consequent to the increasing complexity of diabetes management. Diabetes, for so long an add-on service provided by other medical specialities, had suddenly become a discipline in its own right, resulting in a new breed of Consultant Physician with a dedicated special interest in diabetes. Usually, just one such appointment within each district hospital service required the then relatively select numbers to get together and share clinical needs and experience.

Professional networking, then as now, was of huge value. When reflecting on the issues leading to the formation of ABCD in 1997, it is apposite to note that the Medical and Scientific Section (MSS) of the British Diabetic Association, as related by former (1953) BDA Secretary-General Jim Jackson, "emerged from a feeling of dissatisfaction among diabetologists and research workers, with a perceived need to involve physicians in charge of diabetic clinics countrywide more closely in the activities of the Association.[15] MSS meetings in those days were relatively small, usually housed in one academic lecture theatre, such as with my own first attendance at St Thomas' Hospital in 1974 – we were young aspirants privileged to mix with the diabetes greats of the era. The RD Lawrence Memorial Lecture, for the young British physician (<40 years of age) making a significant contribution to diabetic medicine, became an established annual feature. Robert Tattersall provocatively titled his 10th (1980) RDL Lecture "Are subcutaneous insulin injections obsolete?", a bold prediction, perhaps to prove prescient one day. Tattersall's talk was chaired by the inspirational clinical scientist, Arnold Bloom, who himself delivered the 33rd Frederick Banting Lecture two years later (1982), describing his pioneering project work developing a UK register of all children with newly diag-

Figure 3. Ipswich Diabetes Education Workshop



Educational Pioneer Dr John Day

nosed diabetes, from which much new epidemiological knowledge was obtained.[16]

Recollecting the 1970s, now almost a half century ago, one inevitably remembers formative professional years with a considerable degree of fond nostalgia – the indelible memory of George Alberti providing us with a taxi service when we arrived in Southampton to attend the first Advanced Postgraduate Course in Diabetes (1976), a prestigious teaching faculty of diabetes mega-stars. Educational opportunities got better and better. Dr John Day (Ipswich), under the auspices of the EASD Diabetes Education Study Group (Figure 3), introduced us to a challenging interactive workshop experience, where we had to confront our own present teaching limitations and learn how to do better.[17] One of those attending this first Ipswich workshop was a young Charles Fox (Northampton), whose own teaching enthusiasm and patient-centred empathy over four decades has driven a highly regarded Diabetes Counselling course at Knutson Hall; participants return with evoked emotion but with much improved communication skills.

And so diabetes education proliferated. Soon meetings were getting bigger and bigger, and as diabetes became more and more popular as a speciality, so the numbers wishing to get together were expanding. Moreover, diabetes was no longer the sole prerogative of the consultant physician – a multi-disciplinary service had developed, providing a diversity of professional skills.

Key messages

- The "unspeakably wonderful" discovery of insulin provided dramatic relief from the nightmare of the starvation diet" and the prospect of longevity
- Pioneering studies of glycaemic control eventually established the clear relationship between control and the development of long-term complications
- New "designer" insulins with novel pharmacokinetics provided imaginative flexible therapeutic options for individualised diabetes management
- The revolutionary concept of patient self-monitoring of blood glucose was arguably the most significant milestone in diabetes care

A very early advocate of diabetes education for the multidisciplinary team was the charismatic Isle of Wight physician Dr Arun Baksi, whose annual conferences, held at Shanklin from 1982, will be remembered as exceptional in promoting a remarkable team-building foundation.[18] These individual educational citations, pioneering as they were, are of course but a prelude to today's plethora of educational opportunities. We have seen small group meetings progressing to very large multidisciplinary conferences, as more healthcare professionals get drawn to the stimulating world of diabetes. In some ways this outcome has been a victim of its own success, such that the more intimate face to face interaction of smaller gatherings has been lost. That was one of the factors leading to the emergence of ABCD,[19] initially considered concerning but now firmly embedded as one stream in the flourishing world of diabetes, all working to common cause. John Wales, Founder member and first Chair of ABCD,[20] would have been proud to have witnessed the excellence and success of this Insulin Centenary Meeting.

Conclusion

The period of time from the early 1970s to the millennium was associated with substantial and most positive developments in diabetes, all leading to progressive improvement in the treatment of diabetes with better outcomes and an overall increase in quality of life experience. Restructuring the insulin molecule with novel pharmacokinetic activities provided therapeutic options about which we had previously been in ignorance. Uncertainty concerning the importance of attaining good diabetes control was revoked, with emerging studies, culminating in the DCCT, clearly favouring good control over "laissez-faire". For my generation these were 'golden years' with a continuous sequence of exciting innovations, and it is gratifying to observe that the same experience continues with the present generation.

Conflict of interest None.
Funding None

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Insulin – the sharp end of the needle: experiences of 48 years with diabetes

HUW ALBAN DAVIES

Br J Diabetes 2022;**22**(Supp1):S19-S22

Key words: living with diabetes, developments, self-care

Introduction

One hundred years ago the first human life was saved by the injection of insulin. My story is not about the remarkable doctors and scientists who developed this life-giving treatment and made insulin injections possible. I am going to tell you about the 14-year-old boy, Leonard Thompson, who received that first injection and about one of those who came after him. Leonard had been kept alive for three years after developing diabetes by being restricted to a diet of grapefruit, meat and thrice-boiled vegetables which amounted to as little as 450 calories a day. On admission to Toronto General Hospital he was desperately unwell, with his hair falling out, his abdomen bloated and his 1.8m frame cadaveric at 29kg. His body was producing ketones from fat metabolism and he was nearing coma. Leonard's parents, Harry and Florence, agreed to experimental treatment with an extract of foetal calves' pancreas. The first injection produced little response and he developed an allergic reaction. However, the pancreatic extract was purified and this proved effective, with his blood sugar showing a steady reduction from a very high level. Leonard's condition stabilised and he was able to leave hospital and continue with school and, later, to earn his living (Figure 1a). The dramatic impact of purified pancreatic extract on the children treated is illustrated by the examples shown in Figure 1b and 1c.

Personal experience

My own story covers nearly 50 of the 100 years since that first injection, and I will give an idea of what it has been like to have had diabetes during that time. My symptoms developed in Zululand during my elective period as a medical student in 1974, and diabetes came to light a few months later when I was asked to provide a urine specimen for the staff medical at University College Hospital, London (UCH). Such is the power of the mind to ignore unwelcome facts that only when I had the specimen bottle in my hand did I realise that I had diabetes and that I had known that I had had it for some time although the knowledge was suppressed until it was

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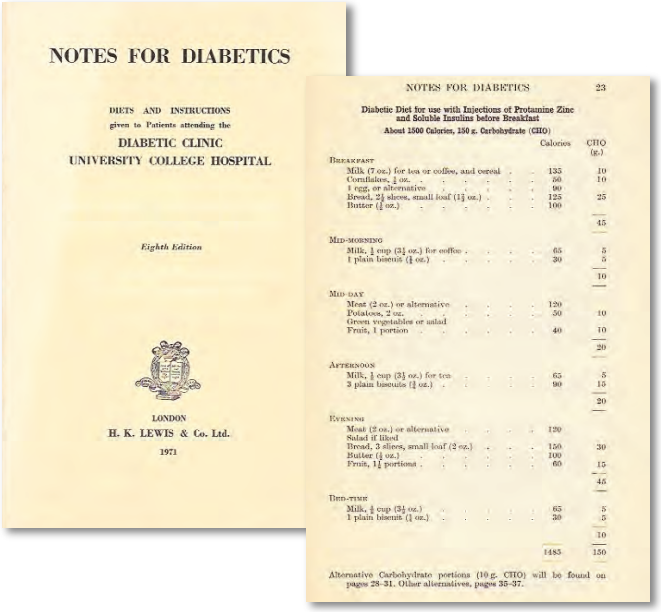
Figure 1. **a.** Leonard Thompson, who received the first injection of insulin on 11th January 1922 when he was 14 years old. This photo was taken of him in later life. **b&c** Two children with T1DM in early 1922 before and after insulin.

Figure 2. 'Notes for Diabetics' from University College Hospital, London published in 1971. There were six meals and snacks and the 10g exchanges and calorie values for these are shown.



NOTES FOR DIABETICS

DIETS AND INSTRUCTIONS
given to Patients attending the
DIABETIC CLINIC
UNIVERSITY COLLEGE HOSPITAL

Eighth Edition

LONDON
H. K. LEWIS & Co. Ltd.
1971

NOTES FOR DIABETICS 23

Diabetic Diet for use with Injections of Protamine Zinc and Soluble Insulins before Breakfast
About 1500 Calories, 150 g. Carbohydrate (CHO)

	Calories	CHO (g.)
BREAKFAST		
Milk (7 oz.) for tea or coffee, and cereal	135	10
Cornflakes, ¾ oz.	50	10
1 egg, or alternative	90	
Bread, 2½ slices, small loaf (1½ oz.)	125	25
Butter (½ oz.)	100	
		45
MID-MORNING		
Milk, ½ cup (3½ oz.) for coffee	65	5
1 plain biscuit (¼ oz.)	30	5
		10
MID-DAY		
Meat (2 oz.) or alternative	120	
Potatoes, 2 oz.	30	10
Green vegetables or salad		
Fruit, 1 portion	40	10
		20
AFTERNOON		
Milk, ½ cup (3½ oz.) for tea	65	5
2 plain biscuits (½ oz.)	90	15
		20
EVENING		
Meat (2 oz.) or alternative	120	
Salad if liked		
Bread, 3 slices, small loaf (2 oz.)	150	30
Butter (¼ oz.)	100	
Fruit, 1½ portions	60	15
		45
BED-TIME		
Milk, ½ cup (3½ oz.)	65	5
1 plain biscuit (¼ oz.)	30	5
		10
	1485	150

Alternative Carbohydrate portions (10 g. CHO) will be found on pages 28–31. Other alternatives, pages 35–37.

Figure 3. Ten gram exchanges for different types of carbohydrate foods. These were weighed out using the kitchen scales.

forced on me. This was despite the fact that I had been revising for medical finals and had diligently studied the pages on diabetes.

With the diagnosis confirmed I was admitted to a ward. The consultant on the team responsible for me was not at all understanding about the needs of a person who has developed a condition that will affect their life profoundly, although not necessarily cut it short. Fortunately, his second in command, the senior registrar, had a different idea about how to communicate with someone who has to come to terms with an event that significantly alters his life and who needs to be told what life with diabetes will be like. He took the time to tell me that I would be able to do everything, or almost everything, that I wanted to do and that I needed to absorb a good deal of knowledge. I wouldn't remember it all at first because I was in a state of shock but that was understood and it would be repeated. This doctor showed a great deal of empathy and from the start I felt that someone had an understanding of my own particular needs and didn't think 'well, he's a doctor, so he'll know what it's all about'.

This is the first theme I want to address: what people with diabetes want from those who look after them. I believe that they want to feel that they are on the 'inside track' and that the advice that they are given applies particularly to them and to their own situation. The great changes that are affecting the lives of people with T1DM at the present are technological but I would argue that the movement that happened in the 1980s, towards patient-centred care, had an equal if not greater effect. To explain the relationship a person with diabetes wants with his carer, I would look to my own experience as a sailor. You are in command as the helmsman, but you want an expert navigator whispering in your ear to advise the course and to warn of dangers ahead. I have had a number of expert navigators, and I am grateful to all of them.

The next theme I would like to take up is the balance between food and insulin. When I first developed diabetes this was resolved in a straightforward and authoritarian way with a diet sheet and a single injection daily of lente insulin. There were six prescribed meals and snacks, which needed to be closely followed in order to stay out of trouble from the insulin which was active for the whole 24 hours. The UCH diet was derived from RD Lawrence's weighed diabetic diet with black and red lines (or rations) which was introduced in 1925. Since then it had been successively modified so that the black (weighed) portions became 10g exchanges of carbohydrate. The 10g exchanges could be interchanged with others, which were found on a different page of the UCH 'Notes for Diabetics' (Figure 2). However, my first diet would have been a lot more generous than the 150g diet shown here because of the need to gain weight as a newly diagnosed person with diabetes. Ten gram exchanges were the building blocks from which diets were constructed and I look back in awe to those rigid early days of weighing and strict carbohydrate counting using the kitchen scales (Figure 3). But I am also grateful for the discipline that came with it, which sets one up well for a life with diabetes. It is certainly true that in the early days the food that was staple for a person with diabetes was unexciting, as shown by a selection of meals given to patients in hospital in the 1980s (Figure 4). The need to count carbohydrate exchanges and if necessary to weigh foods was enormously eased when commercial food packaging began to print the carbohydrate and energy contents of foods. This also allowed a far greater variety of food choices because for many of the things that it was tempting to eat there was no information available from other sources. Packaging gave information about more sophisticated options like puddings and ready-made meals.

No talk about diabetes in those early days would be complete without showing the instrument of torture – a glass syringe that

Figure 4. Examples of meals served for people with diabetes in hospital in the 1970s and1980s in accordance with dietary prescriptions of that time.

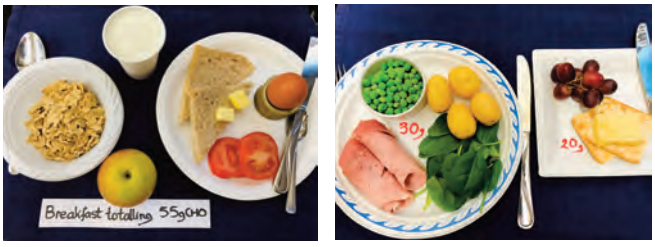


Figure 5. A glass and metal insulin syringe used in the 1970s, despite the fact that disposable needles and syringes were available. They were cleaned with alcohol.

was cleaned with alcohol (Figure 5). The large-bore, non-disposable needle was painful and it was a relief that you only had to inject insulin once a day. Later on came twice-daily regimens with mixed soluble and isophane insulins. With the new regimen insulin activity was pre-ordained 12, rather than 24, hours ahead and with it came a different approach to diet. The proportions of fast- and longer-acting insulins could be varied and it was the job of the dietitian to fill in the area under the curve of the insulin action profile with meals and snacks so that the exchanges added up to an amount that was appropriate for insulin activity. This gave a more flexible choice of diet options but it still seemed that it was the area under the curve, rather than the individual, that was in control of their diabetes. A big breakthrough came in 1985 with the Novopen. The Novopen was an absolute wonder with its modern, slick, state-of-the-art, dial-up precision (Figure 6). Injections could be made in company, into the calf, without any fuss. It is hard to over-emphasize what a difference it made to our lives, getting away from the bother and stigma of ampoules and syringes. The Novopen was revolutionary, rather than incremental, one of the greatest improvements in my life with diabetes.

The evolution of testing systems has been a journey from exploring the past to being able to foretell the future. When I started, chemistry experiments were conducted using Benedict's copper reagent, which changes colour in urine from blue to yellow in the presence of reducing sugars: 2 drops of urine and 10 drops of water in a test tube with a tablet of reagent (Figure 7). The problem with urine tests was that the contents of your bladder give an

Figure 6. The Novopen was introduced in 1985. It allowed discreet injection with insulin and did away with ampoules and syringes.

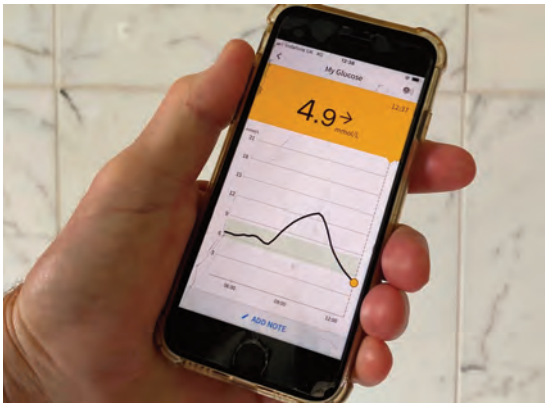
Figure 7. The Clinitest method for testing the concentration of sugar in the urine.

The dark blue colour of the reagent indicates a negative test.

indication of what your blood sugar had been in the variable time since you last urinated, making them of limited use for future guidance. In retrospect I am sure that urine tests were more useful to diabetes doctors rather than to their patients because, flawed as the tests were, they gave some basis for giving advice which was, after all, the object of the consultation. At this time, to keep myself in reasonable shape I tended to bounce off hypos because my hypo awareness was so good. Hypos have been a constant theme in my life, as they are with everyone who takes insulin. For the first couple of decades my sensitivity was exquisite, and I could hold my fingers up to look for fine trembling before any other symptoms developed. As years went by the symptoms blunted but I have always been able to spot my hypos. At present an awareness of cognitive misfiring and a feeling of failure or doom are sure signs of a low blood sugar.

Self-monitored blood glucose systems were introduced in the early 1980s, part of the enormous technological revolution that changed the experience of having diabetes from that time on. These systems were an enormous advance and they made possible the multiple injection regimens which were facilitated by the Novopen. With the ability to monitor blood sugar in real time the amount of carbohydrate eaten could be balanced against a calcu-

Figure 8. A Freestyle Libre flash testing blood sugar trace shown on an iPhone. The future trend can be extrapolated and action taken.



lated dose of insulin. I worked out for myself the ratio of insulin that was required for an amount of carbohydrate, as well as the units of insulin needed to correct a high blood glucose, long before formal education came along. The principles of this new approach which featured dose adjustment for normal eating are absolutely liberating and they put everyone who follows them on the inside track. The introduction of DAFNE courses and their widespread availability means that all people with T1DM are able to liberate themselves from fixed portions and predictable meals.

The situation today, with flash monitoring systems, has advanced the ability to match insulin to the body's needs to a different league altogether. This is demonstrated by the sugar graph on my iPhone Libre app (Figure 8). The trace is obtained instantly, without trauma, and there is no limit to the number of times I can do it. This makes it possible to make any number of adjustments with corrective doses and interruptions of insulin delivery. Importantly, it shows a trend line which indicates what my sugar is likely to be some time into the future, and the out-of-range alert enables me to take action when my attention is otherwise distracted. This is an enormous advantage which gives a great feeling of control and has given me a considerable improvement in my HbA_{1c} without extra effort.

The introduction of insulin pumps in the early 2000s was an important advance in the treatment of diabetes but my own relationship with pumps did not get off to a good start. I was an early adopter but didn't get on with my first pump, mainly because I found it a bit of an intrusion, particularly in bed at night. However, I came back to pumps and I am now an enthusiastic user. The freedom from injections, the capacity to stop basal insulin delivery and the ability to deliver dose adjustments at will and with no fuss are all a boon. The ability to adjust basal levels during the night helps to avoid hypoglycaemia when unguarded. Pumps plus – those with artificial pancreas features are the future and I am looking forward to having one.

Key messages

- In the first sixty years after the introduction of insulin diabetes was controlled in a necessarily authoritarian way.
- The two main changes in my life with diabetes have been the growth of patient-centred care beginning in the 1980s and of technological advances from the 1990s onward. Together they have transformed the lives of people with diabetes.
- The main aim of people with diabetes is to live a life which is no different to their peers.

Credit where it is due

Before finishing I have to acknowledge and give credit to my partner in all this, good times and bad. And there have been some bad times, such as the time when I needed help with a hypo fit in the middle of the night. My wife, Jenny, has been the helmsman's first mate and she knows as much about my diabetes as I do and has advised, reminded and at times taken over the steering when the helmsman has gone 'off duty'. Her instinctive awareness of my developing hypos would more than equal a trained hypo hound, I am quite sure.

A last word about Leonard Thompson, who we celebrate as the pioneer for all people with T1DM. Leonard lived for 13 years after being saved by insulin. He worked as a clerk for a drug company and died of pneumonia, no doubt a complication of poorly controlled diabetes. After Leonard's death the Beach Metro, a newspaper from where the family lived, reported that Dr Banting asked a family friend if the boy had had any fun.

"Yes, he had some fun. He used to get drunk nearly every weekend."

"Well, I'm glad he had some fun," commented Banting

And who are we to disagree? Leonard was the same as his peers and what a person with diabetes asks is to live a life that is no different from those who do not have diabetes.

Conflict of interest None.
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Acknowledgements I am grateful to Professor Ken Shaw for letting me use the images in Figure 2 and 5, and to Mrs Judith Webb for letting me use the images in Figure 3 and 4.

1993 - The Diabetes Control and Complications Trial (DCCT)

ROBERT EJ RYDER

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Key words: Diabetes Control and Complications Trial, HbA_{1c}, microvascular complications, hypoglycaemia, type 1 diabetes

Introduction

Before we consider the DCCT and its findings, it is worth reflecting on what the situation was before that great day in June 1993 when the DCCT was unveiled. I became a consultant in 1991, and I well remember being told at that time by my colleague, Professor Gareth Beevers, "you know, Bob, there is no evidence whatsoever that what you do for your patients with diabetes makes any difference". Professor Beevers was a leading figure in the world of hypertension and he was involved in the many studies showing the benefits of reducing blood pressure on cardiovascular and cerebrovascular outcomes.[1,2] It was galling at the time, that to some extent, what Gareth said to me was true and indeed it was very difficult to argue against. All that changed with the DCCT.

The results of the DCCT were presented at the 53rd scientific sessions of the American Diabetes Association (ADA) on 13th June, 1993. I was there for the occasion and the astonishing thing, for all of us who attended that meeting in Las Vegas, was that none of us realised what was coming. The first clue that something special was happening was all the television cameras outside a lecture theatre as we approached. None of us had seen anything like this before when attending international scientific meetings and this suggested that "something was up". We had no idea what.

DCCT design

The trial included 1,441 patients divided into a primary cohort (n=726) and a secondary cohort (n=715) (Figure 1). The primary cohort consisted of people who did not have diabetic retinopathy and the secondary cohort consisted of people who did have diabetic retinopathy. Each cohort was randomised into those who received "conventional therapy'', which amounted to whatever was the standard diabetes care delivered routinely in the United States at the time, and into another group who were labelled 'intensive therapy'' (Figure 1). The features of intensive therapy are shown in figure 2.

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Figure 1. DCCT randomisation

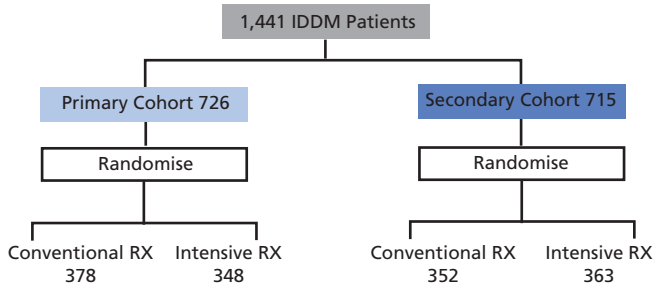
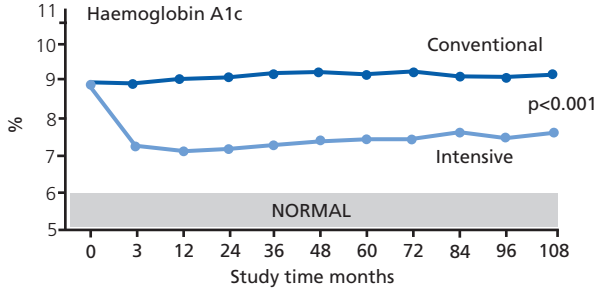


Figure 2. Intensive therapy method

- 3 or more daily injections or insulin pump
- 4 or more blood glucose tests daily
- Frequent dietary instruction to help achieve goals
- Monthly clinic visits
- Integrated tream care

Figure 3. Impact of intensive therapy on glycaemic control



Glycaemic control

By applying the measures shown in figure 2 to the intensively treated group, the mean HbA_{1c} was reduced considerably and significantly compared to the conventional group (Figure 3). A summary of the results shown in figure 3 is that over the decade of the study the conventional group maintained HbA_{1c} of about 9% whereas the intensively treated group maintained a HbA_{1c} of about 7% - a 2% difference.

Diabetic retinopathy

To assess the impact of this sustained improvement in glycaemic control on diabetic retinopathy, fundus photography was used

Figure 4. **a**. The cumulative incidence of sustained three-step change in diabetic retinopathy in the primary cohort, comparing the conventionally treated group with the intensively treated group. **b**. The cumulative incidence of sustained three-step change in diabetic retinopathy in the secondary cohort, comparing the conventionally treated group with the intensively treated group.

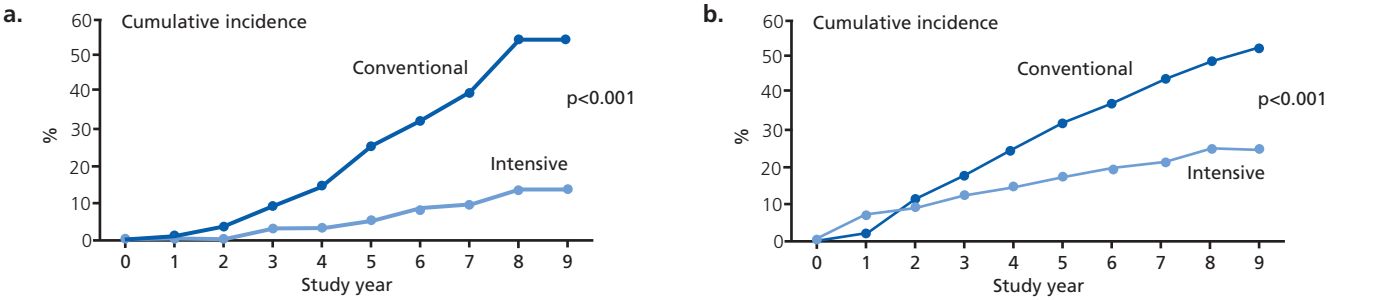
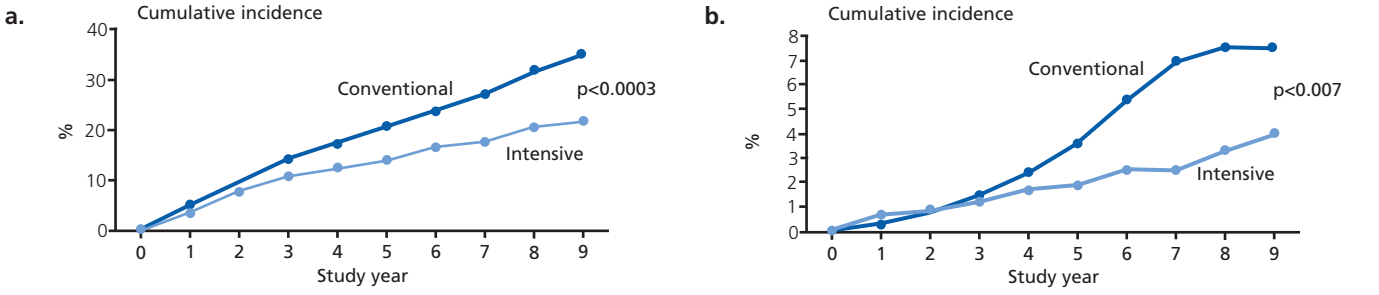


Figure 5. **a**. The cumulative incidence of microalbuminuria ≥40mg/24hr in the combined cohort, comparing the conventionally treated group with the intensively treated group. **b**. The cumulative incidence of albuminuria ≥300mg/24hr in the combined cohort, comparing the conventionally treated group with the intensively treated group.



to assess the severity of retinopathy. For this purpose, the trialists described what was termed a ''sustained three-step change". This was defined as a change observed by fundus photography of at least three steps from baseline that was sustained for at least six months. Those doing the grading were of course blinded as to which group the patients were in. Figure 4a shows the difference in sustained three-step change between the conventional and intensive arms in the primary cohort (76% reduction) and figure 4b shows the difference in the secondary cohort (54% reduction).

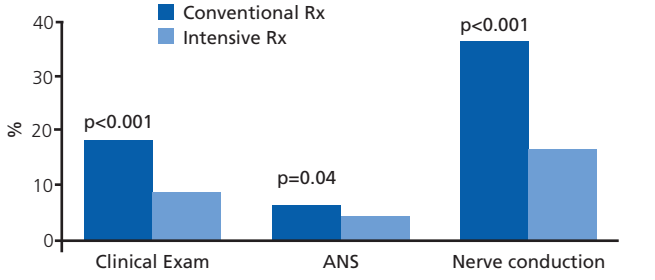
Diabetic nephropathy

Figure 5a shows the impact of the intensive therapy on microalbuminuria >40mg/24 hours in the combined cohort. There was a 34% reduction in the primary cohort and a 43% reduction in the secondary cohort. Figure 5b shows the impact of the intensive therapy on macroalbuminuria >300mg/24 hours in the combined cohort.

Diabetic neuropathy

Figure 6 shows the impact of the intensive therapy on the prevalence of neuropathy at five years. Whether it was checked by clinical examination, or measurement of the autonomic nervous system or by nerve conduction there was a significant reduction in neuropathy.

Figure 6. The 5-year prevalence in neuropathy in those without baseline neuropathy as assessed by clinical examination, measurement of the autonomic nervous system, and by nerve conduction



Hypoglycaemia

In figure 7 the risk of severe hypoglycaemia is presented. It shows a significant increase in risk in the intensively treated group compared to the conventionally treated group (roughly a 3-fold risk).

Risk vs. HbA_{1c}

Figure 8a shows a secondary analysis which was undertaken to assess the rate of retinopathy progression according to HbA_{1c}

Figure 7. Severe hypoglycaemia in the combined cohort comparing the intensively treated group with the conventionally treated group

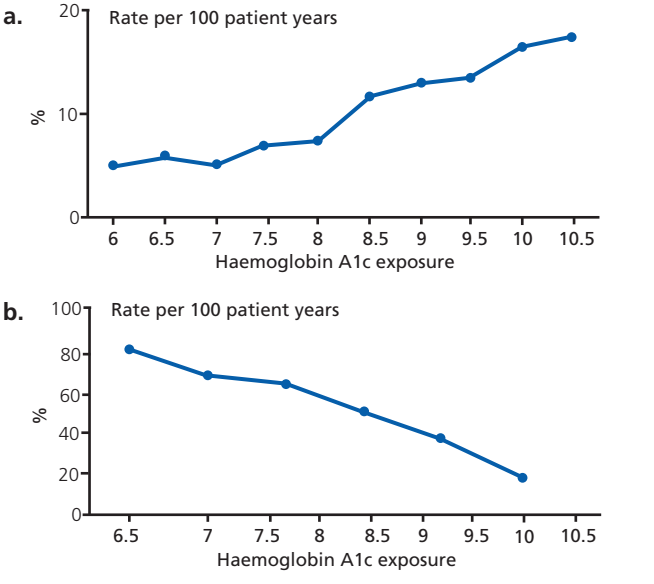
	Episodes/100 patient years		
	Intensive	Conventional	Risk ratio
Severe	62	19	3.3
Coma/Seizure	16	5	3.0
ER/Hospital	9	4	2.3
Deaths	0	0	–

exposure. It shows that the higher the HbA_{1c}, the higher the rate of retinopathy progression. Figure 8b shows a secondary analysis which was undertaken to assess the risk of hypoglycaemia according to HbA_{1c} exposure. It shows that the lower the HbA_{1c}, the higher the risk of hypoglycaemia.

Summary

The DCCT trialists summarised the impact of intensive therapy on microvascular complications as a reduction in retinopathy of between 27% and 76%, in nephropathy of between 34% and 57% and in neuropathy of 60%. The take-home message was overall that the microvascular complications were reduced by about 60% through a maintained improvement in HbA_{1c} of 2% (i.e. from 9% to 7%) over a decade. As shown in figure 8, the trialists also showed that the higher the HbA_{1c} the greater the rate of retinopathy progression but, conversely, the lower the HbA_{1c} the greater the risk of severe hypoglycaemia.

Figure 8. **a**. The rate of retinopathy progression according to HbA_{1c} exposure; **b**. Risk of hypoglycaemia according to HbA_{1c} exposure



Key messages

- Before the results of the DCCT were presented at the ADA in Las Vegas in 1993, there was uncertainty as to whether improving glycaemic control reduced microvascular complications – the DCCT provided the definitive proof
- The take-home message was that, overall, the microvascular complications were reduced by about 60% through a maintained improvement in HbA_{1c} of 2% (i.e., from 9% to 7%) over a decade
- The results also showed that the higher the HbA_{1c} the greater the rate of retinopathy progression but, conversely, the lower the HbA_{1c} the greater the risk of severe hypoglycaemia
- Thus emerged the challenge of finding ways to improve glycaemic control without increasing hypoglycaemia risk and this remains the challenge today, 100 years after the first use of insulin

The legacy of the DCCT

Seventy-one years after the first injection of insulin into a person with type 1 diabetes, we finally knew from the DCCT that improving glycaemic control reduced the microvascular complications of diabetes. We also knew that utilising the intensive therapy methods employed in the DCCT increased the risk of severe hypoglycaemia. Thus emerged the challenge of finding ways to improve glycaemic control without increasing hypoglycaemia risk, and this remains the challenge today, 100 years after that first use of insulin. Three months after their presentation at the ADA in June 1993, the results of the DCCT were published in the *New England Journal of Medicine*.[3]

It was especially gratifying for me personally to be able to return to the UK from that amazing event in Las Vegas in June 1993 and to be able to tell Gareth Beevers that he was wrong!

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Impaired awareness of hypoglycaemia

STEPHANIE A AMIEL

Abstract

Impaired awareness of hypoglycaemia (IAH), defined either clinically as the loss of subjective awareness of hypoglycaemia before the onset of cognitive impairment or biochemically as the loss of symptom perception until plasma glucose has fallen below 3 mmol/L (54 mg/dl), is the major modifiable risk factor for severe hypoglycaemia in T1DM and possibly in insulin-treated T2DM. This paper tells the story of IAH, its pathogenesis and its implications and the treatment strategies used to address it.

Br J Diabetes 2022;**22**(Supp1):S26-S31

Key words: hypoglycaemia, hypoglycaemia awareness, severe hypoglycaemia

Introduction

Impaired awareness of hypoglycaemia (IAH) may be defined as the diminished ability to perceive the onset of hypoglycaemia before the onset of cognitive dysfunction sufficient to alter behaviour and/or to prevent the coordination and execution of self-treatment. Normal counter-regulation to a falling blood glucose concentration is impaired in insulin-deficient diabetes: insulin action is maintained by exogenous injection or by drug-induced endogenous insulin secretion, and glucagon responses to hypoglycaemia are impaired.[1] Detectable defects in cognition start at a plasma glucose of 3 mmol/L (54 mg/dl),[2] a slightly lower concentration than that required to stimulate the counter-regulatory stress response and the symptoms of hypoglycaemia. In IAH, the glucose concentration required to drive the latter is reduced to well below 3 mmol/l,[2] explaining how the protection from severe hypoglycaemia (episodes which need to be treated by others because of cognitive dysfunction in the person experiencing the hypoglycaemia) that is afforded by timely self-treatment is lost. IAH is associated with a 6-fold increase in risk of severe hypoglycaemia in adults with T1DM,[3] and 17-fold increase in risk in people with T2DM who require insulin.[4] IAH affects 20 – 40% adults with T1DM,[3,5] even in the age of continuous glucose monitoring.[6] Although sometimes referred to as "hypoglycaemia associated autonomic failure" it is not associated with diabetic peripheral or autonomic neuropathy.[7]

The state of IAH in people with diabetes who are at risk for hypoglycaemia (those on insulin and insulin secretagogues) is diagnosed through the patient history, inspection of home monitoring records with the patient and sometimes in discussion with family members. The UK's National Institute of Health and Care Excellence (NICE) was one of the first bodies to mandate assessment of awareness status in people with diabetes at risk for hypoglycaemia at least annually in their guidelines, recommending use of the Gold score (Figure 1a).[8,9] The question used by the UK's DAFNE patient education system, asking people whether they usually experience symptoms of hypoglycaemia below, at or above 3 mmol/L (Figure 1b) is another quick method of assessment.[7] It is less subjective than the Gold score and less well established in the literature, although the association with risk for severe hypoglycaemia is at least as strong.[5] The more complex but very well validated Clarke score measures hypoglycaemia experience as well as awareness status,[10,11] and other scoring systems are used in research.[12,13,14]

IAH and its attendant increase in risk for severe hypoglycaemia has been demonstrated to be stressful for partners and family members.[14,15] More recently, IAH has been shown to be associated with higher scores for anxiety and depression,[16] illustrating the mental health burden of the condition on the people with diabetes and IAH themselves.

Who is at risk for problematic hypoglycaemia?

We have known for a long time that risk for severe hypoglycaemia is skewed. In one clinic-based study, 60% of adults with TiDM did not report any episodes of hypoglycaemia over a year.[17] In fact, 10% of the population reported nearly 70% of all severe hypoglycaemia. Increasing diabetes duration, and perhaps associated increasing age, and complexity of co-morbidities were unmodifiable risk factors – IAH was the one major modifiable risk factor left. The link between IAH and severe hypoglycaemia persists even with the use of continuous glucose monitoring (CGM).[6]

The management of IAH

There is an evidence-based pathway for the management of problematic hypoglycaemia (IAH plus more than one severe hypoglycaemia episode in a year) in T1DM.[18] Structured education in flexible insulin dose adjustment is probably the most powerful way to reduce severe hypoglycaemia and improve awareness status,[19,20] with benefit demonstrated in largely unselected populations. CGM and intermittent retrospectively monitored CGM (Flash) with alarms are of proven benefit, the former in people with IAH and/or a history of severe hypoglycaemia,[21] the latter

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in a less selected population.[22] Replacing intermittent injections of insulin with continuous subcutaneous insulin infusion (pump) therapy also has older evidence to show benefit in reducing severe hypoglycaemia,[23] and the automated regulation of insulin delivery by pumps responding to data from linked CGM systems, including hybrid closed-loop systems, shows evidence of benefit.[24] Useful effects have been observed in populations at risk,[25,26] although protection from severe hypoglycaemia has not been seen in all studies,[27] and some have not focused on high-risk populations.[28] Ultimately, replacing the lost beta cells by islet or whole organ pancreas transplantation provides near-complete protection from severe hypoglycaemia as long as there is residual endogenous insulin secretion.[29,30]

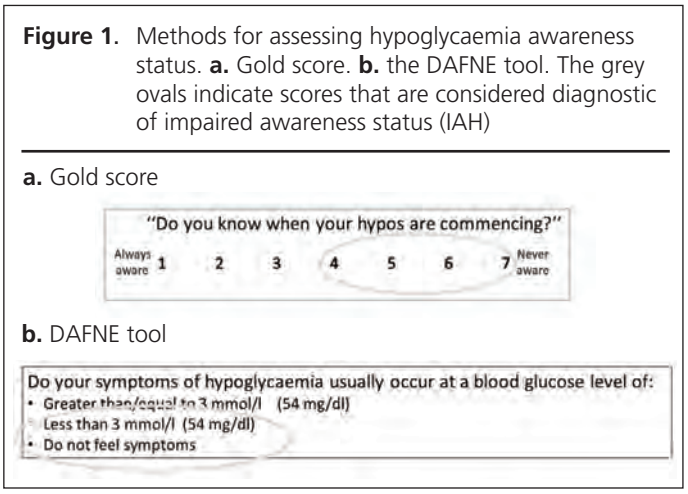
Despite the success of these strategies, and the increasing sophistication of technological approaches to insulin replacement, there is still a need for new approaches. Anecdotal evidence of severe hypoglycaemia in people with diabetes who are on the most advanced technology persists,[31,32] and all the studies that show reduced severe hypoglycaemia in populations at high risk by education or technology show residual severe hypoglycaemia episodes.[5,20,21,24,25] In populations with IAH, technology has often failed to restore awareness.[21,23] There is of course also the issue of access to technology: it is likely to be a long time before everyone at risk for insulin-induced hypoglycaemia is able to have a closed-loop system they can manage themselves. But there are also issues around human engagement with technology, especially while it remains less than perfect. In one study where CGM was added to pump therapy in a population with high rate of IAH, nearly 20% of participants stopped using the technology for reasons such as alarm fatigue, local and technical problems or just not wearing it enough to gain benefit.[33]

The pathophysiology of IAH

IAH is associated with a defective counter-regulatory response: the triggering of hormonal and symptom responses happens at a lower plasma glucose level while the glucose threshold for cognitive dysfunction remains more or less fixed.[27] The defective counter-regulation is inducible by recurrent exposure to plasma glucose concentrations below 3 mmol/L.[34] The causality of antecedent hypoglycaemia has been established by its reversal – defective symptomatic responses to hypoglycaemia in experimental studies can be restored, sometimes with restoration of adrenaline responses, by avoidance of exposure to plasma glucose of less than 3 mmol/L.[35,36]

We have learned through neuroimaging studies that the central response to induced hypoglycaemia in IAH includes changes in activation of brain regions involved in stress responses and symptom perception but also of regions involved in emotional salience, aversion and memory, arousal and decision-making which are different from the responses seen in people without diabetes and those with diabetes but with preserved hypoglycaemia awareness.[37,38] Education plus technology can reduce Gold score and severe hypoglycaemia experience and can normalise responses in the brain's anterior cingulate cortex but not in frontal cortical regions such as the orbitofrontal cortex and dorsolateral pre-frontal cortex.[39] It is possible that some people have a predisposition to develop IAH as a response to hypoglycaemia: early data suggest increased prevalence of alexithymia and extremes of perfectionism in people with IAH.[40] These are personality traits which are thought to be established in early life and they would, at least in theory, predate the diagnosis of diabetes and problematic hypoglycaemia. Clinic-based studies have shown that about one third of people with T1DM at high risk for severe hypoglycaemia (25% of the whole clinic) expressed low concern about it;[41] in a qualitative study, 13 of 17 people with entrenched problematic hypoglycaemia did not describe a high level of worry about it.[42] They described thoughts about their hypoglycaemia that are perceived as barriers to hypoglycaemia avoidance – most notably, prioritisation of hyperglycaemia avoidance, normalising their asymptomatic hypoglycaemia and minimising concerns about hypoglycaemia.[42] De Zoysa created a 19-item questionnaire to help identify some of these thinking patterns, the Attitudes to Awareness (A2A) questionnaire, for use in people with problematic hypoglycaemia.[43] Such patterns have now been described also by people with problematic hypoglycaemia using CGM.[44]

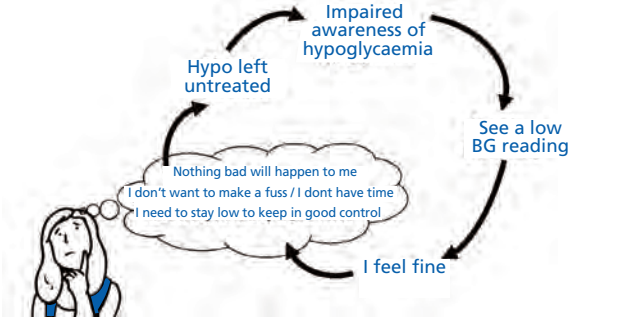
Figure 1. Methods for assessing hypoglycaemia awareness status. **a.** Gold score. **b.** the DAFNE tool. The grey ovals indicate scores that are considered diagnostic of impaired awareness status (IAH)



A novel approach – the HARPdoc programme

The described research suggested a need for a novel approach to hypoglycaemia avoidance and regain of awareness for a particular group of people with IAH that focuses on cognitions around hypoglycaemia. A team of diabetes physicians, educators and people with diabetes, led by the clinical psychologist, created a programme for small groups of individuals with otherwise treatment-resistant hypoglycaemia based on the evidence and using psychological theory, specifically motivational interviewing techniques and cognitive behavioural theory, to address cognitions around hypoglycaemia that act as barriers to hypoglycaemia avoidance and regain of awareness. We called the cognitions that were barriers to hypoglycaemia avoidance "thinking traps". An important principle underlying the programme is the "thinking trap" vicious cycle, in which IAH causes a person experiencing a low blood glucose to feel fine, endorsing and empowering the unhelpful thoughts, leading to delayed or absent action taken to treat the hypoglycaemia, and therefore prolonging and contribut-

Figure 2. The thinking traps vicious cycle, showing how impaired awareness of hypoglycaemia permits the entertainment of thoughts that tend to lead to undertreatment of hypoglycaemia, experience of which creates the counter-regulatory deficits that underpin impaired awareness



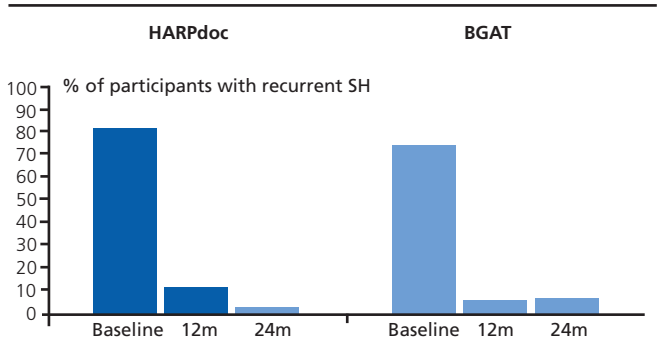
Taken from the HARPdoc course materials, 2021, copyright King's College London

ing to the maintenance of the IAH (Figure 2).

The programme was tested in a pilot in the UK's DAFNE programme,[45] it not being suitable for people whose hypoglycaemia may be driven by lack of factual knowledge about insulin dose adjustment around lifestyle events to minimise hypoglycaemia risk. After adjusting for educator and participant feedback in the pilot, the programme was refined into the current HARPdoc programme. This is a curriculum-driven group intervention delivered over six weeks by two experienced diabetes educators who have been trained and supported to deliver it by the clinical psychologist. The programme uses motivational interviewing and cognitive behavioural theory, focusing tightly on addressing cognitions believed to act as barriers to hypoglycaemia avoidance. We tested it in a randomised controlled trial against Blood Glucose Awareness Training, BGAT,[46] an earlier psycho-educational programme, also manualised, designed to be delivered by one educator in eight 2-hour sessions which addresses knowledge and behaviours to predict and minimise both high and low extremes of glucose.[47] We chose this programme because of its proven ability to reduce severe hypoglycaemia and improve hypoglycaemia awareness.[48] NICE recommends it for people with problematic hypoglycaemia complicating their T1DM management but it has never been tested in people who have already completed a structured education programme such as DAFNE, which is in common usage in the UK. There was interest in its impact on hypoglycaemia that persisted or had recurred post-DAFNE. One of the psychologists from the team that had created BGAT joined our trial team, as BGAT was not currently in use in the form in which it had been trialled and it needed updating to reflect newer insulins and monitoring systems. We also needed to re-configure the programme to be delivered over the same time frame (four full-day face-to-face group sessions over six weeks, with one-to-one contact in weeks 4 and 5 optional for the BGAT participants).

The clinical trial data are still being analysed but the baseline data and the primary and main secondary outcomes are published.[49,50] As anticipated, the trial, which had three centres in the

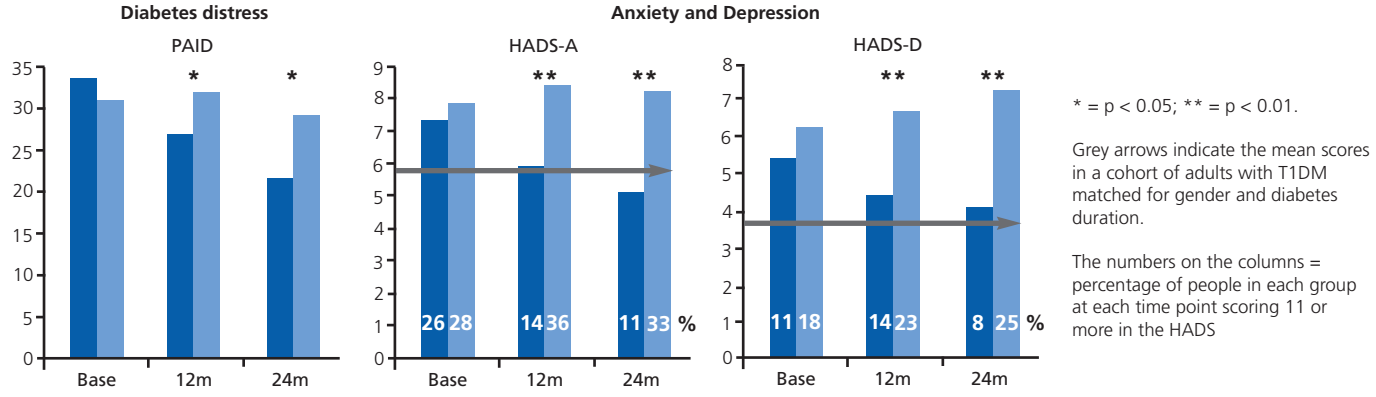
Figure 3. Percentage of people with recurrent severe hypoglycaemia (more than one episode per year) at baseline and 12- and 24-month follow-up in the HARPdoc RCT



UK and one in the US, recruited people mostly of long diabetes duration (mean±SD 35.8±15.4 years) of whom more than half had had problematic hypoglycaemia for ten years or more despite having undertaken structured education in flexible insulin therapy and remaining under the care of specialist teams, with access to latest technology. We were recruiting between 2017 to 2019 and hybrid closed-loop systems were not available but pumps and real-time continuous glucose monitoring (CGM) were. It is relevant that while nearly 80% of individuals had been offered pumps and more than 60% CGM, fewer than half were using any form of technology at recruitment. Accepting that the better the technology the more acceptable it will be to people with T1DM, the present evidence suggests that people with entrenched IAH may struggle either to engage with it or to get the expected benefits when they do.

The trial was designed as a superiority study, intended to show that HARPdoc was more effective than BGAT in reducing severe hypoglycaemia in this very high risk population (baseline rate of severe hypoglycaemia mean±SD 27.9±7.2) who had previously completed another structured education programme. Our primary outcome was the difference in rates of severe hypoglycaemia at either or both of the follow-up times of 12 and 24 months. The final trial result was negative, for BGAT reduced severe hypoglycaemia to a median of zero, making it difficult for HARPdoc to do better! The statistical analysis plan did not include a comparison of the changes in hypoglycaemia over time but Figure 3 shows that both programmes were very effective, with just a hint that the impact of HARPdoc continues to evolve over two years, which was in line with one of our hypotheses (that the impact of HARPdoc would be better sustained because of having addressed important cognitions that underpinned the IAH). There was no difference between the two programmes on Gold scores of hypoglycaemia awareness status, although we can note that HARPdoc increased the proportion of people scoring 3 or less (aware) from zero to 36.6% at 12 months and 43% at 24 months. There were, however, potentially clinically important secondary outcomes for the trial in which HARPdoc was superior to BGAT, and these included the mental health scores. Scores for diabetes distress, anxiety and depression were high at baseline compared with a comparator group matched for

Figure 4. Impact of HARPdoc (dark blue) and BGAT (light blue) on scores for diabetes distress (the Problem Areas in Diabetes questionnaire) on the left, Anxiety (Hospital Anxiety and Depression Scores – Anxiety) in the centre and depression (Hospital and Anxiety Depression Scores – Depression) on the right. HARPdoc is associated with lower scores compared to BGAT at 12- and 24-month follow-up.



diabetes duration and gender but without problematic hypoglycaemia.[49] The scores were significantly lower at both 12 and 24 months in the HARPdoc group (Figure 3).[50] Although still being analysed, preliminary analyses from the implementation science analysis of the trial suggest that both participants and educators rated HARPdoc higher than BGAT for acceptability, appropriateness and feasibility and that HARPdoc is the more cost-effective programme for reasons that are still being investigated.[51]

Conclusions

A cohort of people with T1DM and problematic hypoglycaemia persists despite deployment of best treatment. At present the estimate for prevalence of this cohort lies between 4 and 8% of the adult population with T1DM. They are a highly vulnerable group, with impaired mental health and quality of life. They express thoughts that drive behaviours that impair their ability to avoid hypoglycaemia. It is possible, and probably cost-effective, to address these thoughts with an intervention that can be offered after structured education, and ideally also continuous glucose monitoring, have failed to resolve their situation. While continuing improvements in technology may help, they are unlikely to resolve the problem for these people in the foreseeable future. In a very recent report from the US Type 1 Diabetes Exchange population, reported at the EASD of 2022, Professor Laffel described 16-19% of people using diabetes therapeutic technology who continue to report severe hypoglycaemic events, including those using hybrid closed loop.[52]

Conflict of interest SAA has served on advisory boards for NovoNordisk and Medtronic and spoken at educational events sponsored by Sanofi and NovoNordisk in the past three years. She is a co-investigator in the EU IMI HypoRESOLVE programme. The HARPdoc RCT was sponsored by the Juvenile Diabetes Research Foundation, with additional support from the NIHR S E London CLAHRC and from Dexcom. The views expressed here are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Key messages

- Impaired awareness of hypoglycaemia (IAH) in diabetes greatly increases risk of severe hypoglycaemia and may be associated with impaired mental health status
- Awareness status should be measured routinely in consultations with people at risk – those using exogenous insulin or insulin secretagogues
- Addressing thoughts about hypoglycaemia may be necessary for some with IAH to achieve better outcomes from the therapeutic pathway.

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A brief history of the UK Prospective Diabetes Study

RURY R HOLMAN, FOR THE UKPDS GROUP

Abstract

The UK Prospective Diabetes Study (UKPDS) epidemiological findings confirmed that T2DM is not a "mild" disease, with roughly 50% of patients having clinically evident complications at diagnosis, emphasising the need for its early detection and treatment. Hyperglycaemia was identified as an independent coronary heart disease risk factor, with progressive hyperglycaemia shown to be a major pathophysiological feature of T2DM, driven by declining beta-cell function. People with T2DM and hypertension were found to be at double jeopardy for any diabetes endpoint, and worsening kidney function was shown to increase the risk of death substantially.

The UKPDS 20-year trial results were the first to demonstrate that diabetic complications are not inevitable but can be prevented by more intensive blood glucose control and by metformin therapy, changing T2DM management guidelines worldwide. The UKPDS also showed that tighter blood pressure control prevents diabetic complications; the benefits of the glucose and blood pressure interventions are additive.

The UKPDS 10-year post-trial monitoring study was the first to identify the T2DM glycaemic and metformin legacy effects, with early more intensive therapy having continuing benefits long after the trial terminated. The trial demonstrated the need to achieve good glycaemic control as early as possible to minimise the risk of future complications.

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Key words: Type 2 diabetes mellitus, risk reduction, legacy effect

Background

The UK Prospective Diabetes Study (UKPDS) was conceived in the years of uncertainty following the premature termination of the University Group Diabetes Program (UGDP) study in the late 1960s, which appeared to demonstrate excess cardiovascular mortality with tolbutamide and excess all-cause mortality with phenformin. I joined Robert Turner as his first research fellow in Oxford in 1975 and undertook a series of studies examining 24-hour plasma glucose profiles in people with and without type 2 diabetes (T2DM). Contrary to the prevailing view that plasma glucose values in T2DM rose progressively during the day and returned to normal with fasting overnight, these studies demonstrated that subjects had highly repeatable elevated early morning glucose values, the magnitude of the elevation reflecting their individual degree of insulin deficiency. We concluded that T2DM is an endocrine disease of relative insulin deficiency and that a logical treatment for it would be hormone replacement therapy.[1]

My further studies showed that fasting normoglycaemia could be achieved in people with diet-treated T2DM, either by increasing endogenous insulin concentrations with a long-acting sulfonylurea (chlorpropamide) or by providing exogenous insulin supplementation in the form of subcutaneous long-acting insulin injections (ultratard).[2] When I presented these findings at the International Diabetes Federation Congress in Delhi in November 1976 the audience were sceptical about the value of achieving normoglycaemia, and in particular the suggestion that insulin might become a first-line therapy. Given this feedback, and the results of the UGDP, Robert and I concluded that a major clinical trial was needed to demonstrate the potential benefits of good glycaemic control on clinical outcomes and the possible utility of early insulin treatment. By the time we returned to the UK we had agreed the protocol for what was to become the United Kingdom Diabetes Prospective Study (UKPDS), which commenced just one year later in December 1977 with the aid of a small grant from the Clothworkers' Foundation.

Study design

The UKPDS was a 20-year randomised, controlled, clinical outcome trial of 5,102 people with newly-diagnosed T2DM that ran in 23 English, Scottish and Northern Ireland hospital centres from 1977 to 1997. Participants were allocated to an intensive blood glucose control strategy with sulfonylureas or insulin or (if overweight) metformin, or to a conventional blood glucose control strategy, primarily with diet. Those who also had hypertension were randomised to tight or less-tight blood pressure control in a factorial design.[3] The trial closed out on September 30th 1997, with the results presented the following year at the 1998 EASD meeting in Barcelona.

Following termination of the trial, all 3,277 surviving participants entered a 10-year post-trial monitoring study and returned to their usual care provider. No attempt was made to maintain randomised therapies; mean HbA_{1c} and blood pressure values rapidly became similar between groups, as did their glucose-lowering and antihypertensive therapies with the new more stringent post-UKPDS management guidelines for T2DM that were being rolled out. Post-trial monitoring closed out on September 30th 2007, with the results presented the following year at the 2008 EASD meeting in Rome.

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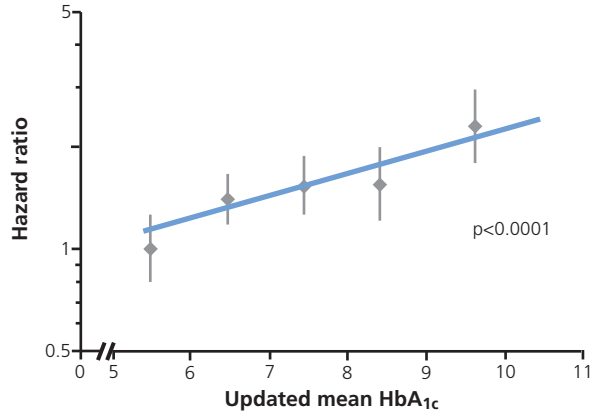
Figure 1. Log-linear relationship between coronary heart disease risk and glycaemic exposure, expressed as updated mean HbA_{1c} values.[7]



Epidemiological findings

Observational analyses conducted during the trial identified a number of key epidemiological findings that transformed our understanding of T2DM. These included: 1) at diagnosis there was an unanticipated high rate of complications, with approximately half of all patients having clinically evident tissue damage such as retinopathy or an abnormal ECG;[3] 2) the identification of progressive hyperglycaemia as a major pathophysiological T2DM feature, with mean HbA_{1c} values rising inexorably over 10 years irrespective of treatment modality;[4] 3) the driver for progressive hyperglycaemia was shown to be a concomitant decline in HOMA-derived measure of beta cell function, with an average annual reduction of 4% over four years irrespective of allocated therapy;[5] 4) hyperglycaemia was shown to be a major independent modifiable risk factor for coronary heart disease, with Robert Turner renaming the "deadly quartet" (high LDL-cholesterol, low HDL-cholesterol, hypertension and smoking) as the "deadly quintet";[6] the relationship between the log hazard ratio for coronary heart disease and the updated mean HbA_{1c} was shown to be a straight line (Figure 1), suggesting that a 14% relative risk reduction for coronary heart disease might be achieved for each one percentile decrement in HbA_{1c};[7] 5) the UKPDS was the first study to identify that participants who were hypertensive in addition to having T2DM were at double jeopardy, with a 45% greater risk of experiencing the UKPDS aggregate outcome of any diabetes-related endpoint compared with those who had T2DM alone.[8] This double jeopardy finding led to the factorial-design addition of the Hypertension in Diabetes Study (HDS); 6) the major impact of worsening nephropathy increasing the risk of death. Although the annual rate of progression from no nephropathy to microalbuminuria, to macroalbuminuria, and to end stage renal disease was only 2.0–2.8%, the corresponding annual risks of death were 1%, 3%, 5% and 19%, respectively.[9] This finding led to a much greater focus on renal impairment in T2DM and methods to prevent it.

Table 1 Relative risk reductions (RRR) and P values for the 20-year interventional trial (1997) and the subsequent 10-year post-trial monitoring study (2007). P values <0.05 shown in bold.

		1997	2007
Glucose Study (Intensive vs. Conventional)			
Any diabetes-related endpoint	RRR:	12%	9%
	P:	**0.029**	**0.040**
Microvascular disease	RRR:	25%	24%
	P:	**0.0099**	**0.001**
Myocardial infarction	RRR:	16%	15%
	P:	0.052	**0.014**
All-cause mortality	RRR:	6%	13%
	P:	0.44	**0.007**
Metformin Study (Intensive vs. Conventional)			
Any diabetes-related endpoint	RRR:	32%	21%
	P:	**0.0023**	**0.013**
Microvascular disease	RRR:	29%	16%
	P:	0.19	0.31
Myocardial infarction	RRR:	39%	33%
	P:	**0.010**	**0.005**
All-cause mortality	RRR:	36%	27%
	P:	**0.011**	**0.002**
Blood Pressure Study (Tight vs. Less tight)			
Any diabetes-related endpoint	RRR:	24%	7%
	P:	**0.0023**	0.31
Microvascular disease	RRR:	37%	16%
	P:	**0.0092**	0.17
Myocardial infarction	RRR:	21%	10%
	P:	0.13	0.35
All-cause mortality	RRR:	18%	11%
	P:	0.17	0.18

Results

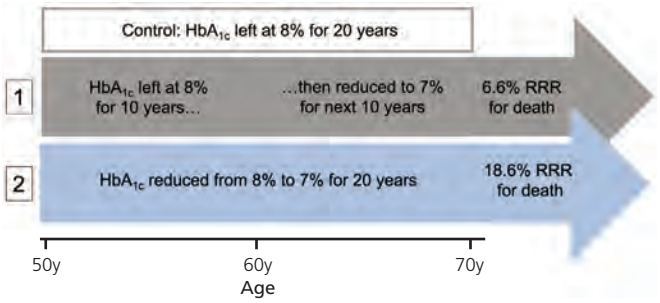
Glucose study

A median HbA_{1c} difference of 0.9% (7.0% vs. 7.9%) was achieved in 3,867 participants with sulfonylurea/insulin therapy, compared with conventional therapy, during a median follow-up of 10.0 years. This resulted in a 12% relative risk reduction in any diabetes-related endpoint and a 25% relative risk reduction in microvascular disease, but no significant reductions in the risk of myocardial infarction or death (Table 1).[10] Following the further post-trial median follow-up of 8.2 years, significant relative risk reductions remained for any diabetes-related endpoint (9%) and microvascular disease (24%), with emerging benefits for myocardial infarction (15%) and all-cause mortality (13%).[11] We dubbed these continuing and emerging benefits of prior more intensive glucose control a glycaemic "legacy effect".

Metformin study

A median HbA_{1c} difference of 0.6% (7.4% vs. 8.0%) was achieved in 753 overweight participants with metformin therapy, compared with conventional therapy, during a median follow-up of 10.7 years. This resulted in a 32% relative risk reduction in any diabetes-related endpoint, a 39% relative risk reduction in myocardial

Figure 2. Two simulated treatment scenarios for a 50-year-old male with newly-diagnosed T2DM and an HbA_{1c} of 8%.[18]



infarction and a 36% relative risk reduction in all-cause mortality (Table 1).[12] Following the further post-trial median follow-up of 8.8 years, significant relative risk reductions remained for any diabetes-related endpoint (21%), myocardial infarction (33%) and all-cause mortality (27%).[11] We dubbed these continuing benefits a metformin "legacy effect".

Blood pressure study

A median systolic blood pressure difference of 10/5 mmHg (144/82 vs. 154/87 mmHg) was achieved in 1,148 participants with tight, compared with less tight, blood pressure control during a median follow-up of 8.4 years. This resulted in a 24% relative risk reduction in any diabetes-related endpoint and a 37% relative risk reduction in microvascular disease, but no significant reductions in the risk of myocardial infarction or death (Table 1).[13] The benefits of intensive blood glucose control and tight blood pressure control were shown to be additive (p for trend = 0.024).[14] Following the further post-trial median follow-up of 8.0 years, no significant relative risk reductions were seen for any diabetes-related endpoint, microvascular disease, myocardial infarction or all-cause mortality, demonstrating that there was no "legacy effect" for prior tight blood pressure control.[15]

First-line insulin therapy

Concerns about the possible adverse effects of insulin therapy on cardiovascular disease in T2DM were raised whilst the UKPDS was underway, with the Veterans Affairs Diabetes Feasibility Trial reporting an apparent excess of non-fatal cardiovascular events in a study of 153 men randomly assigned to a standard insulin treatment group or to an intensive therapy group.[16] A subgroup analysis of the UKPDS glucose study, comparing participants randomised to first-line insulin therapy with those allocated to conventional therapy, allayed these fears, at least in people with newly-diagnosed T2DM. Numerical relative risk reductions were seen with insulin therapy for any diabetes-related endpoint (13%), myocardial infarction (13%) and all-cause mortality (7%), with a statistically significant 30% relative risk reduction for microvascular disease (p=0.015).[10] The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial, which randomly assigned 12,537 people with cardiovascular risk factors plus impaired fasting glucose, impaired glucose tolerance or T2DM to receive insulin glargine or standard care, demonstrated a neutral effect on cardiovascular outcomes, confirming that insulin therapy did not increase cardiovascular risk in this population.[17]

Key messages

- Diabetic complications are not inevitable and can be prevented by improved blood glucose control and by improved blood pressure control
- The benefits of improved blood glucose and improved blood pressure control are additive
- The glycaemic "legacy effect" in type 2 diabetes highlights the need to achieve good glycaemic control as early as possible to maximise potential benefits
- The metformin "legacy effect" shows enduring risk reductions for myocardial infarction and all-cause mortality
- First-line therapy with insulin does not increase the risk of cardiovascular disease in type 2 diabetes

Glycaemic legacy effect

The glycaemic legacy effect is likely driven by the lifetime impact of early exposure to hyperglycaemia, possibly mediated by oxidative stress, generation of AGE proteins or epigenetic changes leading to enhanced expression of proinflammatory genes. Lind *et al*. have shown that historical HbA_{1c} values appear to explain the glycaemic legacy effect, with older values having a substantially greater impact on the risk of all-cause mortality than more recent values.[18] Using modelled UKPDS data, they performed a simulation exercise for two hypothetical treatment scenarios for a 50-year-old male with newly-diagnosed T2DM and an HbA_{1c} of 8%. In scenario one, the modelled impact on the risk of all-cause mortality of leaving the HbA_{1c} at 8% for 10 years and then reducing it to 7% for the subsequent 10 years, compared with leaving the HbA_{1c} at 8% for 20 years, was a 6.6% relative risk reduction (Figure 2). In scenario two, where the HbA_{1c} was reduced to 7% for 20 years from the time of diagnosis, the modelled impact on the risk of all-cause mortality was a relative risk reduction of 18.6%, an effect almost three times greater. These HbA_{1c} analyses and simulations emphasise the crucial importance of establishing and maintaining near-normoglycaemia from the time T2DM is diagnosed in order to minimise the risk of complications and to prolong life.

Summary

Starting in 1977, the UKPDS randomly allocated people with newly-diagnosed type 2 diabetes to an intensive blood glucose control strategy with sulfonylureas, insulin or metformin, or to a conventional blood glucose control strategy, primarily with diet. The 20-year trial results, published in 1998, showed that diabetic com-

plications are not inevitable and that the risk of problems experienced by people with T2DM, including heart attacks, kidney failure and vision loss, can be reduced by good glycaemic control. UKPDS was a landmark trial that changed guidelines worldwide to recommend intensive blood glucose control for everyone with T2DM. This meant that the therapies and blood glucose levels in the two UKPDS groups rapidly became similar. Despite this convergence, the 10-year post-study follow-up analysis (published in 2008) showed that the reduction in the risk of diabetic complications continued for up to 30 years, identifying legacy effects of early intensive blood glucose control with insulin or sulfonylurea therapy, and with metformin therapy.

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The early noughties - Treating to Target

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Key words: Type 2 diabetes, insulin dose, basal insulin, Treat to Target, insulin glargine, fasting glucose, HbA_{1c}, 100 years insulin anniversary

80 years after the discovery of insulin, the early noughties

The era 80 years after the discovery of insulin, the early noughties, could perhaps be labelled the "Treat to Target" era. The United Kingdom Prospective Diabetes Study (UKPDS), as described elsewhere in this supplement by Professor Rury Holman,[1] showed that whilst the microvascular complications were reduced in the intensive arm, the HbA_{1c} relentlessly rose as beta cells relentlessly failed (Figure 1a) no matter whether patients were in the intensive or conventional treatment arm. The study also showed that the lower the HbA_{1c} the less likely there are to be microvascular events (Figure 1b).

Diabetes care in the UK in the 1990s

Against this background it is worth considering what diabetes care was like in the 1990s when I was a young, newly appointed consultant. The typical referral letter from GP to hospital consultant read: "Glycosuria – please do the needful". The majority of GPs considered diabetes to be a hospital problem and most patients were referred. Diabetologists were relatively few in number in those days, and most also covered endocrinology and general medicine as well as all aspects of diabetes care. The upshot was that diabetes clinics were swamped, and care was very much less than optimum. The approach to treatment of type 2 diabetes (T2DM) was not particularly aggressive (Figure 2). Patients tended to have poor glycaemic control and to remain with poor glycaemic control. Once the patient was reluctantly started on insulin, the approach to dose adjustment was lax and unaggressive, and poor glycaemic control persisted (Figure 3).

As the noughties commenced, things were starting to improve with more and more diabetes centres coming into existence, more consultant diabetologists being appointed, increasing numbers of Diabetes Specialist Nurses and primary care becoming more involved. Nevertheless, reluctance to start insulin remained and when eventually the patient was started on insulin, typically it was on twice-daily insulin mixtures and typically the dose was increased by two units for each dose when the Health Care Professional (HCP) met the patient. The frequency of the adjustments depended on availability of HCPs. Typically, oral hypoglycaemic agents (OHA) were discontinued when insulin was started.

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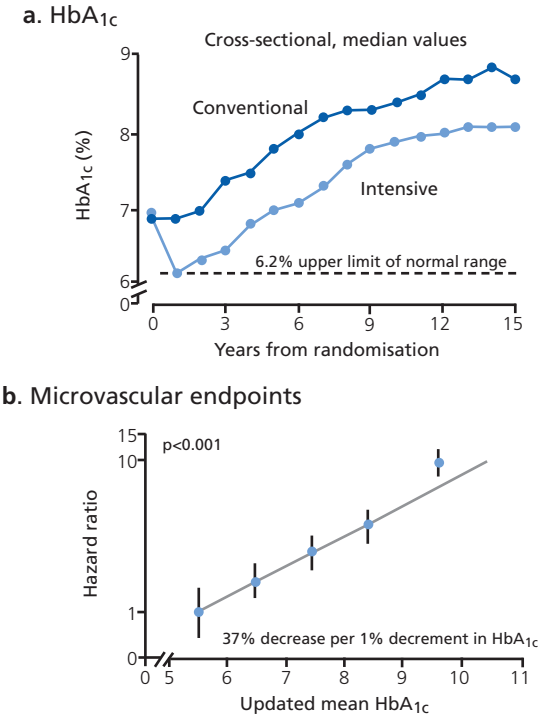
Figure 1. **a.** Change in HbA_{1c} with time in the UKPDS. HbA_{1c} relentlessly deteriorates with time, both for patients in the conventional treatment arm and in the intensive treatment arm; **b**: The hazard ratio for microvascular events at different levels of HbA_{1c} in the UKPDS. As the HbA_{1c} rises the risk of microvascular events increases



Figures 1a and 1b are adapted from the slides shown at the presentation of the UKPDS at the EASD in Barcelona in 1998.

The revolution from Finland

It was at this time that the work of Professor Hannele Yki-Jarvinen, from Finland, came to great prominence and made a considerable difference. The era and her contribution were especially memorable because of the way many of us got to know of her

Figure 2. An illustration of the typical management of a person with T2DM during the 1990s

- Diet wait a few months
- Reinforce diet wait a few months
- Patient misses appointment - a few more months pass
- Reluctantly add OHA in low dose – wait a few months
- Patient misses appointment - a few more months pass
- Increase the OHA dose by a small amount - a few more months pass
- Reinforce diet - wait a few months
- Increase OHA again - a few more months pass
- Patient misses appointment - a few more months pass
- Increase OHA again - a few more months pass
- Add another OHA - a few more months pass
- Patient misses appointment - a few more months pass
- Increase dose of second OHA .....
- Eventually switch to insulin with reluctance .....

HbA_{1c} remains Persistently elevated whilst weeks turn into months and months turn into years

OHA, oral hypoglycaemic agents

Figure 3. An illustration of a typical approach to insulin treatment in a person with T2DM during the 1990s

- Typically, most patients on twice daily insulin mixtures
- Dose adjustments by health professional from time to time – depending on availability of health professional
- Typically, the health professional would increase each dose by 2 units at each consultation

HbA_{1c} remains Persistently elevated whilst weeks turn into months and months turn into years

work. She would present at national and international meetings with great authority and force. Like an Old Testament prophet preaching to the multitudes, she harangued her cowering audiences about how badly they were managing their patients, how awful that was for those patients, and how they could and should manage them very much better – and that it was easy to do that!

Figure 4 outlines the patient-led Treating to Target (T2T) approach that she recommended.[2-4] Her work showed that the best insulin regime was bedtime long-acting insulin with continuation of metformin.[4,5] She pointed out that if, as in the traditional approach, the insulin dose is increased by 4 IU at each two-monthly consultation with an HCP (NB in reality consultations were far less frequent than two-monthly), an increment of only 24 IU/day could be achieved in one year; whereas if the insulin dose is increased by 2 IU every three days by the patient, an increment of 240 IU/day could be achieved in one year (Figure 4b).[4] Even though T2DM is characterised by insulin resistance, it was clear that patient-led T2T would be able to find the optimum dose for most patients relatively rapidly.

The Treat to Target study

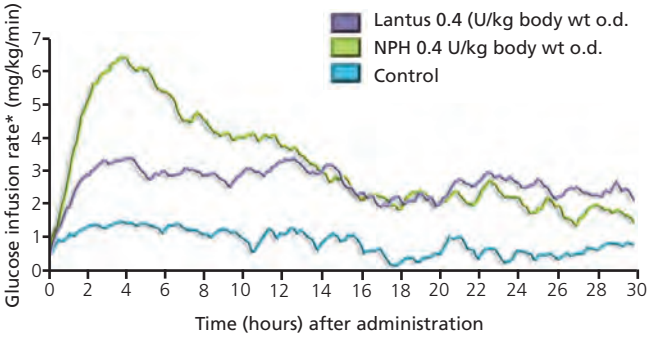
At about this time the first long-acting insulin analogue was launched, insulin glargine. Figure 5 shows the comparison of profile between insulin glargine and NPH insulin, showing a much flatter profile for the former.[6] In the wake of this, the "Treat to Target Study" was undertaken to compare insulin glargine and NPH insulin. The results were presented by Dr Julio Rosenstock and Dr Matthew C Riddle at the EASD in Budapest in 2002,[7,8] and were later published in Diabetes Care.[9] In all, 756 insulin-naïve people with T2DM with inadequate glycaemic control on one or two oral agents (sulphonylureas, metformin, thiazolidinediones) were compared in this 24-week, multicentre, randomized, parallel, open-label trial.[9] The insulin starting dose was 10 IU, and dosage was adjusted weekly by a forced-titration schedule seeking fasting plasma glucose (FPG) ≤5.6 mmol/L (≤100 mg/dL) unless prevented by hypoglycaemia. Figure 6 shows the weekly insulin forced titration algorithm that was used.[9] The study demonstrated that by intention-to-treat analysis, both insulin glargine and NPH insulin achieved good control: mean FPG fell to 6.50 and 6.68 mmol/L and mean HbA_{1c} to 6.96 and 6.97%, respectively.[7-9] 57% and 58% of patients in the insulin glargine and NPH insulin groups, respectively, ended the trial with HbA_{1c} ≤7%.[7-9] More patients treated with insulin glargine achieved HbA_{1c} ≤7.0% without experiencing nocturnal hypoglycaemia (33 vs 27%; $p<0.05$).[7-9] Treatment with insulin glargine caused less nocturnal hypoglycaemia than NPH insulin (532 vs 886 events, $p<0.002$, in 40% vs 49% of subjects; $p<0.01$).[7-9]

Figure 4. **a.** The patient-led Treat to target approach promoted by Professor Yki-Jarvinen. Professor Yki-Jarvinen maintained that when this approach was used, most patients would reach target though it might require a lot of insulin; **b.** A comparison between the potential insulin doses achieved during a year following the conventional insulin dosing approach compared to the patient-led treat to target approach of Professor Yki-Jarvinen

a.
- Start bedtime long-acting insulin 10 units
- Patient measures fasting glucose every morning
- If 3 consecutive readings > 5.5 mmol/L patient increases dose by 2 units

b.
- If the insulin dose is increased by 4 IU at each 2 monthly **consultation with a health professional** an increment of only 24 IU/d could be achieved in 1 year.
- If the insulin dose is increased by 2 IU every 3 days **by the patient** an increment of 240IU/d could be achieved in 1 year.

Figure 5. A comparison between the profiles of insulin glargine (Lantus), that of NPH insulin and normal physiological basal insulin. Trial details: A double-blind study in healthy volunteers over three days. Constant plasma glucose level was 5.0 mmol/L



*Determined as amount of glucose infused to maintain constant plasma glucose levels (hourly mean values) n=15. Figure is adapted from reference 6.

The patient-led algorithm wins

Professor Yki-Jarvinen undertook her own version of an NPH vs glargine T2T study, the LANMET study, using her patient-led titration algorithm (Figure 4a) and found a similar result.[10]

To help resolve the issue as to which T2T insulin titration algorithm was best, the USA HCP-led one (Figure 6) or the Finnish patient-led one (Figure 4a), Professor Melanie Davies undertook the AT.LANTUS study to compare the two algorithms in a head-to-head study.[11] This showed a greater improvement in HbA_{1c} with the patient-driven algorithm but with slightly more hypoglycaemia (Figures 7a and 7b).[11]

Inner-city West Birmingham

I was very inspired by the aforementioned harangues of Professor Yki-Jarvinen and became a disciple of hers. I started using a patient-led T2T approach, adapted from the Finnish protocol, throughout inner-city West Birmingham and undertook an audit.

Figure 6. The treat to target forced titration regimen used in the (Treat to Target study). See references 4-6

Start with 10 IU/day bedtime basal insulin dose and adjust weekly – clinic driven

Self-monitored FPG for two consecutive days with no episodes of severe hypoglycemia or PG ≤4.0 mmol/L (72 mg/dL)	Increase in insulin dose (IU/day)
5.6-6.7 mmol/L (100-120 mg/dL)	2
6.7-7.8 mmol/L (120-140 mg/dL)	4
7.8-10.0 (14-180 mg/dL)	6
>10.0 mmol/L (180 mg/dL)	8

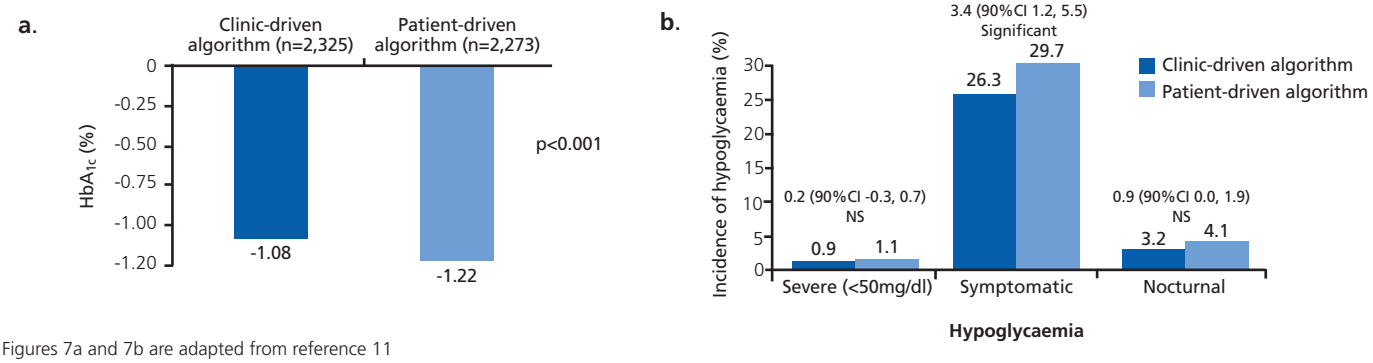
Treat to Target FPG ≤5.6 mmol/L (100 mg/dL)

We were able to conclude that in 'real world' unselected patients in an inner-city area, 41% achieved an HbA_{1c} ≤7%.[12,13] That was a remarkable finding at the time, especially considering how things had been prior to this change of approach (Figures 2 and 3). The learnings from this audit paved the way for the ABCD nationwide audit programme, which started in 2008 and has been going from strength to strength ever since.[14]

Better analogues but patient-driven T2T remains the best way

Since that time, many more agents have become available to be used before insulin is added: these include metformin, sulphonylureas, pioglitazone, gliptins, SGLT2 inhibitors and GLP-1 receptor agonists.[15] If insulin is required, we now have even longer-acting insulin analogues such as insulin degludec and glargine U300,[16] which facilitate improved glycaemic control with even less hypoglycaemia. Nevertheless, if insulin is required, a patient-driven T2T remains, in my opinion, the best way to dose-titrate for many patients.

Figure 7. **a.** In the AT.LANTUS study, significantly greater reduction in HbA_{1c} was achieved with patient-driven than with clinic-driven titration algorithms; **b.** In the AT.LANTUS study, there was no difference in the incidence of severe hypoglycaemia between clinic-driven and patient-driven titration algorithms



Figures 7a and 7b are adapted from reference 11

Key messages

- 80 years after the discovery of insulin, in the early noughties, the "treat to target" approach to insulin dosing led to a revolution in the management of people with T2DM
- Two algorithms emerged, one patient-led and the other clinic-driven. In a head-to-head study, the patient-led algorithm was marginally superior
- The patient-led algorithm was very simple: the patient administers once-daily long-acting insulin at bedtime starting with 10 units. The patient measures fasting glucose every morning and, if three consecutive readings are >5.5 mmol/L the patient increases the dose by 2 units
- The approach allows the patient to find their ideal basal insulin dose much more rapidly than previously used methods. When this approach was introduced in inner-city West Birmingham, 41% of patients achieved a HbA_{1c} ≤7%

HbA_{1c} or Time-in-Range?

As we move into the future in 2022, the question arises as to what is the best way to assess glycaemic control. It is noteworthy that in a head-to-head randomised controlled trial of insulin glargine u300 and insulin degludec,[16] Time-in-Range rather than HbA_{1c} as primary end point was used to assess glycaemic control. It would make an interesting subject for an ABCD debate: "This house supports replacing HbA_{1c} with Time-in-Range as the optimum way to assess glycaemic control from now on".

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Sanger, Hodgkin, Yalow and the impact of insulin analogues

DAVID RUSSELL-JONES

Br J Diabetes 2022;**22**(Supp1):S40-S41

Key words: insulin analogues, insulin structure, insulin treatment

History

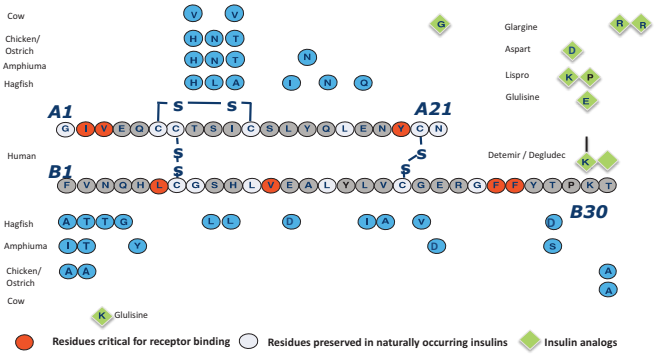
The discovery of insulin by Banting, Best, Collip and Macleod is considered to be one of the great medical and scientific triumphs.[1] The year was 1921: it also happens to be the year that another Nobel Prize-winning scientist, Rosalyn Yalow, was born and a year in which Dorothy Crowfoot was at school in Norfolk. She wanted to study chemistry but girls had few such opportunities so she had to travel to the boys' grammar school to be allowed to study this subject. Both of these girls would grow up to be Nobel Prize-winning scientists who made outstanding contributions to the understanding of insulin. Frederick Sanger, while working at Cambridge, won his first Nobel prize for elucidating the amino acid sequence of insulin.[2] Following this discovery and using insulin crystals, x-ray crystallography studies were performed and the discovery of the 3-dimensional structure of insulin was achieved by Dorothy Crowfoot (who became Dorothy Hodgkin on her marriage).[3] Thus, insulin had led the way as being the first hormone to be isolated (Banting, Best, Collip and Macleod), the first protein to have its amino acid structure determined (Sanger) and finally, the first to have its 3-dimensional structure elucidated (Dorothy Hodgkin).[1,2,3] All of these advances were groundbreaking and led to the award of Nobel prizes. The last major problem was that peptide hormones were at such low concentrations in the bloodstream (picomol) that measurement was only possible using bioassays and the glucose-lowering effect in live animals. Rosalyn Yalow and her colleague Solomon Berson were able to construct and invent the radioimmunoassay, which allowed insulin to be measured even though it is in picomolar concentrations.[4] This great advance was also rewarded with a Nobel Prize.

Physiology and evolution of insulin

Following these landmark studies many people became captivated by the physiology of insulin; many elegant studies have led to our physiological understanding that insulin lowers glucose by suppressing endogenous (predominantly hepatic) glucose production through a receptor-mediated action on glycogenolysis and gluconeogenesis.[5] In addition, at higher concentration insulin stimulates peripheral glucose uptake, also reducing blood levels. Insulin has major regulatory effects on free fatty acid liberation from adipose and protein metabolism.[5] Its homeostatic function is a central controlling mechanism in metabolism of all animals. Following the discovery of the insulin receptor, maps of insulin and insulin receptor interaction were produced. These have allowed a great physiological understanding of insulin structure and functional relationships to be developed.

Although insulin is highly conserved in evolution, there are some differences in amino acid structure between species (see Figure1).[6] Insulin can be identified in very simple organisms and a recognisable insulin molecule is present in invertebrates and all vertebrates.[6] Strong evolutionary pressure has led to the conservation of amino acids particularly in areas that are known to be involved in close association and binding to the insulin receptor and also those important for 3-dimensional conformation.

Figure 1. The evolution of insulin and insulin analogue structures



(Adapted from Herring R, Russell-Jones D. Diabet Med 2018;35:1320–8)

Insulin analogues

From a position of understanding of specific amino acid interactions, it has been possible to modify the insulin structure for therapeutic benefit to create insulin analogues with altered pharmacokinetic and pharmacodynamic properties. Both short- and long-duration analogues have enabled more physiological insulin replacement via the subcutaneous route, which has led

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https://doi.org/10.15277/bjd.2022.361

Figure 2. Impact of insulin analogues

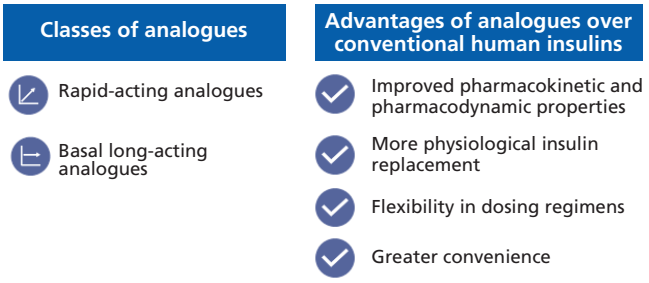
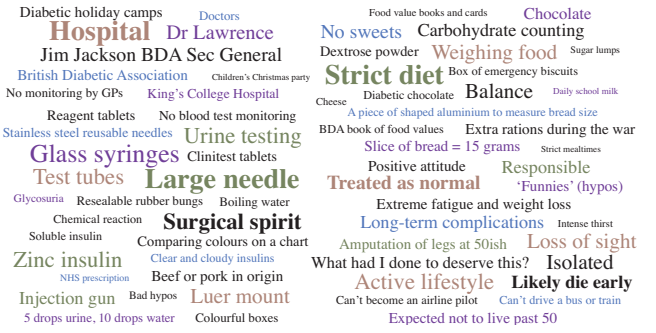


Figure 3. Life with diabetes 50 years ago



(Adapted from Russell-Jones D, Herring R. Diabet Med 2021;38:e14642)

Figure 4. Life with diabetes in 2021

(Adapted from Russell-Jones D, Herring R. Diabet Med 2021;38:e14642)

Key messages

- Insulin was the first peptide hormone to have its amino acid sequence and 3 D structure to be determined
- Insulin Analogues have been designed from a positon of knowledge of receptor binding and function
- Insulin treatment has changed dramatically over the last 100 years leading to benefit

to improved diabetes control and convenience for millions of people with diabetes treated with insulin. In 1978, the first successful production of human insulin was produced by recombinant DNA technology in Escherichia coli. This was achieved by a team of specialists led by Robert Crea and David Goeddell.[5] Insulin became the first genetically manufactured drug to be approved by the FDA. The development of these technologies has allowed the production of pure insulin analogues in unlimited supply for the benefit of people with diabetes worldwide. These insulin analogues have transformed diabetes care and have allowed better insulin replacement, producing superior diabetes glucose control and ultimately fewer complications and lesser morbidity. The advantages of analogues are displayed in Figure 2.

Impact of treatment in different eras

To illustrate the impact of improved diabetes care on people with T1DM we performed an interesting study in which we contacted people who had received 50-year, 60-year and 70-year medals for living with diabetes. Their recollections and views on what it was like when they were first diagnosed were gauged by words and phrases that they submitted to us. From this we created a word cloud of their experiences, which is seen in Figure 3. In addition, we asked young adults and teenagers who have been diagnosed recently to provide similar short words and phrases. A word cloud of their experiences has also been created, as shown in Figure 4. As can be seen from looking at the two figures, there is a marked difference in the patient experience between the ages, highlighting the advances made in treatment and life in general. These word clouds succinctly sum up the advances made in diabetes care and the impact of modern treatments over the last 100 years.

Conflict of interest I Have received research grants and honoraria for advisory boards from Dexcom, AstraZeneca, Novo Lilly, Nordisk and Sanofi,
Funding None.

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Reflections on 60 years of caring for people with diabetes

ALEX D WRIGHT

Br J Diabetes 2022;**22**(Supp1):S42-S43

Key words: Insulin, b.glucose, DCCT/UKPDS

It was a special upside-down year, 1961, the numerals being the same when rotated upside down. It was the year that the fine black and white £5 note and the farthing coin ceased to be legal tender. I never handled a £5 note as we were paid in what seemed like farthings, with £60-70 per month after deduction of hospital board and lodging fees. But we did look smart.

Alex D Wright 1961

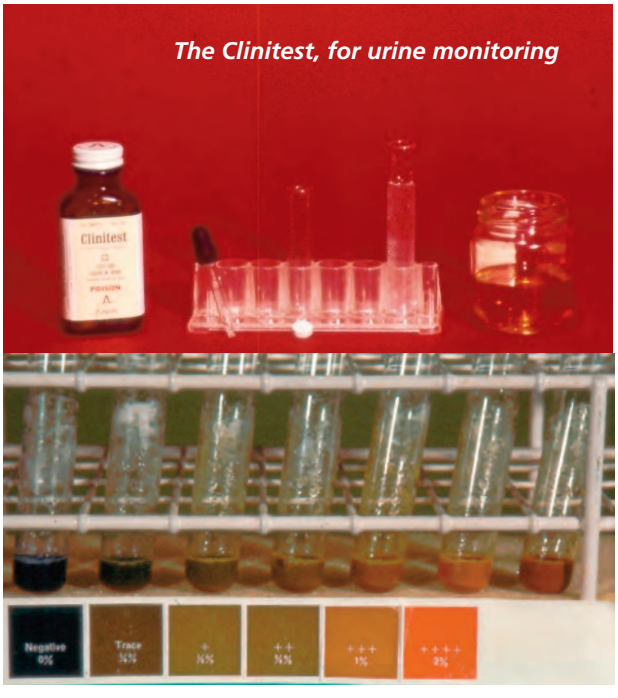
My first encounter with clinical diabetes was when I was a clinical medical student, when I was secretary of the medical history society and invited RD Lawrence to give a talk in the medical school. It was an inspiring evening and I treasure his thank you letter afterwards that sent me best wishes for the future. My first job in 1961 was locum house physician to the diabetes unit at King's College Hospital, London. The job included the responsibility for all the insulin prescriptions throughout the hospital. This provided continuity and some safety in an area where mistakes are easily made but the arrangement deskilled other staff.

A glass syringe kept in a spirit-proof case

Insulin was available in 40 and 80 units/ml strengths (rarely 20 units/ml) and was administered by a 1ml insulin glass syringe graduated in 20 marks. The syringes and needles were sterilised in a boiling water bath and patients usually kept them in spirit-proof cases. Knowledge of the 2x and 4x tables was essential, but mistakes between marks and units were commonly made. The introduction of a standard 100 units/ml strength in 1981 was a great step forward though the subject remains complicated with 200, 300 and 500 units/ml strengths available. The use of a numeral within the name of some modern insulins is another potential source of confusion.

The drawing up of a dose of insulin from a multidose vial requires considerable manual dexterity. The introduction of plastic syringes was a great boon but created a disposal problem. Another step forward in 1981 was the idea of an insulin pen: the first NovoPen was launched in 1985. A pen containing a cartridge of insulin with a disposable needle provides simple, portable equipment that can be used anywhere. Freedom from injections came with the introduction of insulin pumps, another impressive technical advance.

The house physician at King's was also responsible for out-of-hours venous blood sugar measurements using a Folin and Wu colorimetric technique. This took about 20 minutes to perform in a side ward. Monitoring of diabetes for both patients and diabetes staff was otherwise based on urine testing using Clinitest.



The Clinitest, for urine monitoring

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Blood glucose strips

The introduction of blood glucose strips for measurement of capillary glucose, based on a glucose oxidase method, was a great breakthrough. Dextrostix arrived in 1965. This was enhanced by the first glucose meters in 1980 and by continuous blood glucose monitoring more recently.

The expansion of drugs for treating diabetes during my working lifetime has been enormous. My British National Formulary (BNF) of 1960 cost 7s. 6d. and contained five BP insulins - Insulin Injection, Protamine Zinc Insulin Injection, Insulin Zinc Suspension, Insulin Zinc Suspension (Amorphous) and Insulin Zinc Suspension (Crystalline)-- and listed isophane insulin/NPH insulin and two oral agents for diabetes, tolbutamide and tolazamide. Metformin had been introduced in 1958 but was not included in the BNF of 1960. Phenformin was withdrawn in about 1977. Antimicrobials included chloramphenicol, chlortetracycline, oxytetracycline and tetracycline, erythromycin, neomycin, penicillin, sulphonamides and streptomycin, isoniazid and PAS. Cardiovascular drugs were limited to mersalyl, chlorothiazide, hydroflumethiazide, reserpine, hydralazine, digoxin and digitalis. Blood pressure-lowering drugs were extremely limited: we did not even have methyldopa. We had to learn metric and imperial equivalents (vol: 10 minims=0.6ml; 20 fl oz=l pint; wt: 1 grain=60mg [for example a quarter of morphine was 15mg]; 1 oz = 28g; 16oz = 1 pound). Fortunately, as a house officer I was given the option of using metric prescriptions.

A modern BNF costs about £58.00. My BNF 80 for September 2020 to March 2021 contains four rapid-acting insulins, four intermediate-acting insulins, two intermediate-acting combined with rapid-acting insulins, three long-acting insulins, and two long-acting insulins combined with liraglutide or lixisenatide. In addition, a range of other medications is included such as metformin, five sulphonylureas, an alpha glucosidase inhibitor, pioglitazone, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, meglitinides, and sodium glucose co-transporter 2 inhibitors together with various therapeutic combinations. The list continues to grow.

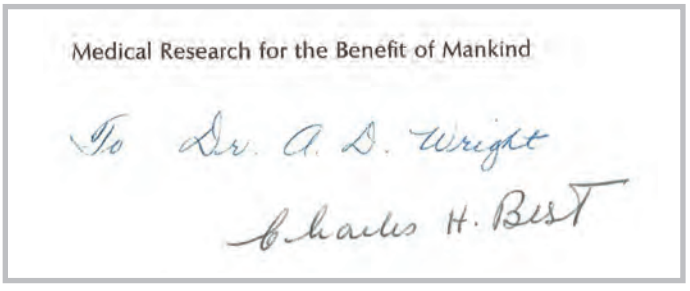
Proof that glycaemic and blood pressure control are vital for the long-term outcome in diabetes was shown by the DCCT for T1DM and by the UKPDS for T2DM. The results from these two studies and from various national data collections have been invaluable in quantifying risk. The presentation of the UKPDS results at the EASD meeting in Barcelona was a thrilling moment in which I was honoured to take a part. The establishment of annual screening programmes for patients with known diabetes has been another welcome innovation which helps to detect evidence of micro- and macro-vascular disease. Perhaps less well established is the principle of risk stratification for complications: it has such a practical application in preventing loss of sight and amputations, which sadly still occur. The large clinical studies have also taught us that diabetes is a progressive disease.

Professional and patient education in diabetes was introduced with the first use of insulin in the 1920s and has developed into impressive, well-structured programmes that can be adjusted to differing needs.

Summary

Great advances have occurred in every aspect of diabetes during my working life, including the number and range of therapies available, the relative ease of blood glucose monitoring, a greater understanding of the need for good glycaemic and blood pressure control and the better detection and care of complications. My hope is that the next generation will see more results from programmes that aim to prevent diabetes.

It has been an exciting 61 years in clinical diabetes, with many great colleagues and long-suffering patients. I leave you with a torch and inspiration from the 50th anniversary of the isolation of insulin in Toronto.


Medical Research for the Benefit of Mankind

To Dr. A. D. Wright

Charles H. Best

Key messages

- Advances in monitoring and therapy of diabetes
- Better understanding of complications of diabetes
- Prevention strategies are important

Conflict of interest None.
Funding Novo supported the meeting on the 100 years of insulin discovery.

Handing control to the patient - structured education in diabetes

SIMON HELLER

Br J Diabetes 2022;**22**(Supp1):S44-S47

Key words: Structured education, type 1 diabetes, flexible intensive insulin therapy (FIIT)

This year we celebrate the centenary of the discovery of insulin, when researchers at the University of Toronto successfully treated the first individual with T1DM. It was undoubtedly a major breakthrough. Insulin transformed children and adults destined to die within 2-3 years into healthy individuals within a few weeks and many went on to live full and productive lives. Yet the optimism that the ready availability of insulin would result in a cure for a previously fatal disease was gradually replaced by a realisation that insulin was not a panacea. Over the years that followed, many of those on treatment developed serious microvascular complications resulting in blindness, amputation and renal failure. It gradually became clear that keeping glucose levels close to normal was key. But since blood glucose had to be measured in hospital labs and those with diabetes were only able to measure glucose in their urine the challenges of keeping levels at target were immense. Episodes of severe hypoglycaemia were common, and many authorities considered it too dangerous to attempt to keep glucose at near-normal levels.

With the advent of glucose monitoring in the late 1970s, pioneers such as Berger and Mühlhauser realised that this revolutionary technology could be used by patients at home to enable them to manage their diabetes themselves. Positive trial results were ignored by many healthcare professionals and it took another 30 years for the UK diabetes establishment to adopt this approach. In this chapter I describe how structured education in diabetes was developed, the evidence for its effectiveness and the remaining challenges which still need to be overcome.

Following the discovery of insulin, most healthcare professionals were slow to realise that it is the person with diabetes (or their family) who holds the key to implementing effective self-management. Yet there were some professionals around the world who grasped this. Perhaps the first was Elliot Joslin, who was working in Boston when insulin was discovered. He realised rapidly that for treatment to work properly the patients had to be trained to be their own doctors and had to learn to adjust insulin themselves. He wrote a manual for patients in the early 1920s and, in a paper he wrote in 1946, he reflected that any insulin therapy was "a waste of time and money unless the patient was thoroughly instructed to manage his own case".[1]

Karl Stolte, a paediatrician working in Rostock in Germany, argued in 1929 that children should be allowed to eat freely with insulin adjusted according to the amount of glucose in their urine.[2] It appears this was too much for the medical mainstream in Germany at that time and his insights went unheeded. Some British physicians did grasp the importance of self-management. RD Lawrence, whose own life was saved by the discovery of insulin, became head of the diabetes department at King's College Hospital and by 1929 had written two books, "The Diabetic Life" and "The Diabetic ABC" which provided instruction on managing diabetes for both professionals and patients.[3]

However, the general view in the UK was that doctors should remain in charge of treatment. Robert Tattersall, who together with Peter Sönksen and Clara Lowy were the first clinicians to introduce blood glucose monitoring into clinical practice in 1977, has written that an abstract, describing the Nottingham experience in using the technology in pregnancy, was rejected by the then BDA Medical and Scientific meeting. Furthermore, during the subsequent meeting, the proposition that patients could monitor their own blood glucose was met 'with incredulity' and a view that even if it was possible, 'it would be dangerous'.[3]

Yet at the same time, others in Europe realised the potential of self-monitoring of blood glucose (SMBG) to transform diabetes care by using the technology as part of a structured training package. Jean Philippe Assal had, with others, developed the concept of Therapeutic Education,[4] an approach incorporating principles of modern adult education to promote self-management skills encouraging patient autonomy. Mühlhauser and Berger, working in the WHO centre in Düsseldorf, incorporated SMBG into a structured education course diabetes teaching and treatment programme (DTTP).[5] They attempted to reproduce the physiology of insulin secretion therapeutically by separating insulin delivery into a longer-acting basal insulin (with NPH insulin injected twice daily) to control blood glucose in between meals and they covered meals with soluble insulin given before eating.

In the UK, carbohydrate exchanges had been used to impose a rigid eating pattern in response to fixed doses of insulin prescribed by the physician, which meant expecting adults and children to eat the same amount of carbohydrate (CHO) at the same time each day. In marked contrast, the DTTP promoted 'dietary freedom', with no forbidden foods and those with diabetes calculating their own insulin dose based on anticipated CHO intake and current

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blood glucose values. The course was delivered to groups of 8-10 adults over five days in an inpatient setting. Controlled trials demonstrated both improved glucose levels and reductions in severe hypoglycaemia. In an influential prospective observational study involving more than 9,500 adults in multiple German centres, HbA_{1c} had fallen by 7 mmol/mol (0.7%) to 60 mmol/mol (7.6%) and the incidence of severe hypoglycaemia had fallen significantly by ~50% to 0.21 episodes per individual per year.[6]

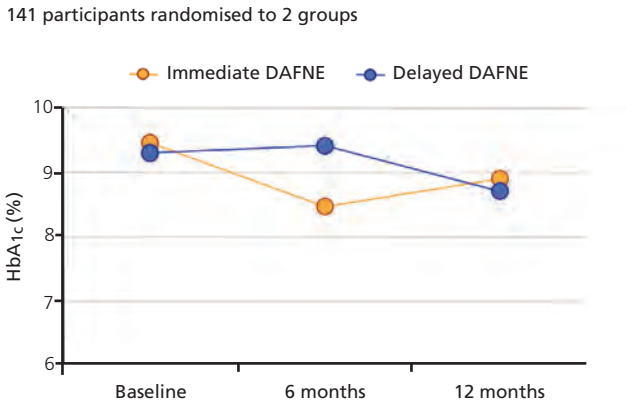
Yet despite this powerful evidence, published in high quality journals, centres in the UK either ignored or dismissed this work. In the early 1990s, carbohydrate exchanges had been discarded as futile, with the realisation that asking individuals to eat the same amount of carbohydrate at the same time every day was unrealistic for most. But in the absence of structured education, insulin was dosed haphazardly, and the prevailing approach was something called 'healthy eating'. Armed with their experience of the success of the DTTP, Berger and Mühlhauser were forthright in their criticisms of centres and countries where systematic training was not provided.[7] They condemned the haphazard approach, selective use of the literature and claims of lack of resources to justify this stance. In particular, they emphasised the waste of time and money of using glucose monitoring without teaching patients how to use the results.

DAFNE results

Provoked by those comments during a lecture from Berger at the Helsinki IDF in 1997, delegations from three UK centres led by Sue Roberts attended the Düsseldorf centre and, having viewed the course, were impressed. They returned to the UK and, supported by one of the last Diabetes Project grants funded by Diabetes UK, they translated the curriculum into English (with the help of the Düsseldorf team) and conducted an RCT.[8] In all,169 participants either attended training immediately (immediate DAFNE) or acted as waiting list controls and participated in DAFNE training six months later. At 6 months, HbA_{1c} was significantly lower in immediate DAFNE patients (mean 8.4%) than in delayed DAFNE patients (9.4%). The impact of diabetes on dietary freedom measured by ADDQOL was significantly improved in immediate DAFNE patients compared with delayed DAFNE patients, as was the impact of diabetes on overall quality of life. General wellbeing and treatment satisfaction were also significantly improved. Improvements in quality of life were significant by one year. Thus, the trial confirmed that structured education could effectively improve biomedical outcomes and in addition led to marked benefits in quality of life and other psychological outcomes.

Subsequent studies have confirmed these results. In the REPOSE trial, DAFNE and multiple daily injections (MDI) were compared to DAFNE and pumps. The HbA_{1c} improved by 6mmmol/L in both groups at two years, with improved psychological outcomes and major reductions in severe hypoglycaemia.[9] A 12-month observational study conducted in 600 DAFNE graduates over 12 months reported falls in HbA_{1c} and severe hypoglycaemia, together with reductions in anxiety and depression.[10] Forty percent of those with impaired awareness of hypoglycaemia experienced improved recognition. Another study, exploring the effect of DAFNE training on acute admissions, has shown substantial reductions in ketoacidosis and severe hypoglycaemia, emphasizing the cost saving attributable to falls in diabetic emergencies after DAFNE training.[11] Finally, the DAFNE collaborative, unlike most other UK structured education programmes, conducts annual audits demonstrating a mean reduction in HbA_{1c} of 0.7mmol/mol with 50% of DAFNE graduates achieving an HbA_{1c} below 59 mmol/mol.[12]

Figure 1. Glycaemic control in the DAFNE trial



DAFNE Study Group, *BMJ* 2002 F=57.2, df=1, p<0.0001

These results and uncontrolled reports from other programmes in the UK confirm that 4–5 days of structured education, delivered to groups and teaching flexible intensive insulin therapy, result in clinically relevant falls in HbA_{1c} and rates of severe hypoglycaemia and improved awareness of hypoglycaemia. They also lead to marked improvements in quality of life, anxiety and depression and are highly cost-effective.

Current NICE guidance, recently updated, continues to emphasise both the benefit of structured education programmes and the importance of attendance.[13] The DAFNE trial and subsequent roll-out, together with provision of other similar courses, has changed practice in the UK. DAFNE is now delivered in around 75 centres throughout UK (roughly 50% of those responsible for care of adults with T1DM) and courses have been delivered to more than 50,000 individuals. Yet, despite these successes, DAFNE and perhaps other similar courses in the UK report levels of HbA_{1c} which fail to reach UK and international targets. In recent research we have focused on the limitations of current structured education and looked to others who have expertise in behavioural science, clinical psychology and technology to develop a more effective intervention.

Developing DAFNE further

With initial programme grant funding from NIHR, Lawton and Rankin conducted a series of qualitative research studies with DAFNE graduates. After a DAFNE course, participants reported markedly improved psychological outcomes, including quality of life, but they let glucose targets slip over time.[14] Participants found it particularly challenging to maintain glucose diaries or reflect on progress. Relatively few maintained glucose levels

sufficient to prevent complications, reporting barriers such as reduced confidence and poor mathematical skills. They requested individualised follow-up and refreshers. We also found inconsistent course delivery by educators. We had previously assumed that merely becoming competent in flexible intensive insulin therapy would be sufficient, but it has become apparent that those attending courses require additional support which needs to be incorporated into the programme. Our findings highlighted the importance of regular reviews with DAFNE-trained staff, educational top-ups and better ways of habituating key self-management behaviours.

We concluded that for most adults with T1D, the currently offered five days of skills training plus unstructured, ad-hoc post-course support though valuable was insufficient. The course improved short-term glucose levels and quality of life but failed to establish sustained self-management behaviours effectively enough to improve long-term glucose control and so prevent complications.

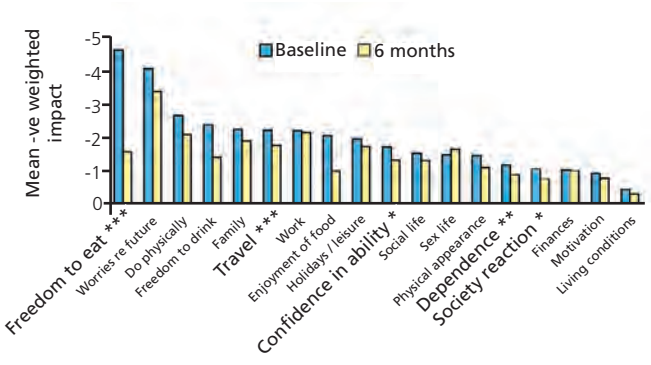
To enable individuals to self-manage diabetes successfully long-term we concluded that we needed to provide:

1) practical skills-based training, incorporating techniques that enable participants to acquire and sustain effective self-care behaviours
2) appropriate ongoing professional support as needed.

With additional NIHR programme grant funding we set out to develop a DAFNE course (which we termed DAFNEplus) that would result in both improved and sustained diabetes self-management behaviours together with better glucose control than is currently achieved without compromising quality of life.[15]

In phase 1 we worked with behavioural scientists who helped us to identify which behaviours we should target to ensure that the competencies which are taught during DAFNE would be sustained. Clinical psychologists in our group have adapted techniques from cognitive behavioural therapy to incorporate what is called cognitive restructuring. We also enlisted the help of bio-engineers who devised approaches which can automatically upload an electronic diary, including continuous glucose monitoring results, to facilitate communication between participants and educators. The professionals then use this information to provide individualized feedback and support, particularly for those who are struggling. We have also added online refreshers to enable DAFNE graduates to revisit educational topics.

Figure 2. Effect of structured skills training on quality of life



DAFNE Study Group, *BMJ* 2002. *p<0.05; **p<0.01; ***p<0.001

The expertise of our qualitative researchers and systematic reviewers was combined to help us identify how we should provide structured support following DAFNE in a meta-ethnographic review of qualitative research in this field. The Follow-Up Support for Effective type 1 Diabetes self-management (FUSED) study combined the results of these synthesised studies to identify elements of effective follow-up.[16] These included working collaboratively to build confidence, building the skills of self-management gradually and incorporating behaviour change science.

Having completed phase 1 with the successful delivery in three pilot centres of the 'DAFNEplus' intervention, we then embarked on a randomised controlled cluster trial in 13 centres comparing standard DAFNE with DAFNEplus. The aim was to recruit 600 individuals in total, with HbA_{1c} as the primary outcome and completion of 1-year follow up in October 2022.[17,18] We were recruiting to time and target until February 2020, when the COVID pandemic brought the trial to a complete halt since face-to-face education was not possible. We finally restarted the trial in August 2021. Our last course will be completed in November 2022, with final results available in late 2023. Unsurprisingly, it has not been possible to restart the trial in all of the original centres due to loss of staff and reduced capacity and the number of participants will fall below the

Table 1. Challenges in maintaining effective self-management following structured education

Challenges after attending course	Participants response to challenges	Recommendations for effective follow-up support
Complexity of life	Shift blood glucose targets	Modelling collaboration and empowerment
Disconnect between effort and reward	Stop or relax self-monitoring	Anticipating and addressing motivation
Lack of confidence in personal judgement	Over-rely on corrective doses	Facilitating social support
Insufficient professional support	Overtreat hypoglycaemia Simplify life by reverting to less flexible eating	• Incorporating new technology • Continuing to build knowledge and skills • Reviewing and ongoing advice on monitoring, treatment, diet, management of hypoglycaemia and exercise

Adapted from Ref 16

Key messages

- Structured education improves A1c, quality of life and is highly cost-effective.
- Acquiring self-management competencies in type 1 diabetes is key to successful self-management and requires structured training and probably ongoing structured support.
- Ensuring all adults with type 1 diabetes have participated in a structured education course should be a major priority in all specialist centres

original target of 600. But we will still have recruited enough people (more than 300) to have sufficient statistical power to identify a significant difference in HbA_{1c} between the two groups.

As we wait for the completion of this study, it is worth reflecting on our current failure to ensure that structured education is accepted as a fundamental component of treatment. The national diabetes audit makes depressing reading in this respect.[19] Although the proportion of adults with T1DM offered structured education has risen from 28% in 2012 to 50% in 2018, the proportion of those attending is unchanged at 13% and has actually fallen from 2015. These data may be an underestimate as this section of the audit is apparently often not completed. Nevertheless, it is surprising that despite the overwhelming evidence demonstrating benefit (particularly in quality of life and cost-effectiveness) and strong NICE guidance, many UK diabetes health professionals fail to convince their patients of its importance. It seems that the powerful criticisms of Berger and Mühlhauser still apply. There would appear to be a strong justification to insist on both better completion and a 'quality standard' of the proportion of adults completing as opposed to 'offered' structured education.

In conclusion, I would submit that 100 years after the first use of insulin, there is now an irrefutable case that structured education should underpin management in all individuals with T1DM. By integrating it with current and future technology, we can ensure that those with this most challenging of conditions are equipped with the tools to maintain glucose levels at levels which will minimise complications, as well as allowing them to lead better lives with diabetes until we eventually find a cure.

Conflict of interest None.

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Islet cell transplantation

YEE SEUN CHEAH

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Key words: Islet transplantation, stem cells, hypoglycaemia

A brief history of islet transplantation

Following the first administration of insulin in man 100 years ago, there has been significant progress in the development and manufacture of insulin, and technology to monitor blood glucose levels and to deliver insulin into the body, in an attempt to mimic normal physiology in people living with diabetes. Despite these therapeutic advances, there remains a significant burden for the individual in self-management of diabetes. Current research into childhood screening for T1DM before dysglycaemia develops,[1,2] and immunological strategies to protect insulin-secreting beta cells from autoimmune destruction,[3] have the potential to delay the need for exogenous insulin therapy. However, for those with established diabetes, beta cell replacement therapy brings the possibility of a life without needing insulin treatment. A synopsis of islet transplantation presented at the ABCD meeting to commemorate the centenary of the first administration of insulin into a human is provided here; for a more extensive review, readers are directed to excellent articles from colleagues in Edinburgh,[4] and in North America.[5]

The first report of allogeneic pancreatic fragment transplantation into the subcutaneous tissue of the abdominal wall of two men with T1DM described only "temporary diminution of the sugar excretion" in one of the recipients, with degeneration of the graft noted in both men, one dying three months later, the other three years later.[6] It was not until 1980, with the introduction of immunosuppression (azathioprine, cyclophosphamide, prednisolone and antilymphocyte globulin induction, with maintenance azathioprine and prednisolone), that the first successful transplantation of allogeneic pancreatic fragments into the spleen alongside renal transplantation took place in an 11-year-old girl, with eventual insulin independence.[7] The development of the glucocorticoid-free "Edmonton protocol" of immunosuppression in 2000 revolutionised islet transplantation.[8] In the original report, seven patients with T1DM and recurrent severe hypoglycaemia or uncontrolled diabetes received sirolimus (mTor inhibitor), tacrolimus (calcineurin inhibitor) and daclizumab (non-T-cell depleting anti-CD25 monoclonal antibody, which targets the T-cell IL-2 receptor) before islet preparations of >4,000 islet equivalents (IEQ)/kg recipient body weight were infused via a percutaneous transhepatic approach into the portal vein. More than 10,000 IEQ/kg recipient body weight were found to be required to reach insulin independence. Thus, a repeat procedure with another donor was often required, resulting in reduction in average blood glucose levels and glucose excursions.

Most islet transplant centres currently use modified protocols involving T-cell depleting antibody induction regimens (e.g. alemtuzumab, anti-CD52 monoclonal antibody or anti-thymocyte globulin, ATG) with etanercept (TNF-α inhibitor) for the first transplant, and basiliximab (non-T-cell depleting anti-CD25 monoclonal antibody) for second or subsequent transplants. Tacrolimus and mycophenylate mofetil (inosine-5′-monophosphate dehydrogenase inhibitor, inhibiting T and B cell proliferation) are used as maintenance immunosuppression.[9] The donor pancreas is prepared by initial perfusion of the pancreatic duct with collagenase before being mechanically and chemically digested in a Ricordi isolation chamber, followed by centrifugation. Unlike the original Edmonton protocol, the pancreas preparation is then placed in culture medium and incubated to permit quality control.[10] In the UK, the minimum release criteria are 250,000 IEQ, purity >50% and viability >70%.[11]

Islet transplantation in the UK and beyond

Between 2008 and 2009, the UK became the first country in the world to commission a national islet transplantation programme for "routine" treatment of severe hypoglycaemia. The UK Islet Transplant Consortium (UKITC) comprises three islet isolation centres (Edinburgh, Oxford and King's College Hospital, London) and seven islet transplant centres (Edinburgh, Oxford, King's, Manchester, Newcastle, Bristol and Royal Free Hospital, London). Current indications for islet transplantation are adults aged 18-65 years with T1DM and recurrent severe hypoglycaemia that has not responded to other therapies (islet transplant alone, ITA), or suboptimal control if they are being considered for simultaneous islet-kidney (SIK) transplantation, or have had a renal transplant and are currently on immunosuppressive therapy (islet after kidney, IAK).[11] Assessment for islet transplantation therefore typically includes ensuring standard care has been optimised, which may involve structured diabetes education, optimisation of blood glucose monitoring and insulin therapy, including the use of continuous glucose monitoring, insulin pump therapy and hybrid closed loop systems, and provision of psychological support.[12] If severe hypoglycaemia remains a problem despite consideration of these educational, technolog-

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ical and psychological interventions, islet transplantation may be considered if there are no contraindications (Table 1).

An example of the benefit of islet transplantation from our own centre at King's can be seen in Figure 1, in which a patient who had been living with T1DM for more than 20 years was experiencing six episodes of severe hypoglycaemia per year despite the use of sensor augment insulin pump therapy. Prior to islet transplantation, HbA_{1c} was 8.3% and sensor data showed widely variable glucose levels with frequent, asymptomatic hypoglycaemia. Six months after islet transplantation, HbA_{1c} had fallen to 6.4%, with greater time in target and no severe hypoglycaemia.

An initial report of 20 patients receiving islet transplantation (16 ITA, 4 IAK) in the UK showed that 80% of recipients maintained graft function, defined as a stimulated C-peptide >50 pmol/L, with a reduction in severe episodes of hypoglycaemia from 20 to 0.3 episodes per patient year including those with graft dysfunction, improvement in hypoglycaemia awareness and HbA_{1c} (from 8.0% to 6.2%) and a reduction in insulin dose of >60%, at 24 months.[13] A more recent report of 84 islet transplant recipients (34 receiving one infusion, 50 receiving two infusions) showed uninterrupted graft survival at 12 months in 68% of single transplant recipients and 94% of two transplant recipients.[14] Of these 70 recipients with uninterrupted graft function at 12 months, graft survival was present in 64% at six years post-transplantation. For those receiving two grafts, a shorter interval between transplantations was associated with greater insulin dose reduction at 12 months.

Table 1 Contraindications to islet transplantation.[11]

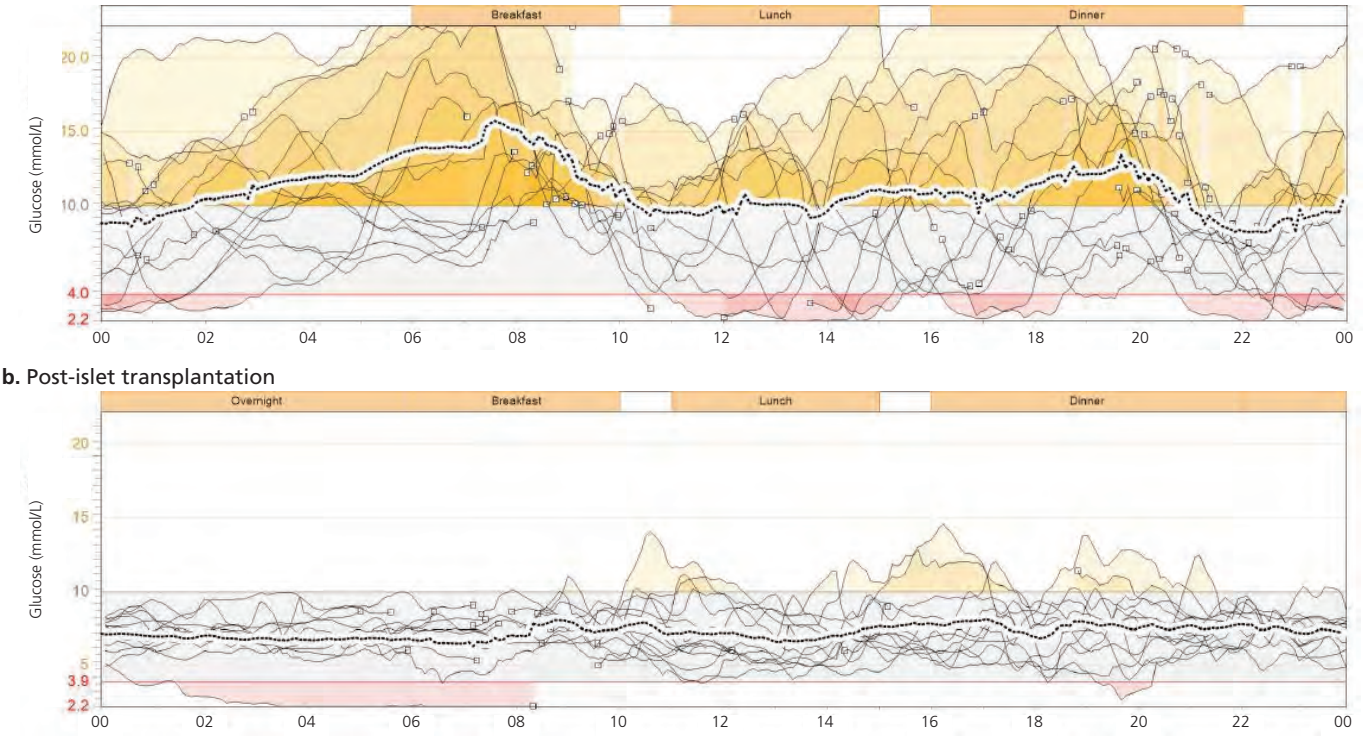
Absolute contraindications:

- Insulin requirements > 1 Unit/kg body weight/day
- Weight >85 kg
- GFR <60 mL/min/1.73m^2 (except in those being considered for SIK or IAK)
- Detectable fasting or postprandial blood C-peptide (>0.3 ng/mL) (100 pmol/L)
- Incurable malignancy
- Active sepsis
- Active peptic ulceration
- Major psychiatric history likely to result in non-concordance
- Inability to withstand immunosuppression
- Excessive cardiovascular risk

Relative contraindications:

- Substance abuse (including tobacco)
- HbA_{1c} >12% (107.7 mmol/mol)
- Body mass index (BMI) >28 kg/m^2
- Progressive, severe complications of diabetes
- Untreated coronary artery disease
- Unstable retinopathy
- Proteinuria >300 mg/day
- GFR 60-80 mL/min/1.73m^2
- Untreated hyperlipidaemia (LDL cholesterol >3.36 mmol/L)
- BP >160/100 mmHg despite maximal treatment
- Chronic infection (e.g. hepatitis B and C, Epstein-Barr virus)
- Liver changes (3x upper limit of normal enzymes, cholestasis, haemangioma)
- Calculated reaction frequency (anti-HLA antibodies) >20%
- Need for long-term oral steroid therapy

Figure 1. Continuous glucose monitoring data **a.** before and **b.** six months after islet transplantation in an individual with T1DM and severe hypoglycaemia.



The Clinical Islet Transplantation Consortium in North America has reported similar outcomes from eight centres participating in the CIT-07 single arm phase 3 clinical trial in adults with T1DM and impaired awareness of hypoglycaemia and recurrent severe episodes of hypoglycaemia.[15] Of the 48 recipients (22 receiving one infusion, 25 receiving two infusions, 1 receiving three infusions), 87.5% at year 1 and 71% at year 2 achieved the primary outcome of HbA_{1c} <7.0% and freedom from severe hypoglycaemia, with improvement in hypoglycaemia awareness. Insulin independence was achieved in 52% of recipients at 1 year and 42% at 2 years.

The Collaborative Islet Transplant Registry (CITR) currently collects data from 40 different transplantation centres in North America, Europe and Australia.[16] The latest registry report this year includes 1,108 ITA, 236 IAK, 49 SIK and 6 kidney after islet transplant recipients, with five years' post-transplantation outcome data. In the ITA recipients, approximately 50% achieved insulin independence one year post-transplant. The prevalence of insulin independence fell steadily each year to approximately 20% at five years. Factors positively associated with insulin independence were related to mass of transplanted islets (higher number of islet infusions, greater number of IEQs infused, donor weight >98 kg), recipient factors (female sex, age above 35 years, negative IA2 antibody, fewer than 43 units insulin/day and HbA_{1c} <6.5% pre-transplant) and immunosuppression (use of IL-2 receptor antagonists, TNFα inhibitor, mTor inhibitors and calcineurin inhibitors). The prevalence of graft function, defined as a C-peptide ≥0.3 ng/mL (100 pmol/L), was higher than that of insulin independence at approximately 80% at one year post-transplant, falling steadily each year to over 50% at five years. Factors associated with higher post-transplant C-peptide were similarly related to the mass of transplanted islets (greater number of islet infusions and the total number of IEQs infused), recipient factors (age 35 years or above, longer [>37 years] diabetes duration, lower diastolic blood pressure, HbA_{1c} and cholesterol levels pre-transplant, use of antihypertensive and lipid-lowering treatments pre-transplant), immunosuppression (TNFα and calcineurin inhibitors) and islets being cultured for ≥6 hours. Despite the progressive fall in insulin independence and C-peptide levels, the absence of severe hypoglycaemia remained high at around 90% during the five-year post-transplant period, with 50% of ITA recipients having both HbA_{1c} <7.0% and absence of severe hypoglycaemia. Higher fasting C-peptide levels (≥1ng/mL [330 pmol/L]) were associated with a higher likelihood of insulin independence, HbA_{1c} <7.0%, fasting blood glucose 3.3-7.8 mmol/L, absence of severe hypoglycaemia and combined HbA_{1c} <7.0% with absence of severe hypoglycaemia.

Future of islet transplantation

The UK islet transplantation programme aims to infuse a total of >10,000 IEQ/kg recipient body weight within 12 months of the first transplant. The CITR data show that the greater the mass of islets transplanted, the greater the likelihood of insulin independence and C-peptide positivity, and importantly the greater the absence of severe hypoglycaemia. The rate-limiting step in all forms of transplantation is the availability of suitable donor organs. Furthermore, good quality donor pancreases may be considered for whole organ transplantation before islet transplantation. The use of human embryonic stem cells (hESC) and induced pluripotent stem cells (iPSC) may pave a way to increase supply of islets for transplantation. Human clinical trials applying the use of hESC are currently in progress.

Vertex pharmaceuticals' phase 1/2 clinical trial is assessing the safety, tolerability and efficacy of VX-880, allogeneic stem cell-derived, fully differentiated insulin-producing islet cells. These islet cells are infused intraportally, similar to conventional islet transplantation,[17] with recipients receiving ATG at induction and tacrolimus and sirolimus maintenance immunosuppression. Data from two individuals with T1DM, impaired awareness of hypoglycaemia and recurrent severe hypoglycaemia, receiving half the target dose of VX-880, were presented in abstract form at the ADA and EASD this year.[18,19] One recipient was insulin-independent by day 241-270, with time in range increasing from 40.1% to 99% and a fall in HbA_{1c} from 8.6% to 5.2%. A second recipient had a 30% reduction in insulin by day 121-150, with time in range increasing from 35.9% to 51.9% and HbA_{1c} falling from 7.5% to 7.1%. No adverse events related to VX-880 occurred in either recipient.

ViaCyte Inc. have taken a different route in their phase 1/2 studies, placing pluripotent stem cell derived pancreatic endoderm progenitor cells in microencapsulation devices that are then implanted subcutaneously. VC-01 is a combination of these endoderm cells in immunoprotective devices such that immunosuppression is not required but transfer of nutrients and oxygen to the enclosed cells occurs. Data from a safety, tolerability and efficacy trial using subtherapeutic doses in 19 recipients with T1DM have been published in abstract form only.[20] Cell survival at explantation was demonstrated for as long as two years but was inconsistent due to foreign body response to the device, with insulin and glucagon detectable on immunohistochemical staining but no reports of insulin secretion. No evidence of immune rejection or sensitisation was found. The study was terminated due to insufficient engraftment.[21] A 26-week study to assess safety and engraftment, and efficacy by means of C-peptide response to a mixed meal, is reported to be ongoing.[22]

VC-02 utilises an encapsulation device that allows direct vascularisation of the endoderm cells, therefore requiring immunosuppression. In a safety, tolerability and efficacy study, individuals with T1DM and hypoglycaemia unawareness received up to four larger dose-finding devices (9cm x 3cm x 1mm) containing 90-120 million cells and up to 10 smaller devices (1.5 cm x 1 cm x 1 mm) containing 6-8 million cells for histological assessment, with ATG induction and tacrolimus and mycophenylate mofetil immunosuppression.[23] Improvements in HbA_{1c}, time in range and hypoglycaemia awareness were observed over the 1-year follow-up period. Total daily insulin requirements fell but insulin independence was not achieved. C-peptide increased in response to a mixed meal, with no difference in response at 26 and 52 weeks. The explanted devices had more glucagon- than insulin-staining cells, with the latter appearing to have a mature beta cell phenotype. However, two out of 15 recipients with-

Key messages

- Islet transplantation is an established treatment in the UK for adults with refractory type 1 diabetes and severe hypoglycaemia
- Whilst 50% of islet transplant recipients achieve insulin independence at 1 year, falling to 20% at five years, over 90% of recipients are free from severe hypoglycaemia.
- Research in the application of human stem cells in transplantation has the potential to address the limited supply of donor organs for islet transplantation.

drew during the first year due to complications from the immunosuppression, and five were withdrawn after nine months due to unfavourable risk-benefit assessment, based on undetectable C-peptide, histology and clinical state of diabetes. In an accompanying report of 17 recipients (six of whom were included in the previous report), six were deemed "responders" with positive C-peptide responses to a mixed meal.[24] Greater numbers of insulin-staining cells were detected in the explants of responders compared to non-responders. Insulin content and secretion per beta cell increased over time. Devices were infiltrated by host-derived fibroblasts, with graft cells comprising 40% of the total cell population in responders and 26% in non-responders.

Lastly, working with CRISPR Therapeutics, ViaCyte Inc. have announced the dosage of the first patient in a Phase 1 clinical trial of VCTX210, which comprises similar devices used in VC-02 to encapsulate gene-edited, stem cell-derived pancreatic endoderm cells that can evade the immune system.[25]

Conclusion

Advances in diabetes technology have produced hybrid closed-loop systems that demonstrate significant improvements in HbA_{1c}, time in range and hypoglycaemia. However, these systems still require a high level of user involvement, and commercially available fully closed-loop "artificial pancreases" are eagerly anticipated. Islet transplantation is an established, safe and effective NHS treatment for recurrent, severe hypoglycaemia in T1DM, offering the individual the opportunity to lead a life closer to that of someone without diabetes. Limitations of islet transplantation include the limited supply of donated islets and the low level of insulin independence at five years post-transplantation. Developments in human stem cell transplantation and encapsulation may help address these limitations, with the potential to avoid the need for immunosuppression.

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The British Journal of Diabetes (and Vascular Disease): a brief history

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Key words: *British Journal of Diabetes and Vascular Disease, British Journal of Diabetes*, open access

The beginnings

The British Journal of Diabetes (BJD) began life as the *British Journal of Diabetes and Vascular Disease (BJDVD)*. It was conceived by Michael and Nina Gibbs (directors of Sherborne Gibbs Ltd [SGL] and MediNews-Cardiology), and by Henry Purcell who was editor of the *British Journal of Cardiology (BJC)*, the publishing model for *BJDVD*. A meeting of the initial editors and several members of the editorial team was convened to determine the scope and mission of the journal (Figure 1). MediNews-Diabetes was set up in April 2001 to publish *BJDVD*, with administrative support from SGL and their excellent production team headed by Helen McDonnell. The *BJDVD* logo of interlocking rings was designed to illustrate a broad coverage of diabetes, vascular disease and their interrelationships beyond glycaemic control. The journal launched in September 2001 at the European Association for the Study of Diabetes (EASD) conference in Glasgow with Clifford Bailey, Ian Campbell and Henry Purcell as editors, Caroline Day as associate editor (who did most of the work), Harry Keen as consultant editor and Michael Gibbs as publishing director.[1]

The core editorial team met regularly to plan content, invite. reviews, encourage original submissions and write commentaries and conference reports (Figure 2). The title and scope of the journal has proved attractive to a readership of specialists in diabetes, endocrinology, cardiology and vascular medicine as well as health professionals in primary care (Table 1). During the first full year (2002) there were six issues totalling 480 pages, comprising 90 papers: nine editorials, 46 reviews, seven original research papers, 10 'achieving best practice', six 'landmark studies', six short case reports, 11 'current topics' plus round-ups of major international meetings and short news items (use of the internet was still in its infancy).

The journal was peer-reviewed, free to publish and free to read (an early open-access model). This was made possible by funding from advertisements, supplements, reprints and translations. A tight production schedule was adopted to ensure topicality and an average reviewing time to decision was typically less than one month, making the journal appealing to authors. Several themed issues provided important compendia of state-of-the-art articles by well-known authorities (Table 2). Of particular historical value were the issues to coincide with the Golden Jubilee (2002) and Diamond Jubilee (2012) of HRH Queen Elizabeth II. Volume 2 covered the

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Figure 1. *British Journal of Diabetes and Vascular Disease*; front cover of first issue 2001, the mission and the logo of interlocking rings.

Figure 2. *British Journal of Diabetes and Vascular Disease* initial core editorial team 2002: Back row left to right: Caroline Day, Mike Kirby, Michael Gibbs, Ian Campbell, Peter Andrews, Peter Grant, Michael Feher. Front row left to right: Harry Howlett, John Petrie, Henry Purcell, John Scarpello, Cliff Bailey. Inset, Harry Keen.

Table 1 Subscribers profession - 2010

General Practitioners	21%
Diabetologists (inc SpR)	35%
Cardiologists	21%
Geriatricians	2%
Pharmacists	2%
Diabetes nurses (DSN)	16%
Hospital nurses	2%

Table 2 Themed issues with guest editors

Issue	Editor	Theme
2002 vol 2 pt 2	Peter Andrews	Nephrology
vol 2 pt 4	Mike Kirby	Sexual dysfunction
vol 2 pt 5	Peter Grant	Cardiovascular disease
2003 vol 3 pt 2	John Scarpello	Neuropathy
vol 3 pt 4	John Petrie	Hypertension
2004 vol 4 pt 1	Johnathan Levy	Insulin
2005 vol 5 pt 1	Alan Sinclair	Diabetes in older people
2007 vol 7 parts of pt 3 & pt 4	Glen Matfin	Drug development and clinical trials
2009 vol 9 pt 1	Tahir Mahmood	Obesity and reproduction
vol 9 pt 5	Tahir Mahmood	Diabetes and reproduction
vol 9 pt 6	Parth Narendran	Type 1 diabetes
2011 vol 11 pt 4*	Peter Schwarz	Diabetes prevention

*BJDVD website hosted the IMAGE - Curriculum for the training of prevention managers. IMAGE (Development and Implementation of a European Guideline and Training Standards for Diabetes Prevention). This European Union funded project (2003–2008) produced the curriculum.

Table 3 International readership - 2009

Europe	46.6%
N. America	29.7%
Africa	11.0%
UK	6.6%
Middle East	2.9%
Asia	2.2%

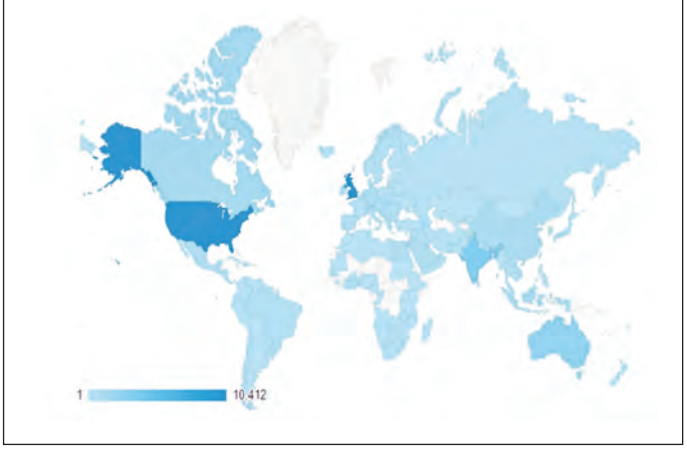
changing face of diabetes healthcare from 1952 to 2002, and volume 12 provided updates of the intervening decade as well as discussion of areas that had seen remarkable change over the previous 60 years.[2,3]

Extended reach

Increasing numbers of submissions of original and detailed research manuscripts of a more academic nature prompted the birth of a sister journal in 2004 – *Diabetes and Vascular Disease Research (DVDRes)* – with Peter Grant as editor-in-chief. Interest beyond the UK also gave rise to a South Africa edition (2005) and a Middle East edition (2006), both of which included additional local content.

In 2008 *BJDVD* was acquired by Sage Publications, but the financial austerity squeeze in the following years reduced income from conventional revenue streams such as advertising. This in turn forced a reduction in the length of the journal to around 52 pages per issues (to curb printing and postage costs). However, *BJDVD* continued to enjoy an international on-line readership (Table 3), and the website consistently attracted visitors from more than 180 countries (Figure 3). Web traffic grew quickly and there were more than 145,000 article downloads in 2011.

Figure 3. Visitors to the *British Journal of Diabetes and Vascular Disease* website between Jan-June 2013.



Some gains and losses

In December 2010 our cardiology editor Henry Purcell stepped down in order to devote more time to his editorship of *BJC*, and Christoph Schindler (Dresden and Hanover) joined (2011-13) to support the journal's cardiological content and growing European interests. By now the editorial team had diversified to include overseas members and additional areas of expertise, but very sadly death took our statistics expert Carole Cull (2007), consultant editor Harry Keen (2013) and Nina Gibbs (2011).

Change of title

In January 2013 the publication format of *BJDVD* changed to Sage Publications' house style and later that year the Association of British Clinical Diabetologists (ABCD) was in search of its own journal and acquired the publishing rights. This acquisition was organised by Chris Walton, Bob Ryder and Rob Gregory, who seized the opportunity to align the journal to the Association. Sage Publications retained the back catalogue of *BJDVD* (2001-2013) and this is available on their website https://journals.sagepub.com/home/dvd. In 2014 the journal adopted the ABCD branding, with its current blue front cover. At this time Ian Campbell stepped across to consultant editor, and editors Cliff Bailey and Caroline Day continued for a further year before becoming consultant editors.[4] The new editors were Paul Grant (2014-16) and Mike Gwilt (2015) before Parth Narendran took over as acting editor-in-chief in April 2016, which was the year that *BJDVD* abbreviated its title to the *British Journal of Diabetes (BJD)*.

Figure 4. *British Journal of Diabetes*: current front cover design.

In 2017 the present editor-in-chief Marie-France Kong and deputy editor Chris Walton took up their positions to consolidate the revised focus of the journal. They are supported by a number of associate editors, a news editor (Umesh Dashora), and an enlarged editorial team with administrative support from Red Hot Irons and production back in the capable hands of Helen McDonnell (figure 4). The journal, which is now published twice yearly, remains free to ABCD members, and the latest information for readers and authors is at https://bjd-abcd.com/index.php/bjd. Submissions are always welcome.

Key messages

- BJDVD
  - Peer reviewed journal, free to publish, free to read
  - 2001 – launched at EASD 37th annual meeting in Glasgow
  - 2008 – published by Sage (now hosts vol 1-13 online)
  - 2014 – became an ABCD journal
  - 2016 – renamed BJD

Conflict of interest None.
Funding None.

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Type 2 diabetes: the problem and the solution

ROY TAYLOR

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Key words: T2DM, aetiology, pathophysiology, pancreas fat, personal fat threshold, remission

Introduction

The 100 years since insulin was discovered have seen major progress in understanding the aetiology of type 1 diabetes. In contrast, type 2 diabetes (T2DM) remained mysterious until recently. Clinical studies and clinical experience had resulted in widespread acceptance of the apparently lifelong, progressive nature of the condition. Discoveries over the last 16 years have permitted these rationalisations to be discarded and the aetiology of T2DM is not now in doubt. It is a condition of excess fat inside the liver and pancreas which can be countered by weight loss. A turbulent 16 years of study has led directly to a therapeutically useful understanding of the condition. Importantly, this can be tailored to the individual.

Defining the problem

Up to the year 2006, T2DM research in Newcastle had been evaluating the problem of liver insulin resistance and fat in the liver, using the new tool of magnetic resonance spectroscopy. It seemed that the liver insulin resistance typical of T2DM was entirely due to accumulation of fat in the liver. If this could be resolved by weight loss then there was at least a partial solution, given that the fasting hyperglycaemia of diabetes is due to excess production of glucose by the liver secondary to insulin resistance.

But what about the other long-recognised contributor to T2DM, namely decreased post-prandial response to a meal? In 1994 Roger Unger had defined the response of beta cells to a small excess of fat.[1] He had the brilliant idea of taking the intact islets from young rodents who would develop T2DM if overfed and showed that pancreatic islets from young rodents who were genetically similar apart from their susceptibility to develop T2DM were completely resistant to fat exposure. This classical physiology experiment defines the reason why some people develop T2DM and others, even if very overweight, do not develop the condition. The ultimate susceptibility to T2DM is genetically determined within the beta cell. In fact, 72% of people with a BMI over 45 do not develop T2DM.[2]

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Working out how these twin observations on liver and pancreas could fit together took some time, but eventually the Twin Cycle Hypothesis emerged after much scribbling and filling sheets of paper with possible pathways and relationships.[3] There was a potentially elegant solution, summarised in Box 1: T2DM might be caused by two vicious cycles interacting, one in liver and one in pancreas. This hypothesis could be tested.

Box 1 The Twin Cycle Hypothesis of Aetiology of T2DM

1. Gradual build-up of fat in the liver results from overprovision of calories over a long period, especially in those people who have a tendency to muscle insulin resistance. Such people store almost no mealtime carbohydrate in skeletal muscle, unlike people with normal muscle insulin sensitivity who store around one third of meal carbohydrate in muscle following a meal so it is converted to fat for storage
2. Over many years the liver becomes less and less able to respond to insulin, so glucose production is unrestrained, causing elevated fasting plasma glucose levels
3. The fatty liver also exports more triglyceride than normal. If this cannot be stored in subcutaneous adipose tissue – a metabolically safe storage depot – then it has to be taken up in ectopic sites, including the pancreas
4. The provision of excess fat to the islets decreases ability to produce insulin rapidly after meals in susceptible people
5. The greater post-prandial plasma glucose rise which results further increases rates of lipogenesis in the liver. Consequently, the Twin Cycles are self-reinforcing

Testing the Twin Cycle Hypothesis

The Counterpoint study (Counteracting the Pancreatic inhibitiOn of InsuliN secretion by Triglyceride) required a method of reliably producing the 15 kg weight loss calculated to be required to remove the fat from liver and pancreas. Rapid weight loss was necessary for the pressing reason that the Diabetes UK grant for the study was for two years in total. An 800-kilocalorie diet could be nutritionally complete, free from the day-to-day burden of making decisions, by use of one packet per meal of a liquid formula diet plus non-starchy vegetables only. This approach, which became known as the "Newcastle diet", was originally a tool developed purely to test the hypothesis.

The results were dramatic.[4] Within seven days of starting the diet and stopping metformin plasma glucose returned to normal (Figure 1), and over eight weeks weight decreased by an average of 15.3 kg. All the predications of the Twin Cycle Hypothesis were confirmed by using magnetic resonance techniques developed specifically for the purpose. The level of liver fat was shockingly high in T2DM and this fell precipitously, accompanied by the return to normal of the initially raised liver glucose production rates.

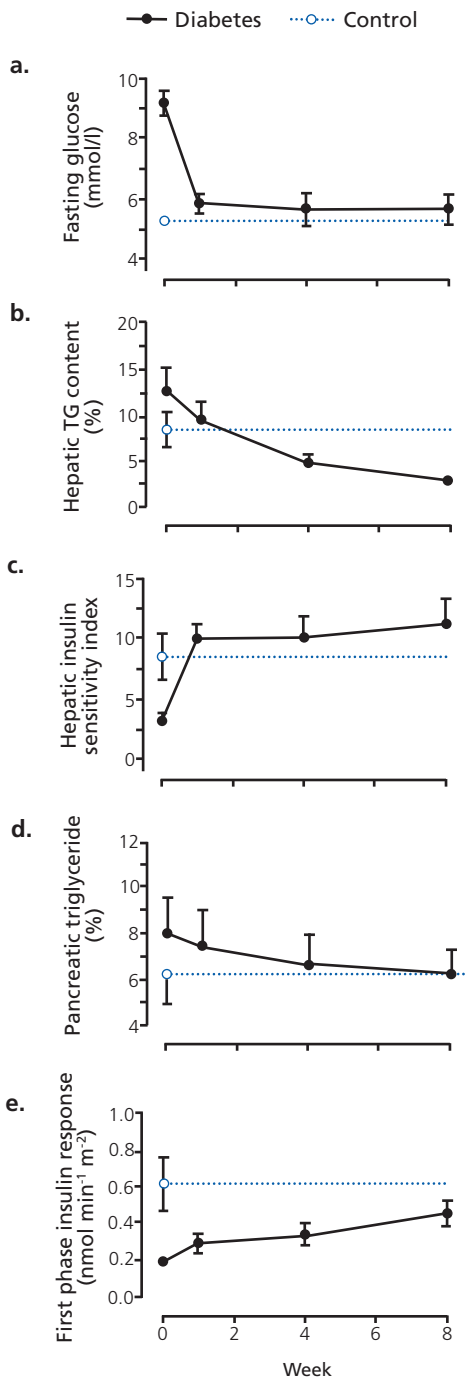

Figure 1. Change in fasting plasma glucose on commencing an 800kcal/day diet and stopping metformin. The change within seven days was shown to be due to a fall in liver fat content, the return of normal hepatic insulin sensitivity and normalisation of hepatic glucose production. A slower decrease in pancreas fat content was paralleled by a slow increase in beta cell function. Data are from the Counterpoint study, which initiated the worldwide interest in diet-induced weight loss for remission of T2DM.[4]

Plasma triglyceride levels decreased to normal and gradually the pancreas fat content decreased. Most excitingly, both the first phase and the maximal insulin secretion rates improved.

The Counterpoint study was first presented to a scientific meeting at the ABCD Newcastle meeting in 2010. The 2011 publication attracted much interest but great scepticism among experts. Doctors 'knew' that T2DM was for life, and scientists were trapped in a belief system that was slow to change. Not so people with the condition! A tsunami of emails were received requesting how-to-do-it details, and the Newcastle University website on diabetes reversal was created (https://go.ncl.ac.uk/diabetes-reversal). A descriptive analysis of the subsequent wave of emails reported that around half the individuals with T2DM followed the advice that ordinary food (but strictly around 800 kilocalories/day) could be used and half used liquid formula diets.[5] The groups were equally successful in achieving return to a fasting glucose of <6.1%. Importantly, the effect of duration of T2DM upon pancreas recovery became clear. Reversal rates according to diabetes duration were: short (<4 years) = 73%, medium (4–8 years) = 56%, and long (>8 years) = 43%.

The beta cell question

There was great antipathy to the notion that fat could cause the decline in beta cell function, particularly among beta cell experts. This may have been a function of the widespread use of high glucose levels rather than fat to induce and study beta cell stress *in vitro*. The major argument raised was that weight loss might cause decrease in intra-pancreatic fat as an unrelated phenomenon, and it was really the starvation-induced decrease in plasma glucose which brought about beta cell recovery.

To test this, groups of people with or without diabetes but achieving equal weight loss were studied. We showed that the fall in pancreas fat occurred only in people with T2DM. There was no acute fall in fat and no change in insulin secretion in people without diabetes. There is an excess of relatively rapidly mobilizable fat in the pancreas of people with T2DM only. Work by Ann Clarke and Domenico Accili showed that the metabolic stress of excess energy supply *in vitro* produced loss of specialised function of beta cells (de-differentiation) and that removal of excess fat allowed re-differentiation with restored function.[6,7] The mechanism underlying central problem of T2DM could now be understood. Beta cell death or apoptosis was not relevant. Together with the Twin Cycle Hypothesis it explained why the incidence of T2DM varied with the nutritional state of populations.

Refining the solution

Two major clinical questions arose from the Counterpoint study. First, would it be possible for T2DM of any duration to be reversed to normal? Second, was the improvement in glucose homeostasis long term or merely a starvation effect that would wane? Our second study, Counterbalance, set out to examine these two questions.

The previous email reports from people with T2DM were confirmed: T2DM was most reversible if the duration of diabetes

was short.[8] In those less than four years from diagnosis, 85% returned to normal compared with 50% of those with greater than eight year duration. These observations have since been expanded by personal reports. It is clear that some individuals retain the ability to return completely to normal despite two decades or more of T2DM.

In the Counterbalance study a six-month period of weight maintenance followed the weight loss phase. There was no weight gain despite only monthly follow-up, and glucose control remained unchanged. The dramatic improvement in beta cell function was fully retained. This accords with the freedom from diabetes during follow-up periods of many years observed in personal patients. Notions of inevitable beta cell decline are unfounded, provided that beta cells remain relieved of the metabolic stress of excess fat.

Reversal and remission

The term 'reversal' was used in the Counterpoint study in respect of reversing the direction of the twin cycles originally hypothesised. It neatly describes the reversal of the pathophysiological mechanisms underlying the return to non-diabetic glucose homeostasis and is the necessary first step for a person with T2DM who is seeking to return to health. It is a very useful clinical concept. However, following the initial studies, attention needed to expand to the clinical course over time, and this is a separate matter. Remission is the appropriate term for this; it has recently been defined by international consensus.[9]

The tool developed to test the Twin Cycle Hypothesis was more successful in routine cinical use than had been anticipated. But whether or not it was simple enough to applied in primary care had to be tested. A study of remission was required.

Remission of T2DM in primary care

Could rapid weight loss for remission be used by primary care nurses with appropriate training? They provide the bulk of clinical care for people with T2DM. A larger study was required to test the concept in a randomised clinical trial. Hence, DiRECT (Diabetes Remission Clinical Trial) was set up as a joint project between Newcastle and Glasgow Universities.[10,11] It was funded as a special project by Diabetes UK. The question was simple, as was the answer - yes.

Remission of T2DM, defined as HbA_{1c} <48mmol/mol for at least six months off all hypoglycaemic drugs, was achieved in 46% of people in the first 12 months. Even at 24 months, 36% were still in remission, off all hypoglycaemic agents despite gradual weight increase. The improvement in overall health and day-to-day wellbeing was documented,[12] as was the cost-effectiveness.[13]

The pressing clinical question now concerns how to avoid future weight regain in the most cost-effective manner. The obvious solution is to change the food environment in simple yet effective ways, such as limiting the amount of sugar added to fast foods and ready meals and preventing deliberate formulation of foods to encourage excess consumption. Governments remain reluctant to act on this, and the question in hand concerns how intensive the follow-up has to be in order to avoid longer-term weight regain.

Interpreting HbA_{1c}

The 'prediabetes' zone of HbA_{1c} is associated with major cardiovascular risks but these are almost entirely a function of the adverse plasma lipid profile. That is not only spinning the twin cycles ever more rapidly but also directly related to atheroma. The slightly raised plasma glucose is not directly causal but rather is an indicator of the very real associated risks.

When the lipid profile is completely normalised, as happens with substantial weight loss, the 10-year risk of cardiovascular events returns completely to normal even if plasma glucose is slightly raised.[14,15] This point is really important to explain to people who used to have diabetes. They do not have pre-diabetes but rather what might be termed post-diabetes. Their health has indeed been restored. The writing is still on the wall – weight regain will certainly result in metabolic deterioration. Annual follow-up at the very least is required.

Understanding the individual

In the course of all our studies it became clear that weight loss is required to achieve remission irrespective of the initial BMI. In the UK at present, around 50% of people have a BMI under 30kg/m^2 at the time of diagnosis of T2DM; around 1 in 8 have a normal BMI. How could this be incorporated into clinical thinking? From the Counterpoint, Counterbalance and DiRECT trials it was clear that decreasing BMI from 45 to 42kg/m^2 produced the same metabolic affects as decreasing it from, say, 27 to 24kg/m^2. It appeared that too much fat inside the organs, irrespective of BMI, could be responsible for T2DM. The UKPDS dataset was ideal for the purpose of examining the concept. Together with Professor Rury Holman a hypothesis paper was published outlining the 'Personal Fat Hypothesis'.[16] This postulated that once subcutaneous fat capacity for an individual had been exceeded then fat would build up in ectopic sites. Thus, even people regarded as having a normal BMI by population descriptors might accumulate fat in ectopic sites if their safe metabolic depot under the skin was inadequate. Weight loss within the normal range would be expected to bring about remission. The ReTUNE study has been conducted to document the response of people with BMI 21-27kg/m^2 to stepwise weight loss. Can a personal fat threshold be defined? Preliminary data suggest that once again the answer may be 'yes', and the final results will be available soon.

Although support from a professional is optimal for any individual wishing to achieve remission by dietary weight loss, many people have opted to go solo. The book *Life Without Diabetes* describes how this can be achieved, offering a choice of practical methods (all profits go to Diabetes UK, which has provided the research funding for these studies of aetiology since 2008).[17] "How does the weight loss work, doctor?" is a common question, and this book provides the answer for people with T2DM and for doctors.

Key messages

- T2DM is a condition of simple aetiology, caused by accumulation of more fat then can be tolerated inside the liver and pancreas
- Weight loss of 10-15% will decrease intra-organ fat, restore normal function and non-diabetic glucose control in most people with T2DM duration of up to six years, and in some people with longer duration of diabetes
- A personal fat threshold determines the weight at which an individual develops T2DM, irrespective of BMI

Summary

The problem of what causes T2DM is resolved and the simplicity of the aetiology is clear. If a person exceeds their personal fat threshold, liver fat will increase with increased fat export to the rest of the body. That sets in motion all the problems of ectopic fat and increases cardiovascular risk. Only in those people with beta cells susceptible to fat excess does T2DM develop, and the Twin Cycle Hypothesis explains why. There is a simple bottom line: if a person has T2DM, they have become too heavy for their own body – nothing to do with the population science concept of obesity. The solution is at hand.

Conflict of interest Member of UK government (SACN) working group on low carbohydrate diets and member of advisory board for the NHSE type 2 diabetes remission programme. All opinions in this article are personal. Author of book: *Life without diabetes*. Lecture fees from Novartis, Lilly and Janssen. Research funding from Diabetes UK.

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Fat – pharmacological therapies

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Br J Diabetes 2022;**22**(Supp1):S59-S61

Key words: Liraglutide (Saxenda®), Semaglutide (Wegovy®), Tirzepatide (Mounjeo®)

It was a pleasure to be asked to speak at the ABCD celebration of the discovery of insulin and its subsequent rapid adoption into clinical practice, truly a major advance in medicine. My remit was to discuss pharmacological therapies for weight reduction. Given the time constraints, I chose to focus on the glucose-lowering therapies which are now being licensed for the management of obesity, how they are being positioned in guidelines and future developments, including ongoing trials.

The introduction of glucagon-like peptide 1 receptor agonists (GLP-1RAs) into the UK in 2007, followed by sodium-glucose co-transporter-2 (SGLT2) inhibitors in 2012, finally gave clinicians glucose-lowering therapies that had the additional benefit of weight reduction. The initial phase 3 trials suggested similar mean weight loss for both drug classes of 2-3 kilograms (kg) over six months. The mode of weight loss for the SGLT2 inhibitors was thought to be calorific loss due to induced glucosuria and so their potential for weight reduction in people with normal glucose tolerance was limited. A recent systematic review and meta-analysis in non-diabetic adults with overweight or obesity has confirmed modest changes in body weight (-1.42kg, confidence intervals [CI] -1.70 to -1.14) and body mass index (BMI) -0.47 kg/m^2 (CI -0.63 to -0.31). I am not aware of any plans for SGLT2 inhibitors to be marketed for weight loss.[1]

In contrast, the impact of GLP-1RAs on weight is not dependent on hyperglycaemia. At a higher dose than that licensed for glucose lowering, subcutaneous liraglutide 3mg OD was found to lower food intake by reducing hunger and increasing satiety, predominantly through effects on the central nervous system rather than slowing gastric emptying.[2] This led to the SCALE phase 3 clinical trial programme in people with obesity/overweight, either alone or with co-morbidities of pre-diabetes, diabetes or sleep apnoea.[3-5] In all groups studied, liraglutide produced statistically superior weight loss compared to placebo, with 46.3–63.2% of trial recruits achieving a weight loss >5%, which is the Food and Drug Administration (FDA) minimum requirement for an anti-obesity licence. Between 23.4% and 33.1% of participants lost more than 10% of their baseline weight.[6] The 3mg dose of liraglutide was generally well tolerated, with the anticipated adverse gastrointestinal effects of nausea, vomiting, diarrhoea and constipation, and was marketed as Saxenda® in 2015.

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Semaglutide

When the once-weekly GLP-1RA, semaglutide, was being assessed in the SUSTAIN phase 3 trial programme, it became clear that this agent had the potential for greater weight loss than liraglutide.[7] As a result, the STEP programme of clinical trials was initiated in people with overweight or obesity, using high-dose (2.4mg) semaglutide, given by subcutaneous weekly injection.[8] Each of the STEP 1-4 trials was placebo- controlled and lasted for 68 weeks; the mean change in body weight from baseline was -9.6% to 17.4%, the lowest reduction being seen in those people with T2DM, as is typically the case.[9-12] In the STEP 1, 3 and 4 studies of people without diabetes, between 50.5% and 63.7% of trial participants achieved >15% weight loss compared with 4.9-13.2% of participants on placebo. The superiority of semaglutide 2.4mg QW over daily Saxenda® was confirmed by the head-to-head STEP 8 trial in people with overweight or obesity without T2DM, treated for 68 weeks.[13] The mean weight reductions were 15.4% versus 6.4%, statistically favouring semaglutide 2.4mg QW, which is now licenced as Wegovy®. The National Institute for Health and Care Excellence (NICE) recommended Wegovy® for 'adults with at least one weight-related condition and a BMI of at least 35 kg/m^2' on 8th February 2022, although it has not yet been launched in the UK (currently anticipated in 2023).[14]

The oral version of semaglutide (Rybelsus®) was launched as a daily glucose- lowering therapy in 2020 and is currently being assessed in the OASIS 1 trial of people who are overweight or living with obesity.[15] This is a placebo-controlled trial of a 50mg dose (compared with the maximum glucose-lowering dose of 14mg OD) in 660 participants, and is expected to complete in May 2023. Other activities in the GLP-1RA space include: the REDEFINE 2 study of CagriSema, a combination of subcutaneous cagrilinitide (an amylin analogue) and subcutaneous semaglutide (both 2.4 mg QW) in people who have T2DM and a body weight above the healthy range, expected to start in 2022;[16] and the unexpected development of an oral small molecule GLP-1RA, danuglipron.[17]

Dual agonists

The most recently developed class of glucose-lowering therapies is the GLP-1/ glucose-dependent insulinotropic polypeptide (GIP)

Table 1 GLP-1 co-agonists in development (phase 1 and beyond)

Drug	Administration	Status	Therapeutic areas
GLP-1/Glucagon Dual Agonists			
Pemvidutide (ALT-801)	sc weekly	phase 1b, 2	NASH, obesity
Cotadutide	sc daily	phase 2b	NASH, T2D w CKD
BI456906	sc weekly	phase 2	T2D, obesity, NASH
Mazdutide (LY3305677)	sc weekly	phase 2	T2D, obesity
Efinopegdutide	sc weekly	phase 2	NASH
OPK8803	sc weekly	completed phase 2/2b	T2D, obesity
DD01	sc weekly	phase 1	T2D w NAFLD
PB-718	sc weekly	phase 1	NAFLD, obesity

Key messages

- Glucose lowering therapies are now being re-purposed as weight loss therapies for people who do not have diabetes
- The weight loss achieved by modern therapies is phenomenal and side-effect profiles are tolerated
- Evidence that weight loss achieved with pharmaco therapy equates to cardiovascular and total mortality benefits is awaited but should emerge in the near future

dual agonists, the first of which was approved in Europe in 2022. Tirzepatide is a 39 amino acid peptide which binds to both the GLP-1 and GIP receptors and *in vitro* has greater potency for GIP. It is conjugated to a 20-carbon fatty diacid moiety which allows for once-weekly subcutaneous dosing.[18] It has been assessed in a large (>27,000 participants) clinical trial programme examining both glucose lowering (SURPASS studies) and weight management (SURMOUNT 1-4). The SURPASS programme has demonstrated impressive glucose lowering across the T2DM spectrum from monotherapy to insulin add-on, with 86-92% of study recruits achieving an HbA_{1c} ≤48mmol/mol on the highest dose (15mg QW).[19] This was superior to active treatment with both insulin degludec and subcutaneous semaglutide 1mg QW and, as a result, the European Medicines Agency (EMA) granted approval in September 2022. Weight reduction, a secondary endpoint in the SURPASS studies of people with T2DM, was equally impressive, with 27-43% of those on the highest dose achieving ≥15% weight loss.

For reasons that are unclear, people recruited into the SURMOUNT studies who did not have T2DM fared even better. In the SURMOUNT-1 trial, the mean percentage weight reduction from baseline to 72 weeks in the tirzepatide 15mg QW arm was 20.9%, compared with 3.1% for placebo.[20] This reflected 56.7% of subjects in this arm achieving a weight reduction of ≥20% and one third (36.2%) losing ≥25% of baseline weight. This led commentators to state that the impact of this weekly drug was equivalent to that of bariatric surgery and the FDA to grant fast-track designation, which will probably lead to an obesity licence in 2023. The dual agonist pipeline is also a very active one, with GLP-1/Glucagon agonism a major therapeutic target (see table 1).

At this point, it may be appropriate to question the widely held view that weight loss will inevitably reduce major cardiovascular (CV) events. This consensus was challenged in May 2022 by Park and colleagues, who reported on a longitudinal follow-up of a nationwide cohort of more than 1.5 million people in South Korea.[21] They found that both weight gain and weight loss of >5% within two years were associated with an increase in major CV outcomes in people with T2DM. This was followed by publication of the 21-year median follow-up of people in the Diabetes Prevention Programme (DPP) and Diabetes Prevention Programme Outcomes Study (DPPOS); this reported that there was no impact of lifestyle modification (or metformin use) on major CV events.[22] Fortunately, the current vogue for cardiovascular studies (CVOTs) in T2DM has extended into the obesity field and so this question should be definitively addressed. The SELECT study is examining the impact of subcutaneous semaglutide 2.4mg QW versus placebo in people with overweight or obesity but not T2DM (HbA_{1c} <48mmol/mol).[23] The trial cohort is large (17,500 individuals) and they all have established CV disease (prior myocardial infarction [MI] or stroke ≥60 days before inclusion) or peripheral vascular disease. The primary endpoint is time to the first occurrence of the composite endpoint of CV death, non-fatal MI or non-fatal stroke (the standard 3-point MACE used in diabetes CVOTs) and the results are expected by 2023.

Finally, back to diabetes: how do these data impact on diabetes guidelines? Judging by the latest iteration of the ADA/EASD consensus report in 2022, the answer is quite profoundly.[24] The report now gives the same standing to glycaemia and weight management as it does to cardiovascular risk reduction. Moreover, semaglutide and tirzepatide are named as 'very high efficacy drugs' for weight reduction though the latter drug does not have any CVOT data and is not due for review by NICE until 2023. Times are indeed a-changing….

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Fat: bariatric surgery and procedures

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Key words: obesity, type 2 diabetes, metabolic surgery

Who would have thought? Surgery as a 'cure for type 2 diabetes (T2DM)'. I would like to introduce one of my patients, Sarah, a 46-year-old woman. She presented 10 years ago, living with obesity (BMI 44) and poorly controlled T2DM. She had been taking insulin for eight years, plus additional GLP-1 agonists and metformin. She underwent several lifestyle interventions for weight loss with little success. She subsequently underwent a Roux-en-Y gastric bypass (RYGB) and was able to come off all insulin and oral antiglycaemic medications. She only takes the recommended multivitamin replacement post-bariatric surgery now. Her HbA_{1c} has been well controlled for several years.

History of bariatric surgery

The first bariatric surgical procedure for weight loss dates back to the tenth century and was carried out in Spain on Sancho, King of Leon also known as 'Sancho the Fat.'[1] King Sancho was living with such severe obesity that 'he could not walk, ride a horse or pick up a sword' and lost his throne. He was escorted by his grandmother to Cordoba, where he was treated by a famous Jewish physician who sutured the King's lips so that he could only be fed a liquid diet through a straw. King Sancho lost half his weight, returned to Leon on his horse and regained the throne!

The 'true' history of bariatric or metabolic surgery started nearly 100 years ago, in line with 100 years of insulin. The story began in 1925, when a report in the *Lancet* described a 'side effect' of a gastrointestinal operation to treat a peptic ulcer.[2] Physicians noticed resolution of glycosuria which, at the time, was used to diagnose 'diabetes'. Similar observations were made in the following decades, with the first metabolic surgical procedure, the proximal-jejunal bypass, carried out by Mr Kremen in 1954.[3] During the 1980s and 1990s, resolution of T2DM after bariatric surgery was noted and reported, including a landmark report by Pories *et al* involving more than 120 patients.[4] In 1999, it was observed that nearly all patients undergoing a biliopancreatic diversion (BPD), a malabsorptive weight loss procedure, had normalised glucose levels post-operatively.

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Professor Rubino, Chair of Metabolic Surgery at King's College London, attempted to carry out clinical trials comparing metabolic surgery to medical therapy in 1999, but at the time they were not deemed ethical. He performed initial studies in rats in 2004 by taking a lean diabetes model and constructing a duodenal-jejunal bypass with preservation of gastric volume.[5] He observed a significant improvement in glucose tolerance following the duodenal-jejunal bypass in this rodent model.

The anti-diabetes effect of duodenal-jejunal exclusion has also been observed with the use of endoscopic medical devices. One of these, the Endobarrier or duodenal sleeve, is a 60 cm impermeable implantable endoscopic duodenal-jejunal liner positioned along the first part of the intestine. It has been shown to induce signicant improvement in glycaemic control in patients with T2DM.[6] In the Revise-Diabesity clinical trial, patients with T2DM were randomised to Endobarrier alone, Endobarrier and GLP-1 agonist liraglutide 1.2 mg or liraglutide 1.2mg alone.[7] The Endobarrier with additional liraglutide demonstrated the greatest weight loss and improvement in HbA_{1c}.

A further procedure, duodenal mucosal resurfacing, uses a heat balloon to resurface the duodenum and has been shown to give improvements in HbA_{1c}, albeit with a relatively small effect on weight loss.[8] These medical devices which involve manipulation of the duodenum support the notion that the first part of the intestine is mechanistically important for regulation of glucose control and weight.

Trial results

Over the last decade, several randomised trials of bariatric surgery vs. pharmacotherapy for the treatment of T2DM have been published.[9] These trials have shown surgical superiority in terms of remission of T2DM, defined as an HbA_{1c} of 6.5% or less in individuals off all diabetes medications for at least one year. The compelling evidence in favour of surgery eventually led to the publication in 2016 of international guidelines for metabolic surgery as a recommended treatment for T2DM among select individuals.[10] In the UK, NICE recommends consideration of metabolic surgery in T2DM for patients with a BMI as low as 30, or 27.5 in South East Asians. The most common procedures worldwide include the RYGB and the sleeve gastrectomy, although insertion of the gastric band has been popular in the past. The BPD is performed less frequently and is the most malabsorptive, although it achieves the greatest remission of T2DM.

Obese Subjects (SOS) trial, a prospective controlled study following patients on lifestyle vs. bariatric procedures, showed

sustained weight loss of about 25% in the RYGB arm 20 years post-operatively.[11]

Why does metabolic surgery work and why do patients feel less hungry after surgery? Traditionally, it was thought that this could be explained by gastric restriction and a smaller stomach size in addition to malabsorption. However, it is clear that significant biological changes take place after a RYGB and a sleeve gastrectomy, which lead to dramatic changes in gut hormones and contribute to a reduction in appetite. Indeed, the GI tract is an endocrine organ and there are significant endocrine differences between diet-induced weight loss and weight loss after metabolic surgery. For example, there is a decrease in the hunger hormone ghrelin and increases in satiety hormones including GLP-1 and PYY after metabolic surgery but increases in ghrelin and decreases in GLP-1 and PYY following diet-induced weight loss.[12] There is a decrease in energy expenditure after a diet but an increase after surgery. There are additional metabolic changes after bariatric surgery, including increases in bile acids and favourable changes in gut microbiota, which lead to increased insulin secretion, increased insulin sensitivity and increased satiation and weight loss.[13]

Duration of remission

How long does remission of T2DM diabetes last after bariatric surgery? The SOS study suggests a remission rate of 72% two years post-operatively which decreases to 36% at 10 years.[14] Remission rates for other studies depend on the definition of remission and the duration of diabetes at baseline. Earlier surgical intervention in those with a shorter duration of T2DM results in a significantly greater resolution of diabetes. Studies also suggest improvements in quality of life, and a reduction in microvascular and macrovascular complications, following metabolic surgery.[15] Factors which make remission of T2DM less likely are age >50 years, duration of T2DM >5 years, use of glucose-lowering drugs other than metformin, use of insulin and baseline HbA_{1c} >53 mmol/mol or 7.3%.[16]

Bariatric surgery is also available for patients with T1DM who are living with obesity. A systematic review in patients with a mean age of 38 and mean BMI of 43 has shown reductions in insulin usage and HbA_{1c} levels in these patients.[17] Bariatric surgery in patients with T1DM needs careful assessment and MDT discussion; it should be advocated in patients when weight loss is likely to be be beneficial in management of glycaemic control.

Bariatric surgery is useful in remission of several metabolic complications of obesity, including improvement in fibrosis in up to 70% of patients at five years in patients with severe obesity and NASH.[18] Metabolic surgery has been shown to give reductions in major CV outcomes, in nephropathy, all-cause mortality and heart failure in the surgical arm compared to the control arm in patients living with obesity and T2DM.[19] A recent Lancet meta-analysis in more than 174,000 individuals looked at survival in patients with and without diabetes after metabolic/bariatric surgery. It showed a significant reduction in overall mortality by 50% but a greater treatment effect in the T2DM cohort, with a 9.4 longer median life expectancy in this group vs. 5.1 years longer in the non-diabetes group in favour of the surgical arm.[20] Studies have also shown benefits in terms of COVID-19 outcomes, with patients who underwent bariatric surgery showing a decreased need for hospitalization, and a reduction in severe COVID outcomes as defined by ITU admissions, mechanical ventilation and death compared to matched non-surgical controls.[21]

Key messages

- Reports of resolution of glycosuria after gastric surgery were published as early as 1925
- Several randomised clinical trials have shown superiority of metabolic surgery vs pharmacotherapy for remission for type 2 diabetes in patients living with obesity
- Metabolic surgery is safe, with mortality rates lower than a laparoscopic cholecystectomy in expert bariatric centres

Is metabolic surgery safe? There safety data are generally good, with 30-day and 5- year re-admission rates from our bariatric centre at King's College Hospital at lower rates compared to other common surgical procedures including hernia repairs and cholecystectomies.[22] Mortality rates are lower than for a laparoscopic cholecystectomy in centres which carry out large volumes of metabolic surgery. Patients will need to be on life-long multivitamins after surgery and there is a risk of nutritional complications if they are not compliant.

The UK currently performs about 5,000 NHS bariatric procedures per year which compares with annual figures of around 50,000 bariatric procedures in France and more than 200,000 hip and knee replacements in the UK. We need to increase the number of metabolic procedures significantly as there are many individuals who will not be able to manage their weight and complications by lifestyle or pharmacotherapy alone.

Summary

The metabolic surgical road has been a long and arduous one. It started in 1925, with reports of the resolution of glycosuria after gastric surgery. Several reports in the 1980s and 1990s observed the resolution of diabetes after bariatric surgery. Experimental evidence in rats linked gastro-intestinal surgery and glucose metabolism. Over the last decade, several randomised clinical trials have shown sustained benefits of surgical treatment for T2DM. This finally led to the publication of much needed guidelines for the surgical treatment of diabetes. Metabolic surgery has been shown to be safe and cost-effective. It has demonstrated remission of T2DM and reduction in overall mortality and cancer risk. It is a life-saving intervention, essential for patients like Sarah.

Looking ahead, there are significant challenges in the provision and delivery of services for people living with complex and severe obesity. Only 50% of the UK offers multi-disciplinary Tier 3 weight management services, which are the stepping stone for Tier 4 ser-

vices where bariatric surgery is offered. We need to increase access to service provision across the UK in order to tackle the significant health inequalities in obesity care and provide cost-effective metabolic surgery to those that need it most.

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The beginning of the end for insulin? – enter immunotherapy for T1DM

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Key words: Immunotherapy, teplizumab, autoantibodies

Although we have treated type 1 diabetes (T1DM) with insulin for more than 100 years, it has been apparent since the discovery of insulitis in the 1960s and islet cell antibodies in 1974 that T1DM is fundamentally an autoimmune disease, not a metabolic disease.[1] Almost all other autoimmune diseases, from inflammatory bowel disease to rheumatoid arthritis, are treated with immunotherapy but not T1DM. In large part this is because of the discovery of insulin: unlike most other autoimmune diseases, a replacement therapy exists for T1DM. As a result, the discovery of insulin can be viewed as both a blessing and a curse. It is a "curse" because most of the major drug companies have developed their large immunotherapy portfolios of drugs for autoimmune diseases other than T1DM, including some such as psoriasis or alopecia areata that might be considered less life-threatening. And it is likely that diabetes practitioners are also partly to blame since they fear immunotherapy since it is a treatment with which they are not familiar.

It is important to remind ourselves of the challenges of insulin therapy. It is not a drug without risk: deaths still occur from underdosage (DKA) and overdosage (hypoglycaemia). According to ONS data, in 2021 in England and Wales, 44 people under the age of 50 died of DKA and 154 died of hypoglycaemia.[2] Set against this, even despite the introduction of CGM and insulin pumps, fewer than 30% of adults and children with diabetes achieve a target HbA_{1c} < 7.0%, or 53 mmol/mol which obviates the risks of long-term complications.[3] Furthermore, insulin management consumes millions of hours of patients and healthcare professional time in training, adjustments, testing and decision-making. Despite this, 36% of children and families continue to need psychological support more than five years after diagnosis (NPDA national audit 2018-2019,[3] and up to 50% of adults with T1DM report significant diabetes-related distress. [4]

There is a large and expanding world of highly selective immunotherapies that does not include the classic immunosuppressents (e.g. cyclosporin, tacrolimus) used in transplantation.

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Figure 1. Progression from multiple islet antibody positive to clinical T1D is almost inevitable.

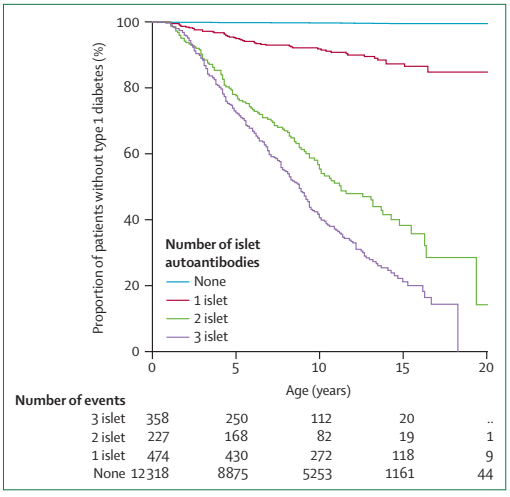

Figure 1: **Proportion of patients without type 1 diabetes in relation to the number of islet autoantibodies after being followed up from birth**
Reproduced from Ziegler and colleagues,[6] by permission of the American Medical Association.

Ziegler AG *et al. JAMA* 2013;**309**(23):2473-9.

Rather, it includes many drugs known as "biologics" that have been widely used and have been very well tolerated in other autoimmune diseases for more than 20 years. Many are monoclonal antibodies, but small molecule inhibitors such as JAK kinase inhibitors are being introduced.[5] At least seven selective immunotherapies have shown efficacy in Phase 2 studies in preserving beta cell function from diagnosis compared to controls.[6,7] These treatments reduce progression of the underlying disease process but do not cause regrowth of beta cells. In current clinical practice, T1DM is diagnosed at the time that insulin replacement is required. This is late in the disease course, when it is estimated that more than 80% of functional beta cells have been lost. When selective immunotherapy is given at this stage, some impact on insulin dose (and in some studies also HbA_{1c} and hypoglycaemia rates) is seen, but it is too late to obviate the need for insulin.

Fortunately, it is possible to diagnose T1DM at an earlier stage. Multiple studies of birth cohorts in relatives of those with T1DM and the general population have shown that 80-90% of asymptomatic children who are found to have two or more islet autoantibodies (including anti-GAD, anti-IA-2, anti-ZNT8 or anti-insulin) will go on to develop T1DM (Figure 1). Once dysglycaemia develops (equivalent to impaired glucose tolerance), levels of hyperglycaemia

Figure 2. ADA classification of the stages type 1 diabetes

Table 2.1—Staging of type 1 diabetes (12,15)

	Stage 1	Stage 2	Stage 3
Characteristics	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• Autoimmunity • Overt hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple islet autoantibodies • No IGT or IFG	• Islet autoantibodies (usually multiple) • Dysglycemia: IFG and/or IGT • FPG 100–125 mg/dL (5.6–6.9 mmol/L) • 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) • A1C 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in A1C	• Autoantibodies may become absent • Diabetes by standard criteria

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; 2-h PG, 2-h plasma glucose.

ADA Standards of Care: *Diabetes Care* 2022;(Suppl1):S17-S38.

diagnostic of diabetes and requiring insulin will develop in more than 80% within five years.[8] This has led to the formal reclassification of T1DM into three stages by the American Diabetes Association, two of them preclinical (Figure 2).[9] Identification of individuals in early stage T1DM raises the possibility of intervening in the disease process before sufficient beta cell function is lost and insulin is required.[10]

Teplizumab

In 2019, Herold and colleagues from Diabetes TrialNet (www.trialnet.org) made the landmark discovery that immunointervention – in this case with the drug teplizumab that causes durable exhaustion of autoreactive T cells – at Stage 2 of Pre-T1DM could prevent the onset of stage 3 (clinical diabetes) by a median of 2-3 years.[11,12] Treatment with this "older" form of immunotherapy involves daily infusions over a 14-day course, but beyond this no further treatment is required and long-term safety seems excellent.[13] The advantages of a 2-3 year delay in the need for insulin are numerous: children (and adults) have 2-3 years during which they are at no risk for hypoglycaemia, have minimal requirement for healthcare, no requirement for treatment or regular blood monitoring and no dietary or lifestyle restrictions, while at the same time improving long-term outcomes by having an additional 2-3 years of near perfect glycaemic control. Importantly, beyond the first 14 days there is no burden of compliance required from the patient, so that even the least engaged people (such as teenagers and young people) can have the same outcomes.[7,14]

This remarkable finding led in 2021 to a historic "public vote" by an expert panel at an FDA scientific review, supporting the view that the benefits of immunotherapy in this form outweigh the risks (Figure 3). Most recently, on 17th November 2022, teplizumab was licensed for use in the USA (Figure 4). It was the first licensed immunotherapy for T1D,[15] contrasting with eight immunotherapies already licensed for psoriasis and similar numbers for inflammatory bowel disease, rheumatoid arthritis and multiple sclerosis.

Figure 3. The historic vote taken at the FDA advisory committee scientific meeting on teplizumab on 21st of May 2021, showing for the first time a vote 10:7 in favour of "the benefits of immunotherapy outweigh the risks".

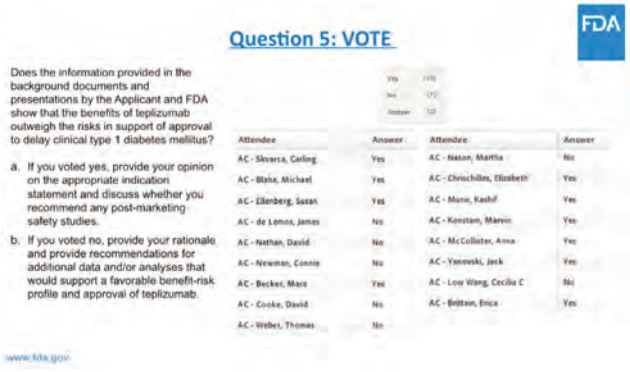

Figure 4. The FDA News release confirming marketing approval for teplizumab on November 17th 2022.[15]

FDA NEWS RELEASE

FDA Approves First Drug That Can Delay Onset of Type 1 Diabetes

For Immediate Release:

November 17, 2022

Today, the U.S. Food and Drug Administration approved Tzield (teplizumab-mzwv) injection to delay the onset of stage 3 type 1 diabetes in adults and pediatric patients 8 years and older who currently have stage 2 type 1 diabetes.

"Today's approval of a first-in-class therapy adds an important new treatment option for certain at-risk patients," said John Sharretts, M.D., director of the Division of Diabetes, Lipid Disorders, and Obesity in the FDA's Center for Drug Evaluation and Research. "The drug's potential to delay clinical diagnosis of type 1 diabetes may provide patients with months to years without the burdens of disease."

Not only does the advent of the first immunotherapy for T1DM provide the first major alternative to insulin since 1921, it necessitates a major change in the model of care. To give immunotherapy before insulin is needed and prevent its being required necessitates screening with autoantibodies to find individuals at stage 2, who are currently asymptomatic and not under medical care. One in 30 first-degree relatives of individuals with T1DM will be in stage 1/2 diabetes, of whom around 10% will be in stage 2.[16] Screening of relatives of patients with T1DM seems a reasonable start as these individuals are identifiable relatively easily identifiable, but this will only identify around 10% of cases since 85-90% of new cases of T1DM come from families with no history of T1DM. A national screening programme will ultimately be required to identify all cases prior to clinical diagnosis (stage 3).[17-19] The use of genetic risk scoring across 40-70 key loci in T1DM to identify those at greatest risk is now well advanced in T1DM.[20] Although it is a major undertaking, screening itself has benefits. Knowing that you or your child are in early stage T1DM markedly reduces late presentations in DKA and can prevent almost all hospital admissions at diagnosis,[21-25] allowing insulin therapy to be introduced in a structured way in the outpatient clinic. Currently, more than 25% of children present in DKA and more than 70% are ill enough to require hospital admission at diagnosis, an experience which many parents find very traumatic and one that can affect engagement with diabetes care for years to come.

Teplizumab is just the beginning. Once patients are identified in early stage T1DM, additional therapies can be introduced alongside or, if the disease appears to be progressing, to delay the need for insuin. Care needs to be taken to avoid excessive immunosuppression in combination therapy, but drugs such as the anti-TNF golimumab, shown recently to preserve beta cell function, are very well tolerated and require only a single subcutaneous injection every two weeks.[26] Oral therapies such as tyrosine kinase and JAK kinase inhibitors, which are already licensed for other autoimmune diseases including alopecia areata, are showing promise.[27] An intriguing recent discovery is that the well known calcium antagonist, verapamil also preserves beta cell function in new onset T1DM by reducing beta cell stress rather than impacting on the immune system.[28,29] This makes it a very attractive candidate for low-risk combination therapy.

The journey has started. Many challenges remain. In addition to national screening, the best way of monitoring disease progression in early phase T1DM is not known and no drug has yet been shown to be effective in the earliest stage (stage 1). Services will have to be reconfigured and all who work in diabetes retrained. Cost-effectiveness will need to considered. Most importantly, the major pharmaceutical companies will need to be engaged as in recent years the application of their increasing large immunotherapy portfolios of drugs has been directed away from T1DM to other indications.

But the prize is in sight. If we can extend the period of not requiring insulin to 6-8 years, the median age of diagnosis will be 18-20, and childhood-onset diabetes will gradually become a disease of the past. Continued beta cell preservation after diagnosis will also make insulin therapy easier and allow many more people living with diabetes to achieve glycaemic targets and avoid hypoglycaemia. Both of these in turn will delay the onset and severity of long-term complications. In the same way that rheumatoid arthritis has been transformed to being a disease of prevention rather than of joint replacement by immunotherapy, insulin will be relegated to "rescue therapy" and more and more patients will live longer, less burdensome and less troubled lives.

Key messages

- Type 1 diabetes can be detected at the preclinical stage by islet autoantibody testing
- Immunotherapy given at the preclinical stage can delay the need for insulin in type 1 diabetes.
- Multiple safe and well tolerated immunotherapies have shown promise in type 1 diabetes and the first has been licensed

Conflict of interest CD has lectured for or been involved as an advisor to the following companies: Novonordisk, Sanofi-genzyme, Janssen, Servier, Lilly, Astrazeneca, Provention Bio, UCB, MSD, Vielo Bio, Avotres, Worg, Novartis. He holds a patent jointly with Midatech plc.
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Dual-hormone Automated Insulin Delivery

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Key words: Dual-hormone Automated Insulin Delivery, closed-loop insulin delivery, glucagon, Type 1 diabetes

Introduction

For the last 100 years, the discovery of insulin has allowed people to live with diabetes. However, the fact that we are using a single hormone to try to replicate the work of the pancreas that uses multiple hormones to maintain glucose homeostasis has meant that for most people, it is impossible to replicate non-diabetic glucose control. Fewer than a quarter of people with type 1 diabetes (T1DM) are able to achieve therapeutic targets,[1] and hypoglycaemia remains a key barrier in our quest to achieve near-normal glucose levels. The role of glucagon in protecting against hypoglycaemia in health is critical, and people with T1DM lose their glucagon responses relatively early in the course of the disease. This is thought to be secondary to the lack of reduction in insulin from the beta cell, as there is a need for reduction in local insulin concentration around alpha cells (together with low glucose) for glucagon secretion to occur.[2] As a result, there is a blunted glucagon response during hypoglycaemia and exercise, increasing the risk of hypoglycaemia. Conceptually, replacing both insulin and glucagon together as part of an "artificial pancreas" makes sense and would allow more aggressive insulin dosing to control glucose rises, since we could rely on glucagon to prevent any resultant hypoglycaemia.

Unlike insulin, glucagon has a rapid onset of action (about five minutes) and time to peak plasma glucagon level of about 15 to 20 minutes.[3] Blauw *et al*. conducted a study to investigate the pharmacokinetics and pharmacodynamics of various glucagon doses at different glucose levels.[4] The authors clamped glucose at 8, 6, 4 and 2.8 mmol and gave different glucagon doses ranging from 0.11 mg to 1 mg. The authors found dose-dependent increases in glucose levels during both normoglycaemia and hypoglycaemia: athe findings from this study support the use of small doses of glucagon during automated insulin delivery.

El Youssef *et al*. conducted a euglycaemic clamp study to investigate the effects of microdoses of subcutaneous glucagon at various insulin doses.[5] They infused at three different insulin infusion rates. At low insulin levels, endogenous glucose production rose proportionately with glucagon dose, whereas at high insulin levels there was no increase in glucose output. This is an important consideration when using low-dose glucagon to treat hypoglycaemia.

Dual-hormone Automated Insulin Delivery (AID)

One of the earlier studies, published in the *New England Journal of Medicine* in 2014, investigated the effects of dual-hormone closed-loop in 20 adults and 32 adolescents who had had TiDM for five years.[6] In this study the control arm used standard insulin pump therapy (only some using continuous glucose monitoring). Rather than having to enter exact carbohydrate content, the meal size was informed (announced) to the algorithm, as "typical", "more than usual", "less than typical" or "a small bite". This system used the tandem T slim insulin pump and iPhone and Dexcom CGM. The authors found significantly better time-in-range with dual hormone closed-loop and reduced time in hypoglycaemia.

In another randomised, three-way, crossover trial, Haider *et al*. compared continuous subcutaneous insulin infusion (CSII) with single- and dual-hormone AID in children aged 9–17 years (n=33) with T1DM during a diabetes camp with unrestricted food intake and physical activity.[7] Each intervention was applied for three consecutive nights. Artificial pancreas interventions started between 2200 h and 2300 h (based on bedtime) until 0700 h. In this study the time spent in hypoglycaemia below 4.0 mmol/L was lowest in dual-hormone AID (0% vs. 3.1% vs. 3.4, dual-hormone vs. single-hormone AID vs. continuous subcutaneous insulin infusion). Additionally, the time spent in target glucose range between 4 and 8 mmol/L was 29% with continuous subcutaneous insulin infusion, 55% with single-hormone AID and 63% with dual-hormone AID.

In another study the authors investigated the benefits of dual-hormone AID and single-hormone AID during exercise.[8] This was a randomized four-way crossover trial (two types of exercise and two types of AID). The two exercise types were either continuous exercise (60% $VO_{2\ max}$ for 60 minutes) or interval exercise (two minutes alternating periods of 85% and 50% $VO_{2\ max}$ for 40 minutes plus two 10- minute periods at 45% $VO_{2\ max}$ at start and end). The study was conducted in 17 adult participants with no carbohydrate ingestion. Two types of AID (single- vs. dual-hormone AID) were applied from 15:30 hours until 19:30 hours. Exercise started at

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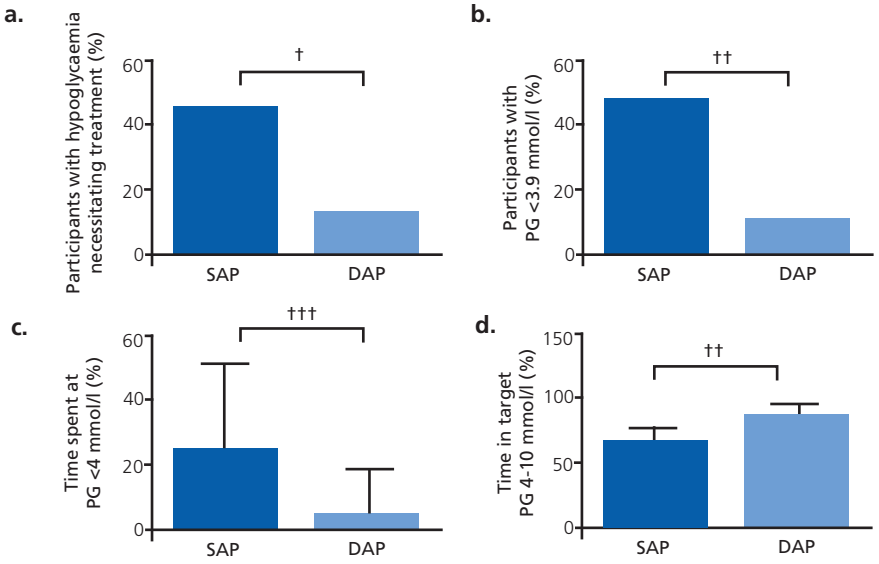
Figure 1. Hypoglycaemia during exercise: single- vs. dual-hormone AID



a. Percentage of participants with hypoglycaemia necessitating treatment
b. Percentage of participants with PG <3.9mmol/l
c. Percentage of time spent at PG <4 mmol/l
d. Percentage of time spent in target (PG 4-10 mmol/l)

For c and d, data are presented as means ± SD

†p=0.02, ††p=0.003, †††p=0.0001

0.11mg (110µg) glucagon per hour exercise. More during continuous than interval exercise

Reproduced from Taleb N *et al*.[8]

18:00 hours with the algorithm informed about exercise (exercise announcement) 20 minutes prior to exercise. The percentage of participants experiencing hypoglycaemia was lower with dual-hormone AID compared to single-hormone AID (Figure 1). In a recent meta-analysis of nine studies comparing dual- vs. single-hormone AID, the time in range was not different but time in hypoglycaemia was shorter with dual-hormone AID (mean difference -1.2% (-1.85, -0.56) in favour of dual-hormone (17 minutes).[9]

Novel glucagon preparations

Dasiglucagon is an analogue of glucagon with seven amino acid substitutions.[10,11] It is physically and chemically stable in aqueous solution and ready-to-use formulation. Biochaperones are polymers, oligomers and organic compounds that can form a complex with glucagon and improve its stability in aqueous solution. Another ready- to-use glucagon is non-aqueous soluble glucagon, G-Pump™ or G-Pen Mini™. Nasal dry powder (Baqsimi) 1mg glucagon per 10mg dry-powder inhaler is also available in the USA.[11]

Mini-dose glucagon for exercise and non-severe hypoglycaemia

In a four-session RCT, the role of mini-dose glucagon was investigated by Rickels *et al* in 15 adults with T1DM on CSII.[12] The trial details are as follows: exercise intensity was 55% $VO_{2\ max}$ for 45 minutes with no intervention, 50% basal reduction, 40g oral glucose tablets and 150mcg subcutaneous glucagon. Outcomes were assessed during 45 minutes of exercise and 30 minutes of early recovery. Basal insulin reduction at the start of the exercise period was no different to control. No participant in the mini-dose glucagon or glucose tablets had an episode of hypoglycaemia. Less hyperglycaemia occurred with mini-dose glucagon. In another randomised crossover trial (two 3-week periods), mini-dose glucagon for treatment of non-severe hypoglycaemia (n=20) was evaluated by Haymond *et al*.[13] This study showed comparable glucose outcomes with mini-dose glucagon and glucose tablets.

Other hormones and approaches

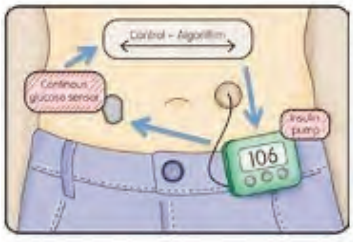
Adding glucagon to insulin is not the only form of dual-hormone automated insulin delivery. Another form of dual-hormone automated insulin delivery (AID) is the combination of standard AID systems with adjunctive agents such as GLP-1 receptor agonists or hormones such as amylin or pramlintide. Most of the work with these adjunctive hormones has focused on reducing the burden of carbohydrate counting for people with T1DM.

Addition of subcutaneous GLP-1 receptor agonists or addition of pramlintide to an ultra-fast insulin (Fiasp) have been shown to improve time in range and to reduce the post-meal glucose excursions following unannounced meals in people on a hybrid single-hormone AID.[14,15]

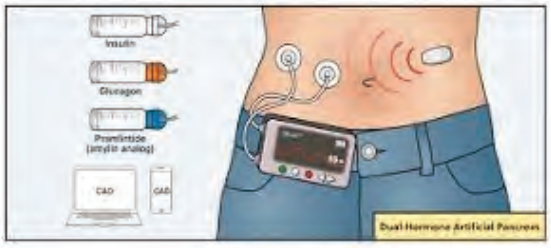
While there are clear theoretical and clinical advantages of dual-hormone closed loops, the possible drawbacks must also be considered. For a long time, there was no such thing as stable soluble glucagon, although the recent launch of pre-mixed liquid stable glucagon products such as Dasiglucagon or Gvoke may make a difference.[10,16] However, since dual-hormone pumps will be more complex and may be bigger, they are likely to cost more. If two cannulas are required, that will also double the consumable costs for tubing and reservoirs. The benefits of these systems must be weighed up in the context of these extra costs (Figure 2). The pros and cons will be different in each individual: for some the pros will clearly outweigh the cons, and for others the opposite will be true.

In summary, stable glucagon preparations are here, and dual-hormone systems that use it have shown improved time in range, although most studies are short-term with small numbers. The long-term safety, effectiveness, acceptability and cost-effec-

Figure 2. Advantages and limitations of single- and dual-hormone AID



- Simplicity
- Adequacy - up to 80% TIR already
- Can be improved with adjuvant therapy if needed
- Safety
- Size/bulk
- Reduced alarms/interventions



- Complexity → increased size / cost and weight of pump
- 2 x reservoirs and canulas that need changing
- Double the risk of site issues / canula occlusion
- Increased risk of alarms / intrusion
- Safety - if insulin or glucagon occlusions are not detected
- Stability of glucagon

Key messages

- Novel more stable glucagon preparations are on the way
- Mini-dose glucagon may become a treatment option for non-severe hypoglycaemia
- Dual-hormone automated insulin delivery (AID) (closed-loop) may be more effective in further reducing hypoglycaemia than single-hormone AID. However further studies are needed at assess longer term safety, effectiveness, acceptability and cost-effectiveness. Increased system complexity and cost may limit its use to certain sub-populations

tiveness of multi-hormone systems, including those with other adjunctive hormones, need to be assessed in larger and longer studies.

Conflict of interest None.

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A journey from the insulin gene to reprogramming pancreatic tissue

KEVIN DOCHERTY

Abstract

This article was written as a contribution to mark the centenary of the first administration of insulin to a human in 1922. Writing from an Aberdeen perspective, an introductory passage will place emphasis on the role of JJR MacLeod, under whose supervision the discovery of insulin by Banting and Best was made. The major thrust of the article, however, will be on the cloning and sequencing of the human insulin gene, and the impact it had on the scientific career of the author. It initiated a journey to find alternative therapies for diabetes that led sequentially though gene therapy, embryonic stem cell-derived islets, and reprogramming. Our experience in these areas will be described, with emphasis on the strengths and weaknesses of each of these approaches.

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Key words: gene therapy and diabetes, embryonic stem cells and diabetes, reprogramming and diabetes, pancreatic transcription factors; Islets of Langerhans

Introduction

The discovery of insulin in 1921 was a remarkable scientific achievement, not least because of the breathtaking speed at which it occurred.[1] The experiments, carried out by Banting and Best in the laboratory of JRR MacLeod in Toronto, commenced in May of that year and involved dog pancreatectomy followed by injection of extracts of atrophied pancreas. By the end of the year, the team, now joined by Collip, had an alcohol extract of pancreas which when injected into pancreatectomised dogs led to a reduction in blood glucose levels. The partially purified factor, insulin, was administered to the first human (Leonard Thompson) in January 2022. In 1923 the Nobel Prize in Physiology was awarded to MacLeod and Banting for the discovery of insulin.

In the short period that they worked together on the discovery the relationship between Banting and MacLeod deteriorated markedly. MacLeod had been on holiday while the project was getting underway, and Banting felt that on his return Macleod took possession of the project and took undue credit for the discovery. This led to a great deal of acrimony: Banting thought that Best deserved some of the glory and shared his Nobel Prize money with him, and in turn MacLeod shared his with Collip. The situation reached such a heated level that Banting, Best and Collip were invited by the Board of Governors of the University of Toronto to write their accounts of the discovery. These documents, along with an account supplied by MacLeod, established that the original idea initiating the fundamental research was Banting's but that the work could not have been taken to fruition without the advice, facilities and support provided by MacLeod.[2] A narrative then developed in which MacLeod's role was marginalised – the forgotten man.

As a result of the ensuing unpleasantness, in 1928 MacLeod left Toronto, returning home to Scotland to take up the Chair of Physiology at the University of Aberdeen, his alma mater. His research there was hindered by ill health, and he died at the early age of 59 in 1935. In his will he donated his Nobel Gold Medal and Citation to the University of Aberdeen, where copies are on display in the Institute of Medical Sciences. His will also contributed to funding a Professorial Chair in Biochemistry. The author of this article is proud to be the third holder of the MacLeod-Smith Chair of Biochemistry. Access to archival material has gone a long way to ensuring that MacLeod's contribution to the discovery of insulin is now fully recognised and appreciated.[3]

The centenary celebrations prompt us to highlight some of the major scientific advances since then that have progressed our understanding and treatment of diabetes. These might include the sequencing of the insulin protein by Sanger, the elucidation of the crystal structure of insulin by Hodgson, the development of a radioimmunoassay for insulin by Yalow, and the discovery of proinsulin by Steiner. However, the breakthrough with possibly the most important impact came about through the efforts of three competing groups based on the east and west coasts of the USA. These groups came together to co-publish a landmark paper that described the cloning and sequencing of the human insulin gene.[4] The importance of this scientific breakthrough was that it kick-started a whole new era in diabetes research. To some extent it initiated studies on the genetics of type 1 diabetes (T1DM), and to this day the most important genetic component to the disease can be mapped to the insulin locus on the short arm of chromosome 11. Sequencing the insulin gene very quickly led to the large-scale production and availability of human insulin and in turn to the development of insulin analogues that are at the forefront of treatment for T1DM. It prompted a rush to understand how the insulin gene was regulated, and to the discovery of the transcription factors (TFs) involved in this process. These TFs play a major role in cell fate decisions in the developing pancreas, and as these processes became understood in detail, their use was vital in generating alternative sources of islets from pluripotent cells.

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This article is written from a personal perspective and should not be taken as an extensive review of reprogramming. At an early stage my lab became interested in how the human insulin gene was regulated,[5] and our work contributed to the identification of a key transcription involved,[6] and the structure of the adjacent hypervariable region.[7] We were keen to exploit the clinical applications of these findings and the route took us sequentially through gene therapy, replenishable supplies of islets from embryonic stem cells, and reprogramming. There now follows a brief account of our experience in each of these areas.

Gene therapy for diabetes

For us gene therapy for diabetes involved the administration of an insulin gene DNA construct to patients. The idea was that the injected DNA would be taken up by cells and transcribed and translated into protein that would be secreted constitutively into the blood stream. The assumption was that expression would be retained for some period of time and would obviate the need for daily insulin injections. There were three main challenges.

The first was which cell to select for expression of the exogenous gene and how to promote efficient uptake into this cell type. At that time (the 1990s) in vivo gene therapy had been directed at several monogenetic disorders and mostly involved viral-mediated gene delivery. The field underwent a major setback in 1999, however, with the tragic death, following administration of a normal gene within an adenoviral vector, of a patient (Jesse Gelsinger) who had been recruited to a safety trial for gene therapy for ornithine transcarbamylase (OTC) deficiency. The news that an experimental treatment had killed a basically healthy volunteer represented a major setback for the field of gene therapy. After many years the field eventually recovered, and gene therapy is now an extremely attractive area of medicine.

For these reasons our approach at that time was to avoid the use of viral vectors and to use instead naked DNA, which was injected directly into the muscle. Muscle was selected as the most amenable site of injection. The uptake of DNA was very inefficient and sowed doubts in our mind as to the viability of this approach.[8-10] However, there is a strong argument for revisiting this approach using gene delivery systems such as advanced adenoviral constructs and RNA-mediated systems as developed for the Covid-19 vaccination programmes.

The second challenge was related to the processing of proinsulin to insulin that in the pancreatic beta cells involves two proteolytic enzymes (PC2 and PC1/3). The problem was that non-neuroendocrine cells lack PC2 and PC1/3. This was surmounted by engineered site-directed mutagenesis of the proinsulin cleavage site between the B-chain/C-peptide junction (Arg-Arg) and the C-peptide/A chain junction (Lys-Arg) to be recognised by furin, an endoprotease that is expressed in muscle and a wide variety of other cell types. When transfected into a muscle line this furin-cleavable construct was efficiently processed to mature insulin and expressed at the same level as wild type proinsulin.[11] This suggests that furin-cleavable (pro)insulin constructs will work in a variety of cell types in the context of gene therapy.

The third problem was how to regulate secretion of insulin from the transduced muscle cells. In the beta cell insulin is stored in secretory granules and released in response to changes in circulating blood glucose levels. Muscle lacks this regulated secretory pathway and would constitutively secrete insulin as it was synthesised. If secreted at very low levels, as expected, this may not be problematic, and a very low background level of insulin in T1DM, and indeed T2DM, patients might be of therapeutic value. However, ideally one would prefer some regulation of insulin release in response to glucose. Importantly, the insulin gene responds to glucose stimulation via pathways that are not well understood although the major regulatory sequences and TFs have been identified. Because these TFs are mostly beta cell-specific, glucose-responsive regulatory sequences within the insulin promoter would be unlikely to work in muscle. Fortunately, the L-type pyruvate kinase (PK) gene is regulated by glucose through known DNA sequences that would function in muscle. We therefore constructed a hybrid gene contained the PK regulatory sequences upstream of the insulin (engineered for cleavage) coding sequences. This worked extremely well (unpublished data); improvements might involve a global screen of DNA libraries for sequences that are glucose-responsive in muscle.

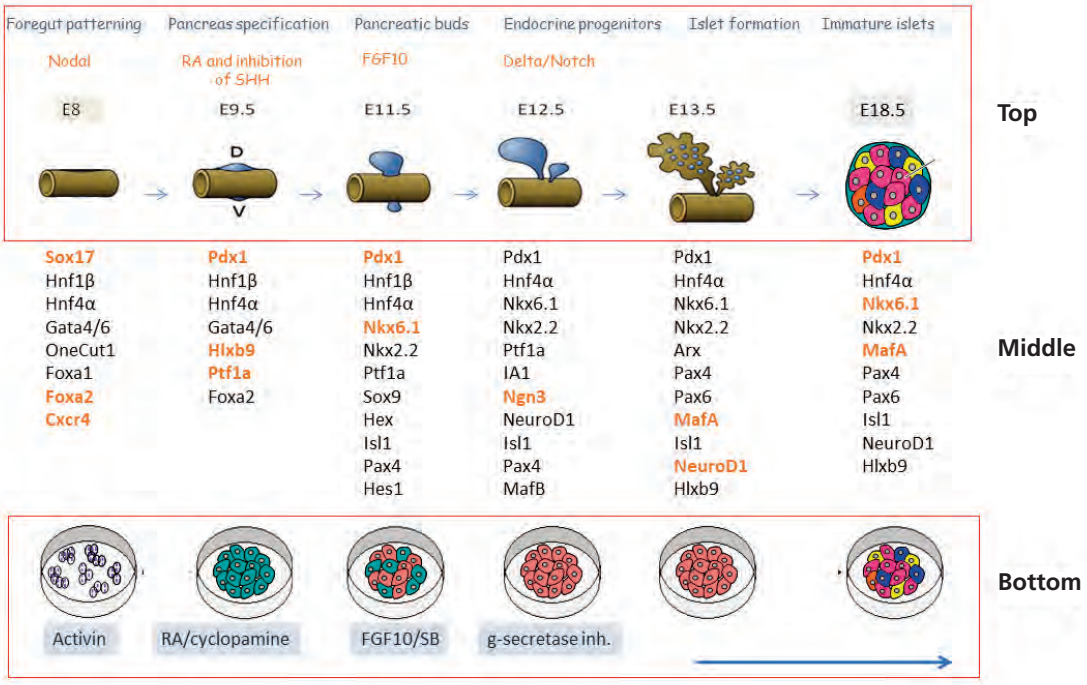
In conclusion, despite our previous reservations about safety issues of viral transduction and low levels of expression, *in vivo* gene therapy (muscle directed) has without doubt a role to play in the treatment of T1DM and T2DM.

A replenishable supply of islets from embryonic stem cells

Cadaveric islet transplantation, based on the Edmonton protocol,[12] is an NHS- funded clinical service in the UK. It can both reduce the frequency of severe hypoglycaemic events (SHE) and improve hypoglycaemic awareness (IHA) in more than 90% of patients.[13] However, widespread application is limited by the lack of suitable donor pancreases, with only 30-40 transplants carried out each year in the UK. The problem is compounded by the fact that the procedure typically requires at least two islet infusions from multiple donors. As a result, transplants are targeted at patients suffering from SHE and IHA who struggle to control their diabetes with conventional insulin therapy. These patients represent 10% (SHE) and 5% (IHA) of the total T1DM population (350,000 in the UK) and the available transplants go nowhere near to meeting this target.

One way of addressing this unmet demand might be to grow islets in culture. However, this has proved virtually impossible. Embryonic stem cells on the other hand grow well (expanded) in culture, whilst maintaining pluripotency, and theoretically can be induced to differentiate towards any cell type. In the case of pancreatic islets, the approach is to recapitulate in a culture dish the events that occur in the developing pancreas.[14] The overall strategy that we employed is shown in Figure 1. The top panel is a simple schematic showing stages in the developing mouse pancreas. (The human pancreas follows similar pathways, although over a much-extended time scale.) By embryonic day 8 (E8) the primitive endodermal gut tube has formed. At around E9.5 the two lobes of the pancreas grow out from either side of the gut; over a period of

Figure 1. Schematic depicting the approach towards generating islet-like cells from embryonic stems cells (ESCs) and induced pluripotent cells (iPSCs)



The **top panel** shows the events that occur in the developing pancreas with some of the important factors that drive these processes. The strategy (**bottom panel**) is to mimic these events in a culture dish using ESCs or iPSCs as starting material. Progress is monitored by measuring transcription factors (**middle panel**) by RT/PCR and immunocytochemistry. More sophisticated protocols have been developed, whereby the cells are treated for an extended period of time (30-35 days) resulting in fully functional mature beta cells

days these anlages expand and eventually the two lobes merge. Islet formation commences at around E13.5 with immature islets forming around E18.5, just before birth. Further maturation occurs in the days after birth. These events are controlled by several growth factors that include Nodal, retinoic acid (RA), sonic hedgehog (SHH), FGF and delta/notch signalling, as shown.

The bottom panel depicts how these events can be mimicked in a culture dish. Embryonic stem cells are first cultured in high doses of Activin A to induce formation of primitive endoderm. The cells are then sequentially treated with RA/cyclopamine, FGF, an SB reagent that inhibits liver formation, and a gamma secretase inhibitor. Progress along this pathway can be monitored by measuring by RT/PCR and immunocytochemistry the transcription factors that are expressed at each stage (middle panel). These can be viewed as a barcode, and the closer one gets to the complete barcode the better the outcome.

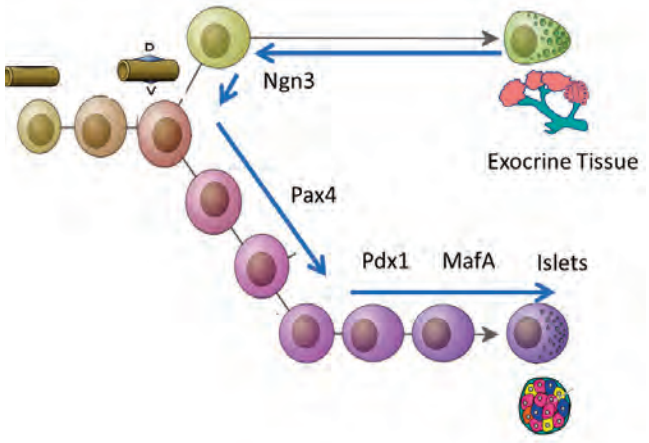
This is typical of the protocols that were developed in our laboratory. In more recent years related protocols have been extended beyond 18 days to generate fully functional islets that exhibit a secretory response to glucose and express levels of insulin close to those seen in adult human islets.[15-17] A biotech company, ViaCyte, has developed methods for encapsulating human ESC-derived islets and human phase 1 safety trials have been underway for several years. For reasons related to the technical difficulties in differentiating human ES cells over extended periods of time and the competition from the large Biotech ventures we terminated this project and moved towards reprogramming.

Reprogramming pancreatic tissue

The reprogramming project arose as a collaboration between our laboratory in Aberdeen and the Scottish Islet Transplantation Centre (SITC), which is located 205 km away in Edinburgh. The SITC was established in 2007, and the first islet transplant into humans took place in 2011. Currently the programme performs around 20-30 transplants per year (it is the major UK centre). The transplant recipients are immunosuppressed and at present the treatment is restricted to adults with SHE and IHA, as described above.

We were involved at an early stage in discussions as to how the unmet demand could be achieved and came up with reprogramming as an alternative to generating islets from ES cells. Islets of Langerhans represent about 2% of the total cell content of the pancreas. The remaining 98% of the tissue comprises acinar cells that produce hydrolytic enzymes and ductal cells that collect these enzymes and direct them to the small intestine. Following extraction of the islets, the left-over exocrine tissue is normally discarded in a manner sensitive to their human origins. Our idea was that the discarded exocrine tissue could be converted into functional islets. Theoretically, if 100% efficient this would generate 50 transplantable units per donor pancreas, which would have a huge

Figure 2. Ball diagram depicting the overall strategy towards reprogramming pancreatic exocrine tissue towards functional islets



During development of the pancreas, around the time when the dorsal and ventral (D and V) anlages appear from the primitive gut tube, there arises a cell type that give rise to both exocrine and endocrine cells. Based on our knowledge of the transcription factors that control these events we predicted that Ngn3 would drive exocrine towards this progenitor cell type and that a combination of Pax4, Pdx1 and MafA would drive differentiation towards islets. This would be further facilitated by inducing an intermediate EMT (iEMT) stage that might exhibit increased plasticity

impact on the roll-out of islet transplantation. Of course, expected efficiency would be nowhere near this but even 10 or so transplantable units per donor pancreas would be a huge improvement on current numbers.

We had been toying with the idea of generating islets from other mature cell types throughout the 1990s, but the concept of transdifferentiation, i.e. converting one mature cell type into another, although championed by some,[18] was met by a great deal of scepticism. Things changed in 2006 with the elegant studies of Yamanaka,[19] who showed that fibroblasts could be converted into pluripotent stem cells (iPSCs) using a combination of four transcription factors, namely Oct4, Sox2, Klf4 and c-Myc (OSKM). Our approach was also to use transcription factors, in this case those that played a pivotal role in cell determination in the developing pancreas. At an early stage in pancreatic development there appears a progenitor cell type that gives rise to the exocrine, ductal and endocrine cells. Which route this cell takes is dependent on the expression of a set of transcription factors that include, amongst others, the keys players Pdx-1, Maf-A, Ngn-3 and Pax-4 (PMNPx). Our overall strategy (Figure 2) was that Ngn-3 would drive the acinar cell population towards this progenitor cell type and that a combination of Pdx-1, Maf-A and Pax-4 would drive the resultant cell population towards a beta cell phenotype. As the project developed, we tested a combination of other pancreatic transcription factors, but none worked better than the PMNPx cocktail.

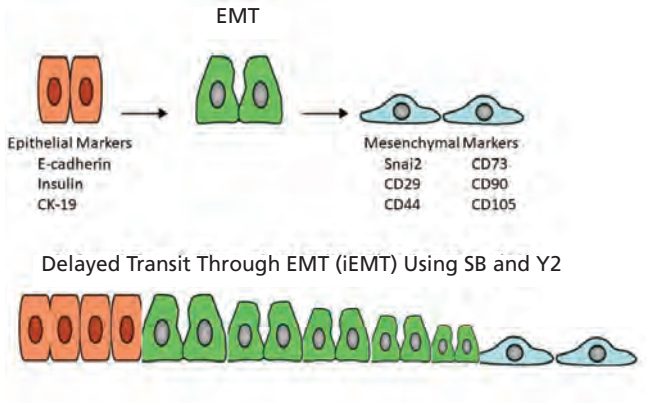
There now follows an account of how the final protocol was developed. Following islet isolation, and with appropriate ethical approval, the low-purity exocrine fraction was transported from Edinburgh to our laboratory in Aberdeen. The digested extract contained clusters of cells measuring between 50-200 microns. Immunofluorescence microscopy showed that the clusters contained predominantly amylase-staining acinar cells and some cytokeratin-19 (CK-19)-staining ductal cells. The presence of islets, as monitored by dithizone staining, routinely represented less than 1% of the total tissue. The exocrine-enriched fraction was then cryopreserved.

For reprogramming the frozen clusters were slowly thawed and plated on tissue culture plates. Over a period of 72h the clusters attached to the dish and an outgrowth of cells with the characteristic appearance of fibroblasts began to populate the empty space on the dish. Initially the outgrowth contained amylase and CK-19 positive cells but this staining, and mRNA levels for these proteins as measured by RT/PCR, diminished with time and were undetectable after 72h in culture. The fibroblast-like cell population could be passaged, providing a considerable expansion in cell number. Routinely the cells were passaged 6-8 times without noticeable changes in the cell population. Passaging beyond eight times would likely lead to culture-dependent clones within such a rapidly expanding population. The resultant cell population exhibited many of the properties of mesenchymal stromal cells (MSCs) in terms of cell surface markers (CD90, CD107 and CD73), and in keeping with the properties of MSCs they could also be induced to differentiate towards osteoblast, chondrocyte and adipocyte lineages under appropriate culture conditions. We showed by genetic lineage tracing that these MSC-like cells were derived from the epithelial clusters by a process of dedifferentiation similar to the epithelial to mesenchymal transition (EMT).[20]

Clearly in order to generate beta cells we would need to convert these MSC-like cells back to epithelial cells, i.e. induce a mesenchymal to epithelial transition (MET). This was effected by culturing the cells in media supplemented with 5-aza-2'-deoxycytidine, sodium butyrate, SB431542 and Y27632 for three days. EMT and its converse MET is a gradual process in which the cells pass through intermediate stages (Figure 3 adapted from[21]). Our rationale was that, even though the cells failed to transit completely to epithelial cells, the intermediate stages would exhibit a degree of plasticity which would enhance the effects of the exogenous pancreatic transcription factors. We had shown previously that KLF-4, one of the Yamanaka factors, could achieve a similar effect in reversing the process i.e. effect a mesenchymal to epithelial transition (MET).[22]

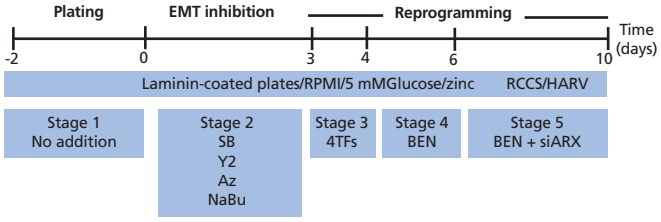
We also attempted to determine if a specific MSC had some memory and hence specific properties related to its origin. We did this by isolating MSCs, by fluorescence-activated cell sorting (FACS), that were genetically marked with the fluorescent marker dsRED. In this system the initial plated cultures that were amylase-positive or islet-derived cultures that were insulin-positive were genetically tagged by introducing by lentiviral transduction a DNA construct in which expression of the fluorescent marker dSRED was under the control of the amylase or insulin promoter. Over a few passages the resultant MSC-like cells continued to express dsREd, thus identifying their cell of origin. However, the results comparing MSCs that were originally Beta (INSdsRED) or acinar (AMYLdsREd) cells were inconclusive. It would be important to resolve this issue, since it is possible that the culture conditions, including properties of the

Figure 3. Generating an intermediate epithelial to mesenchymal transition (iEMT) stage that would enhance cell plasticity



The top panel shows the stages in the EMT, with appropriate markers. The lower panel shows that by using the reagents SB and Y2 we could delay transit through the EMT thus generating an iEMT stage that would exhibit increased plasticity and enhance the effects of the transcription factors

Figure 4. Protocol for generating functional islet-like cells from human exocrine clusters



Details of the protocol are provided in the text

plastic dishes, the coating used and the culture media, may be more important than the tissue source of the MSCs. The implication is that tissues other than pancreas could be used in reprogramming if our hypothesis regarding the plasticity of the intermediate EMT (iEMT) stage were correct.

After three days the transcription factors (PMNPx) were introduced into the cells using replication-deficient adenovirus-mediated transduction. Initially we used four separate viruses, but later we used two viruses, one harbouring Pdx-1 and Maf-A and another Pax-4 and Ngn-3. At that time there were no safety concerns with the ex vivo use of adenoviruses. Viruses containing three transcription factors were less efficient, in that the order in which the TFs were placed relative to the gene regulatory sequences affected the expression levels observed within the cells. At this point the cells were cultured in serum free media supplemented with betacellulin, exendin-4 and nicotinamide, factors that are known to promote beta cell differentiation. These factors alone had very little effect on the expression of insulin as measured by RT/PCR, but significantly enhanced the effect of the exogenous TFs.

The final stages of the differentiation protocol involved treating the cells with an siRNA targeting the transcription Arx which favours differentiation towards glucagon-expressing alpha cells.[23,24] The inclusion of zinc enhanced insulin production, presumably through its requirement for the formation of insulin hexamers. The final stage involved transferring the cells from the culture dishes to a rotating cell culture system (HARV).[25] This step facilitated cell aggregation under effectively microgravity conditions and the formation of islet-like structures.

The final protocol (Figure 4) takes around 12 days and involves plating the isolated human exocrine tissue on laminin-coated plates and culturing in media containing 2.5 mM glucose.[26] Initially, the EMT is partially inhibited using Rho kinase and TGF-β inhibitors in combination with methyltransferase and histone deacetylase inhibitors. Generating this iEMT cell population is particularly important. This is followed by transduction with the exogenous TFs, Pdx1, MafA, Ngn3 and Pax4 and further culture in media containing betacellulin, nicotinamide and exendin-4. Inhibition of endogenous Arx by siRNA is performed towards the final stages of the protocol. The final stage involves culture in a rotating vessel to facilitate aggregation and formation of islet-like structures.

The final product was around 40% endocrine, with a mixture of cells expressing either insulin or glucagon (but not both). The remaining cells were pancreatic MSCs which have the added advantage in terms of the function of the transplanted tissue. The cells were stable as evidenced by the prolonged appearance of human C-peptide in the blood of transplanted mice and the morphology of the transplanted aggregates at periods up to 100 days after transplantation. The reprogrammed cells were responsive to glucose under static incubation conditions and they exhibited a biphasic response to glucose in a perfusion configuration.

In summary, the reprogrammed cells met all the important criteria that would be needed for clinical applications. They expressed fully processed insulin, i.e. they efficiently converted proinsulin to insulin, at therapeutic levels. They efficiently stored, processed and secreted insulin in response to glucose and other nutrients, in a manner similar to adult human islets. They normalised blood glucose levels in an appropriate diabetic animal model. The cells were phenotypically stable. We estimated that one transplantable unit would contain 1-2 billion cells. With efficient expansion of the MSC-like stage each donor pancreas could provide around 10 transplantable units.

We then moved towards taking the project into the clinic.[27] The first stage was to undertake a rigorous assessment of the challenges involved, with a number of go, no-go milestones. The protocol was able to pass an economic viability assessment; it was deemed amenable to scale up under GMP (Good Manufacturing Practices), and no regulatory or licensing issues were identified. However, it was clear that before the project could be taken forward into expensive animal safety and toxicity studies and from there to clinical trials it would require further protocol development and refinement. The major problem was related to batch-to-batch differences in reprogramming efficiency such that it was almost impossible to write rigid standard operation procedures. These differences could in part be related to differences in the donor material

but it was impossible to investigate this since there were clear differences in outcome that could be directly attributed to the protocol.

One potential problem was the distance (205 km) between the islet isolation centre and the reprogramming laboratory. On a good day we would receive the pancreatic tissue within eight hours or so, while on other occasions it was clear that the tissue could be 48h and sometimes 72h old. Regardless of the age of the tissue it was always in good shape, surprisingly, as measured by appearance under the microscope and ability to attach to the culture dish and expand in culture. However, ideally one would place the reprogramming lab adjacent to the isolation lab, and this could easily be arranged. This would also negate the requirement for cryopreserving the clusters and facilitate maintenance of GMP conditions. The major problem, however, was in allowing the clusters to attach to culture dishes and undergo EMT. We felt at the time that delaying EMT through intermediate stages (iEMTs) that might exhibit favourable plasticity would enhance the effects of the TFs, whilst also allowing expansion of the cell population. In fact, we initiated a screening programme for small molecules that would better achieve this goal, with some encouraging hits. An alternative approach might be to maintain the clusters in a bioreactor and optimise the conditions for efficient adenoviral transduction in a 3-D configuration. This would circumvent the potentially unnecessary stages of inducing and then reversing the EMT but would preclude any cell expansion stage. With increased efficiencies and reduced losses it may well be possible to generate a higher yield of transplantable units with enhanced islet-like characteristics.

In summary, our protocol generates β-cells that share many of the properties of adult endogenous β-cells and compare well with surrogate β-cells generated from human embryonic stem cells. Our approach has the advantage that the cells are not at any stage pluripotent, which has important safety considerations. In addition, the reprogramming protocol is relatively simple, cost-effective, adaptable to clinical grade good manufacturing (GMP) conditions, and at 12 days is significantly shorter than the time required to generate fully functional β-like cells from hESCs. We estimate that around 3-5 x 10^8 reprogrammed cells would have a therapeutic effect if transplanted into patients with diabetes; thus one donor pancreas could provide numerous (~10-12) islet grafts. For these reasons we believe that modifications to the protocol as described could lead to a viable cell therapeutic for the treatment of diabetes. One hundred years after the first treatment with a pancreatic extract enriched in insulin we could soon be moving towards administration of insulin via transplantation of reprogrammed alternative cell types.

Summary

The discovery of insulin more than 100 years ago was a team effort, involving a physiologist (MacLeod), a surgeon (Banting), a medical intern (Best) and a chemist (Collip) and very quickly the recruitment of the might of the pharmaceutical industry. Clearly, since the discovery of insulin, there has been a need for new therapeutic approaches that will obviate the need for multiple daily injections and give better metabolic control. Here we have described advances in cell and gene therapy and how ES-derived islet cells are already in clinical trials. It is clear that progress will continue and as experimentalists we should always have a view on how these therapies should be taken to the clinic. It is important to assemble the team as the therapies are being developed rather than wait.

Key messages

- There has been much recent progress in cell and gene therapy to address diabetes
- Encapsulated islets derived from human stem cells are undergoing clinical trials
- Reprogrammed islets from human pancreatic tissue may be taken forward into preclinical studies
- Gene therapy may involve injecting nucleic acids encoding insulin into muscle

Conflict of interest None.

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The flash glucose monitoring revolution: the Sat Nav journey

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Key words: type 1 diabetes, flash glucose monitoring, continuous glucose monitoring

I am setting readers a challenge (Figures 1 and 2). I would like you to drive to Park Row in Leeds, a place you have not visited before. To get there you can drive your car and use your satellite navigation (Sat Nav) system. However, you can only look at your Sat Nav system on four occasions during your whole journey. Are you feeling uncomfortable? No wonder. But this is essentially what we have been asking people with diabetes to do for decades when it comes to glucose monitoring. Asking people with diabetes to check their blood glucose only before meals and before bed provides very limited information about what is happening to glucose levels in between meals and overnight. What would be preferable, of course, is the ability to see the glucose data across the full day, on demand, to check how the journey is going and, most importantly, to arrive safely at the desired destination.

In 2014 the Abbott FreeStyle Libre device became available in the UK, allowing people with diabetes to monitor their glucose levels continuously. The Freestyle Libre flash glucose monitoring device is an arm-worn glucose sensor, the first two versions of which were the size of a £2 coin. The device reads glucose data every minute and transfers this information to a mobile phone app. The person with diabetes can then access their glucose data by scanning their phone over the sensor or, for those without a smartphone, there is a reader which can be used for scanning the sensor and doing glucose checks.

The Impact flash glucose monitoring randomised controlled trial in 2014 demonstrated that the use of flash glucose monitoring in people with well controlled T1DM resulted in a 38% reduction in hypoglycaemia.[1] Interestingly, this reduction in hypoglycaemia occurred after the first fortnight of use, even though the users had no instructions on how to respond to their glucose data. This may initially seem surprising but viewing the data from the device shown in figure 3 makes clear how intuitive it can be for people with diabetes to understand and respond to their glucose levels. For example, in the UK to be safe to drive a car in accordance with the DVLA regulations, your glucose must be above 5.0 mmol/L.[2] In the finger prick example in Figure 3 the glucose reading is 5.3mmol/L, implying that the individual would meet the criteria for safe driving. In the second example with a reading of 5.3mmol/L and a straight across arrow, indicating a steady glucose profile, again this would be reassuring for driving. In the third example with a reading of 5.3mmol/L and a downwards arrow indicating a rapidly reducing glucose level, it is clear that the person would need to take extra rescue carbohydrates to avert the risk of hypoglycaemia.

Figure 1. The challenge

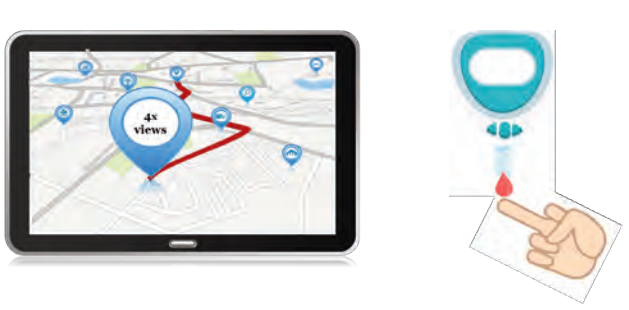

Figure 2. The challenge: the desired option

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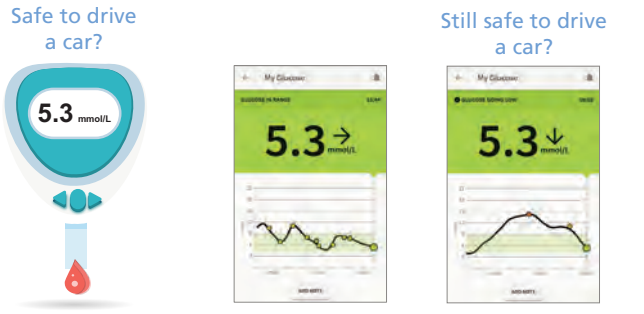
https://doi.org/10.15277/bjd.2022.372

Figure 3. Glucose monitoring and the DVLA

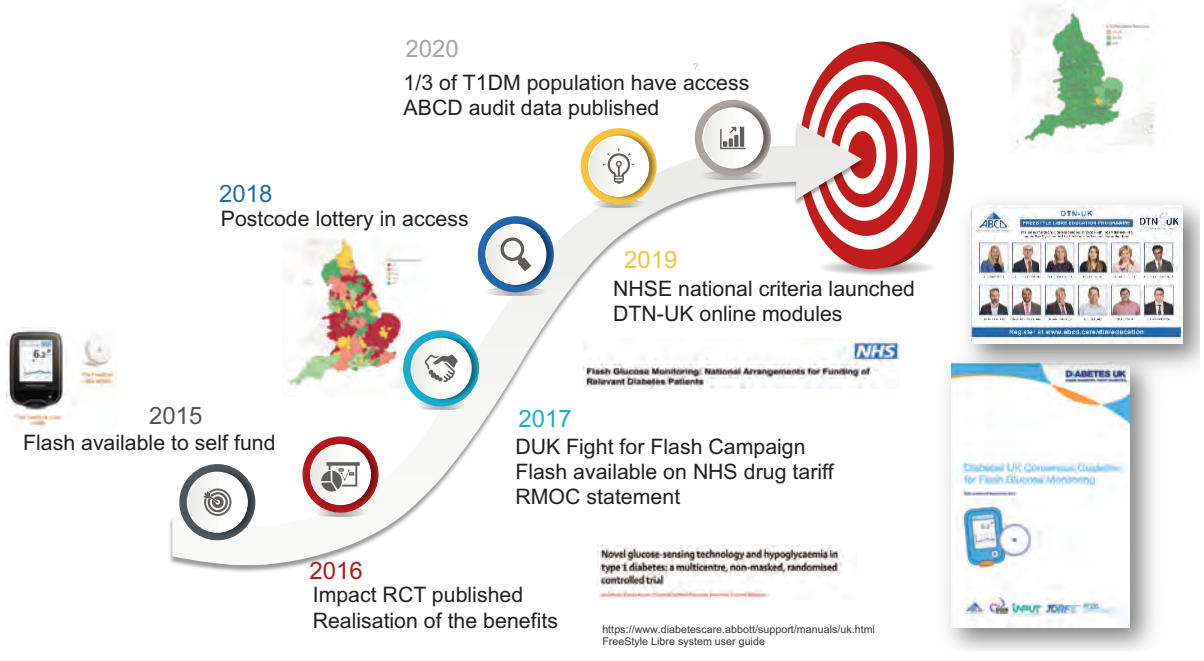


Over the past eight years we have seen a substantial increase in access to flash glucose monitoring. Figure 4 demonstrates the journey to improving access to flash glucose monitoring. This became available initially to self-fund in 2014, and people living with diabetes started to gain insight into the potential benefits. Many were frustrated that such a life-changing device was not available on prescription. Diabetes UK responded on their behalf with their 'Fight for Flash' campaign. Flash glucose monitoring became available on the NHS drug tariff in 2017 but access remained patchy, with the emergence of a post code lottery. In response, NHS England rolled out national access criteria associated with a national reimbursement policy. Interestingly, these criteria included indications such as psychosocial or occupational indications for flash glucose monitoring, opening the doors for wider access for those who were struggling with blood glucose monitoring. Since then, we have seen a substantial uptick in the levels of access. Towards the end of 2022, more than 70% of people living with T1DM have access to this technology, representing the most rapid increase in uptake of a new technology in the history of T1DM.

From 2017 ABCD undertook a national audit of flash glucose monitoring with the aim of understanding better the clinical outcomes associated with using the device. The data, published in Diabetes Care in 2020, demonstrated a - 5.2mmol/mol reduction in HbA_{1c}, with even greater reductions witnessed in those with higher baseline HbA_{1c} values.[3] The other striking finding was a significant reduction in admissions with diabetic ketoacidosis (DKA), hyperglycaemia, hypoglycaemia, paramedic call outs and severe hypoglycaemia. Importantly there was also an improvement in the Gold score (a marker of hypoglycaemia awareness): proportion of those with impaired awareness of hypoglycaemia at baseline reverted to normal hypoglycaemia awareness; reducing from 28% to 18%.[4]

A further concern which some may have when initiating flash glucose monitoring is whether structured education might be needed prior to starting the device. However, in contrast to the assumptions made, our work demonstrated that it did not matter whether somebody had attended structured education or not – HbA_{1c} reduction was seen across the board independent of prior education status.[5] This finding is further supported by the real-world data which showed that during the pandemic lockdown, a period when people with diabetes had limited support from healthcare professionals, there was an improvement in time in range, reflecting improved self-management.[6] Finally, and possibly most importantly, the ABCD audit has also demonstrated that flash glu-

Figure 4. The flash glucose montoring journey in the UK



Key messages

- The uptake of flash glucose monitoring in the UK has increased exponentially in recent years, providing people with diabetes with a more detailed understanding of their glucose levels across the day.
- The use of flash glucose monitoring technology in people with type 1 diabetes is associated with improvements in HbA_{1c}, hypoglycaemia and acute admissions.
- From 2022 on, NICE recommends that we offer people living with Type 1 diabetes a choice of interstitial glucose monitoring devices, designed to meet their individual needs.

cose monitoring is associated with a significant reduction in diabetes-related distress (50% to 26%, p<0.001). (This is a measure of the degree to which people feel they are either failing with their diabetes or feeling overwhelmed by their diabetes.[7])

These data support the case for wider access to flash glucose monitoring in the UK. The most recent development in access was in March 2022, when NICE published their updated guidance on glucose monitoring.[8] It is now recommended that either flash or real-time continuous glucose monitoring should be made available to all people living with T1DM and that the choice of device should be guided by individual needs and the characteristics of the devices available. The challenge in delivering this will, of course, be the associated costs. These concerns will hopefully be offset by the results of Flash UK study, led by Dr Lala Leelarathna, which has recently demonstrated the effectiveness of the FreeStyle Libre device in a randomised controlled trial.[9,10]

The latest development in the flash glucose monitoring journey is the integration of smart pens in the Libreview platform. This will allow clinicians to visualise glucose data alongside insulin data, facilitating a more detailed interpretation and hopefully leading to better support for those using multiple daily injections and flash glucose monitoring. These data will also be available for real-time CGM users with connected pens in the Glooko platform. These latest developments in access to smart pens will finally help to bridge the gap between multiple daily injection users and insulin pump users, providing thorough glucose and insulin data regardless of the insulin delivery modality.

In the past decade we have witnessed a revolution in the access to flash glucose monitoring. The recent NICE update extends this revolution to real-time CGM also, providing choice and the ability to respond to individual needs when discussing glucose monitoring options in clinic. Never before has there been such a rapid increase in diabetes technology. As we move into the era of automated insulin delivery, the future is looking very bright indeed.

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#We are not waiting - DIY APS Do-It-Yourself Artificial Pancreas Systems: The story so far

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Key words: closed-loop, DIY, open-source, technology

Introduction

In 2015 Dana Lewis, a person with diabetes, developed her own hybrid-closed loop system and began the #WeAreNotWaiting movement (Figure 1). These systems, often called "do-it-yourself" artificial pancreas systems (DIY APS) or open-source closed-loop automated insulin delivery systems, combine an insulin pump, a sensor and an algorithm to maintain glucose levels in range. Whilst early versions were "hybrid" – in other words they still required manual bolusing-- the newer versions of the algorithm have been used as a fully-closed loop (no bolus required!) by some individuals. An article written in 2019 provides further detail on these systems and some of the issues associated with them.[1]

These systems filled a gap by circumnavigating the approvals that commercial companies require in order to launch similar systems. There are three systems commonly encountered: OpenAPS, AndroidAPS and Loop.[1] At the time of writing all three systems are unapproved and unregulated. When these systems first entered UK services the evidence was limited. However, self-reported outcomes from users of the systems were encouraging from both glycaemia and safety points of view.[2-4]

At that time, the approach taken across UK diabetes services was inconsistent and guidelines from the General Medical Council and others were unclear.[5] Work was undertaken to explore the opinions of UK healthcare professionals; initial position statements were produced by Diabetes UK and other organisations to support users of these systems.[6,7] We also explored the concerns of individuals with diabetes commencing the use of these systems, and were able to demonstrate that they were less concerned with safety and regulatory issues than healthcare professionals but that they were worried about a negative response from their healthcare teams (Figure 2).[8]

The Association of British Clinical Diabetologists launched an audit in 2019, which I have been pleased to be heavily involved with, and which now contains routine clinical data from more than 100 DIY APS users in the UK.[9] This work was recently reported at the Advanced Technologies and Therapeutics in Diabetes Conference 2022, where we were able to demonstrate that DIY APS are

Figure 1. DIY-APS – the #WeAreNotWaiting movement

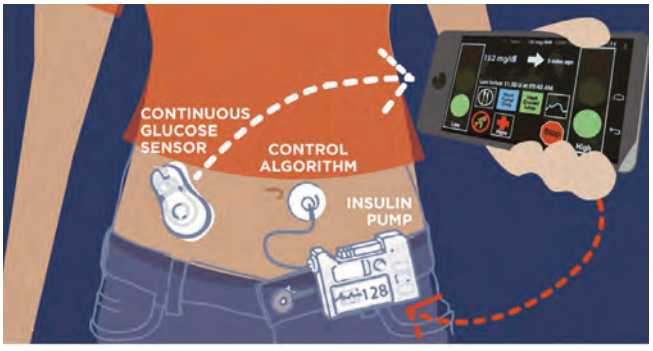

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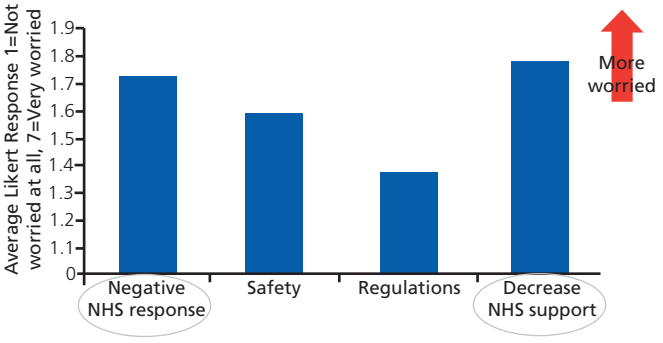
Figure 2. User concerns before commencement



Reference taken from - Crabtree TSJ, Maslen A, Wilmot EG. A44 Oral presentation: initial insights into do-it-yourself artificial pancreas system user expectations and concerns prior to commencement: A pilot questionnaire. DUKPC 2020

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Figure 3. What should our approach be as healthcare professionals?

- We would initiate discussions about DIY APS **but** need to provide full information regarding available options and risks vs benefits
- Checking the basics! (Cannual changes, spare pens)
- We should discuss the risks of DIY APS especially around out-of-warranty equipment if used
- Should continue to support the supply of NHS funded insulin pump, CGM of Flash GM
- Should participate in the ABCD DIY APS audit

associated with improved glycaemia and appear to be safe.[10,11]

In addition to these findings, others have compared DIY APS to commercial systems, often with favourable glucose outcomes (despite often lower HbA_{1c} and higher time-in-range at baseline) and reassuring safety data.[12-14] It is difficult to draw conclusions from observational data but with the systems being actively used in the real world there were limited other means to understand them better in the current cohort of users. That being said, AndroidAPS has recently been put through a randomised controlled trial. The results were recently published in the *New England Journal of Medicine*,[15] and are similar to those seen in the real world.

Whilst glycaemia and safety outcomes are important, the most impressive things often found in users of these systems are the vast improvements in quality of life, sleep and reduced burden of day-to-day diabetes management.[16,17] People come to clinic using these systems and readily report "I don't feel like I have diabetes anymore".

How do we provide practical support to users of these systems? Some of the take- home points are listed in Figure 3. Most people working with diabetes and technology probably feel more comfortable supporting these systems clinically now than they did in the past: the wave of commercial systems and the NHS England pilot project to assess commercially available hybrid closed-loop systems in real clinical use in the NHS have been a crash course in closed-loop insulin management.[18] Other teams have assessed the ethics of the situation,[19] and I was really pleased to see the publication of an international consensus piece on the management of these systems. It is a must-read for anyone who encounters DIY APS users in their clinics.[20]

It will be interesting to see what the future holds. I would encourage anyone seeing users of these systems in clinic to participate in the ABCD DIY APS audit which will continue to undertake surveillance and report outcomes.[9] One thing is for sure: DIY APS seem unlikely to be going anywhere in the short term. They provide an excellent example of citizen science, and the power of the diabetes community advocating for themselves.

Key messages

- Open-source or DIY closed-loop systems were developed by people with diabetes and have been in use since 2015
- These systems are unregulated and unapproved; understanding the ethical situation and management of users of these systems has been complex but we are no supported by robust consensus guidelines
- Data from clinical trials and observational studies suggest that, amongst current users, these systems are likely to be safe and effective

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#We don't have to wait any more Closed-loop systems: transforming the landscape

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Abstract

Hybrid closed-loop systems are transforming the clinical management of T1DM. Large randomised controlled trials of hybrid closed-loop systems have demonstrated safety and efficacy, with significant improvements in glycaemic control compared to control therapy, and there are now several commercially approved hybrid closed-loop systems available in the UK. There is also a growing body of evidence demonstrating the quality of life benefits associated with hybrid closed-loop systems, both for users and also for parents/caregivers and other family members.

We review the clinical evidence supporting currently available hybrid closed-loop systems in the UK and also new systems on the horizon. We discuss the emerging evidence for associated psychosocial benefits of hybrid closed-loop therapy. We also address future challenges around healthcare professional readiness to deliver closed-loop technology and ensuring equitable access across the UK.

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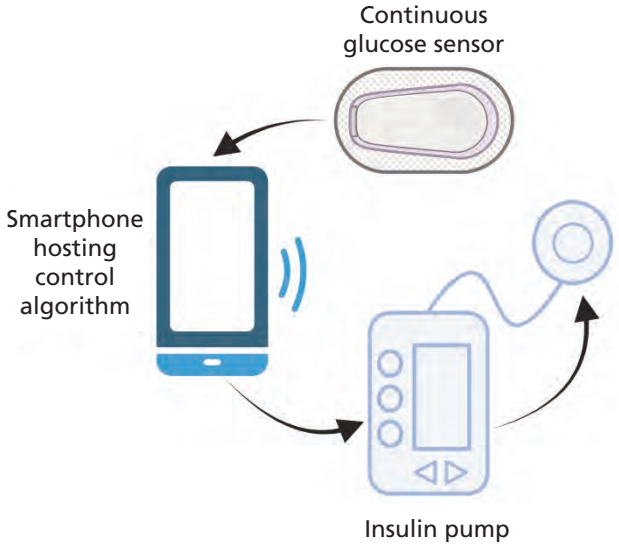
Key words: hybrid closed-loop, type 1 diabetes, quality of life, glycaemic control

What is hybrid closed-loop?

Closed-loop systems are transforming the clinical management of T1DM. These automated insulin delivery systems comprise a subcutaneously worn continuous glucose monitoring device (CGM or glucose sensor), communicating with an algorithm that responds to real-time changes in sensor glucose levels, and modulates the subcutaneous insulin infusion rate delivered by an insulin pump (Figure 1).

Large randomised controlled trials of unrestricted home use of closed-loop systems have demonstrated safety and efficacy, with significant improvements in time in target glucose range (3.9–10.0 mmol/L) and reduced time in hypoglycaemia (<3.9mmol/L) compared with comparator therapies and a favourable effect on HbA_{1c}.[1,2] The first commercial closed-loop system, the MiniMed 670G (Medtronic, Northridge, CA, USA), was approved by the US Food and Drug Administration in September 2016 for use in people with T1DM aged 14 years and older.[3] There are now several commercially approved closed-loop systems available in the UK, with more advanced second-generation systems also being developed and approved.[4] All currently approved closed-loop systems are 'hybrid', requiring users to enter prandial insulin boluses manually but with automation of insulin delivery between meals and overnight.

Figure 1. Hybrid closed-loop system. Created with BioRender.com



What makes a good closed loop?

In order for a closed-loop system to be effective, users should be able to reach individualised target glucose control. The international consensus guidelines recommend over 70% time in target glucose range (3.9 to 10.0 mmol/L) and <4% time below 3.9 mmol/L.[5] Although clinical trials of hybrid closed-loop systems often demonstrate attainment of these targets by the study population overall, real-world data and outcomes in broader groups with more chal-

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Table 1 Currently approved hybrid closed-loop systems in the UK

	Medtronic 670G / 780G	Tandem Control IQ	CamAPS FX
Age	7 years up	6 years up	1 year up & pregnancy
Factory calibration of sensor	780G: ✓	✓	✓
Algorithm setup	TDD, weight, ICR, CF, basal rate	TDD, weight, ICR, CF, basal rate	TDD, weight
Adaptive learning	Overall	None	Overall, diurnal, meals
Bolusing from phone	X	X	✓
Personal glucose target	780G: 5.5, 6.1, 6.7 mmo/L	Overnight 6.1 - 6.7 mmol/L	4.4 – 11 mmol/L
Activity / Ease-Off mode	Now	Now	Now and planned
Boost mode	X	X	Now and planned
Remote monitoring	780G: ✓	Follow	SMS
Automated cloud upload	780G: ✓	X	Diasend (Glooko 2022)
Insulin	Rapid	Rapid	Rapid & ultra-rapid

TDD, total daily dose; ICR, insulin carbohydrate ratio; CF, correction factor

lenging diabetes management have not been extensively reported. In addition to efficacy in attaining target glycaemic control, good closed-loop systems should be easy to use and associated with low diabetes management burden, requiring less than 30 minutes on diabetes-related tasks per day.[6] To improve user experience further and ensure continued use, the burden from the devices, system alarms and technical issues needs to be low.[7]

Available closed-loop systems

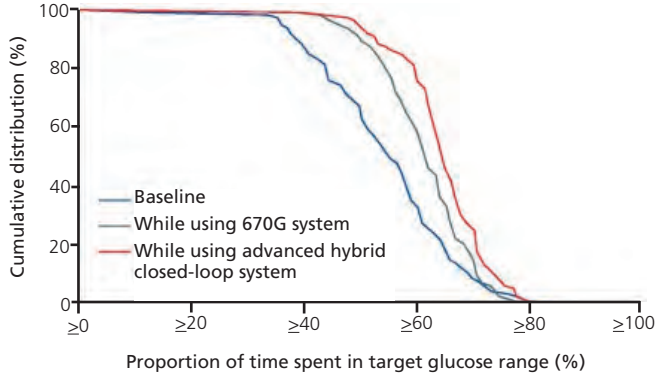
Current commercially available systems include Medtronic 670G and 780G (use from age seven years and upwards), Tandem Control IQ (use from age six years and upwards) and CamAPS FX (use from age one year and upwards and in pregnancy). The systems differ in the way they automate insulin delivery and their specific features (Table 1). The only head-to-head comparison of two different hybrid closed-loop systems compared the first- and second-generation Medtronic systems.[8] Comparisons of efficacy between hybrid closed-loop systems across different studies are hampered by variation in baseline characteristics of participants, study duration and design.

Clinical evidence

Medtronic 670G and 780G

A multinational crossover randomised controlled trial compared the Medtronic 670G with the second-generation Medtronic 780G and involved 113 adolescents and young adults aged 14 to 29 years with T1DM. The baseline HbA_{1c} was 8.1% (65 mmol/mol). The percentage of time that the sensor glucose level was within the target range was 57±12% at baseline, 63±8% during the 12 weeks using Medtronic 670G and 67±8% in the 12 weeks using Medtronic 780G (Figure 2). The percentage of time that the glucose level was below 3.9 mmol/L was 2.3±1.8% at baseline, 2.1±1.4% during the 12 weeks using 670G and 2.1±1.2% in the 12 weeks using 780G. Mean HbA_{1c} was 7.6±0.6% (59±7mmol/mol) after 12 weeks using 670G and 7.4±0.8% (57±9mmol/mol) after 12 weeks using 780G.

Figure 2. Proportion of time spent with glucose concentrations in the range 3.9–10.0 mmol/L, by hour, over 24h period as measured by continuous glucose monitoring, according to the time of day. Data points are hourly median values, and the shaded regions show IQRs (8).



The proportion of time that the system was in auto mode was 75% during use of the 670G system and 86% during use of the 780G system. One severe hypoglycaemic event occurred during use of the 780G system, determined to be unrelated to study treatment, and none occurred in the 670G period.

Tandem Control-IQ

In a multicentre parallel design randomised controlled trial in the US, 168 adolescents (14 years and upwards) and adults with T1DM were randomised to use either Control IQ (the closed-loop group) or sensor augmented pump therapy for six months (the control group).[9] The baseline HbA_{1c} of the study cohort was 7.4% (57 mmol/mol). The percentage of time that the sensor glucose level

was within the target range increased in the closed-loop group from 61±17% at baseline to 71±12% during the six months and remained unchanged at 59±14% in the control group, a between-group difference of 11 percentage points. The difference in the mean glucose level was 0.7 mmol/L in favour of closed-loop and the difference in the percentage of time that the glucose level was below 3.9mmol/L was lower in the closed-loop group by 0.88 percentage points. The difference in HbA_{1c} after six months was 0.33 percentage points lower in the closed-loop group. Closed-loop was active for 90% of the time over six months. No serious hypoglycaemic events occurred in either group; one episode of diabetic ketoacidosis occurred in the closed-loop group.

In a multicentre parallel design randomised controlled trial in the US, 101 children aged 6 to 13 years of age with T1DM were randomised to use either Control IQ (the closed-loop group) or sensor augmented pump therapy (the control group) for 16 weeks.[10] The baseline HbA_{1c} of the study cohort was 7.6-7.9% (60-63 mmol/mol). The percentage of time the glucose level was within the target range during the 16 weeks increased in the closed-loop group from 53±17% at baseline to 67±10% and from 51±16% to 55±13% in the control group, a between-group difference of 11 percentage points. The difference in mean glucose level was 0.7mmol/L in favour of closed-loop and the difference in the percentage of time that the glucose level was below 3.9 mmol/L was lower in the closed-loop group by 0.40 percentage points. Mean HbA_{1c} after 16 weeks was 0.4 percentage points lower in the closed-loop group than the control group. Closed-loop was active for 93% of the time. No episodes of diabetic ketoacidosis or severe hypoglycemia occurred in either group.

CamAPS FX

A multinational crossover design randomised controlled trial in the UK and Europe compared CamAPS FX with sensor-augmented pump therapy in 74 children aged 1-7 years with T1DM. The baseline HbA_{1c} of the study cohort was 7.3% (56mmol/mol).[11] The percentage of time that the sensor glucose was within the target range in the closed-loop period was 72±6% compared with 63±9% during the control period, a difference between treatments of 8.7 percentage points. The difference in mean glucose level was 0.7mmol/L in favour of closed-loop. There was no difference in the percentage of time that the glucose level was below 3.9 mmol/L between the closed-loop period and the control period. The difference in HbA_{1c} after 16 weeks was 0.4 percentage points lower following closed-loop therapy. Closed-loop was active for 93% of the time. One severe hypoglycemia event occurred during the closed-loop period and no episodes of diabetic ketoacidosis occurred in either period.

In a multinational parallel design randomised controlled trial in the UK and US, 133 children and adolescents aged 6-18 years with T1DM and sub-optimal glycaemic control were randomised to either closed-loop insulin delivery or to usual care with insulin pump therapy for six months.[12] The baseline HbA_{1c} of the study cohort was 8.2-8.3% (66-67 mmol/mol. At six months, HbA_{1c} was lower in the closed-loop group than in the control group by 0.3 percentage points. Participants in the closed-loop group used the Cambridge closed-loop algorithm running on a smartphone with either a modified Medtronic 640G pump, Medtronic Guardian 3 sensor and Medtronic prototype phone enclosure (FlorenceM configuration), or a Sooil Dana RS pump and Dexcom G6 sensor (CamAPS FX configuration). Closed-loop usage was low with FlorenceM due to failing phone enclosures (40%) but consistently high with CamAPS FX (93%), impacting efficacy. In those who used the CamAPS FX configuration, time in target glucose range was 15 percentage points higher in the closed-loop group (63±9%) than in the control group (49±13%), with no significant difference between groups in the time spent with glucose below 3.9 mmol/L. The difference in HbA_{1c} after six months was 1.1 percentage points lower following closed-loop therapy with CamAPS FX compared with the control group. Seven severe hypoglycaemia events occurred (four in the closed-loop group, three in the control group) and two diabetic ketoacidosis events (both in the closed-loop group). This study demonstrates that to ensure optimal efficacy of the closed-loop system, usage needs to be consistently high.

A multinational crossover design randomised controlled trial in the UK and Austria compared CamAPS FX with sensor-augmented pump therapy in 37 adults aged 60 years and above with T1DM.[13] The baseline HbA_{1c} of the study cohort was 7.4% (57mmol/mol). The percentage of time that the glucose level was within the target range in the closed-loop period was 80±8% compared with 71±13% during the control period, a difference between treatments of 8.6 percentage points. The difference in the mean glucose level was 0.7mmol/L in favour of closed-loop therapy. There was no difference in the percentage of time that the glucose level was below 3.9 mmol/L between the closed-loop and control periods. The between-group difference in HbA_{1c} after 16 weeks was 0.2 percentage points in favour of closed-loop therapy. Closed-loop was active for 97% of the time. Two severe hypoglycaemia events occurred during the control period and none during the closed-loop period.

Upcoming single hormone closed-loop systems

iLet bionic pancreas

In a multicentre parallel design randomised controlled trial in the US, 165 children and adolescents age 6-17 years old with T1DM were randomised to use closed-loop with insulin aspart or insulin lispro or to a control group using their usual insulin delivery with continuous glucose monitoring for 13 weeks.[14] The time spent in target glucose range increased from 47±17% at baseline to 60±8% with closed-loop compared with 48±19% at baseline to 50±16% with usual care, a difference between groups of 10 percentage points. Time spent with glucose below 3.9 mmol/L was similar between groups. Mean HbA_{1c} decreased from 8.1±1.2% at baseline to 7.5±0.7% at 13 weeks with closed-loop compared with 7.8±1.1% at both baseline and 13 weeks in the control group, a between-group difference of 0.5 percentage points in favour of closed-loop. Three participants in the closed-loop group and one in the control group had a severe hypoglycemia event.

Omnipod 5

No randomised controlled trials have been undertaken with the

Omnipod 5 closed-loop system. Single arm studies demonstrate safety in those aged 2 years and older.[15,16]

Do-it-yourself (DIY) closed-loop systems

The do-it-yourself (DIY) artificial pancreas system (DIY APS) communities develop and apply open-access closed-loop algorithms (e.g. Open Artificial Pancreas System [OpenAPS], DIY Loop and AndroidAPS) which do not undergo regulatory overview and approval. Access is open to anyone but users need to be able to build and maintain their own system, with some support provided from the community itself. Several thousands of people around the world living with diabetes use DIY systems. Until recently, clinical evidence on these systems was limited to observational before-and-after studies. A recent multicentre randomised controlled parallel design study involving 97 participants (48 children aged 7 to 15 years and 49 adults) compared an open-source AID system (a modified version of AndroidAPS 2.8 with a standard OpenAPS 0.7.0 algorithm) with sensor-augmented pump therapy for six months.[17] Time in the target glucose range increased from 61±12% to 71±12% in the closed-loop group and decreased from 58±14% to 55±16% in the control group. No severe hypoglycemia or diabetic ketoacidosis occurred in either group.

Psychosocial impacts

There is growing evidence from qualitative evaluations of the psychosocial benefits associated with closed-loop systems, both for users and also for parents/caregivers and other family members.[18-20] Users describe generally positive experiences, with perceived benefits including reassurance and reduced anxiety, improved sleep and confidence, and the concept of 'time off' from diabetes demands.[19]

While some studies report improved diabetes-specific psychosocial measures, including reduced diabetes distress, improved diabetes treatment satisfaction and fear of hypoglycaemia, these findings have not been consistent and they differ depending on the underlying study population.[14,21-23] One consistent message from qualitative assessments is that for optimal benefits, closed-loop systems need to minimise burden in terms of frequency of alarms, the need for sensor calibration and other user inputs. Issues with connectivity between devices can also have a significant negative impact on usability.[7,24]

Perhaps the greatest quality-of-life benefits have been reported by parents/caregivers of very young children with T1DM.[25] Prior to using a closed-loop system caregivers report daily challenges of keeping their child's glucose within the target range, requiring constant vigilance and a state of alert which negatively impacts on sleep, relationships with others and employment. With closed-loop, caregivers felt the system was able to keep their child's glucose in range after meals, to lessen glucose fluctuations and to offer a level of input beyond their own capabilities. In addition to clinical benefits and reduced workload, caregivers reported sleeping much better, less anxiety and worry about their child's safety knowing that the system would help keep glucose in range, and increased confidence when their child was in the care of others at nursery or school. Caregivers described getting part of their lives back, being able to resume normal activities and some even considered returning to full-time employment.

Quality-of-life benefits also extended to the child, with parents noticing improved mood and concentration in their child and less disrupted sleep due to the more stable glucose. Using the closed-loop system allowed their child to feel more normal, as conversations and activities no longer focused on diabetes management, and parents had more time and energy for everyday family activities, a benefit which also impacted on siblings. People were more willing to invite their child to events, including parties.

Key messages

- Hybrid closed-loop systems are associated with significant improvements in glycaemic control in people living with T1DM
- Evidence is emerging of important quality of life benefits for hybrid closed-loop system users and their families
- Healthcare providers can be slow to embrace closed-loop technologies due to clinical inertia and a lack of time for training. This plays a critical role in affecting access to closed-loop technology in the UK

Call for action

There are clear benefits of hybrid closed-loop technology on both glycaemic outcomes and quality of life in all populations with T1DM. Perhaps the population with the greatest need is very young children, who have the highest variability of day-to-day insulin requirements and the greatest burden of diabetes management for caregivers each day.[6,26]

Despite these widely reported and important benefits, healthcare providers can be slow to embrace closed-loop technologies.[27,28] Clinical inertia, work overload and regional variability play critical roles in affecting access to closed-loop technology. Manufacturers and diabetes technology leaders can help to mitigate this by supporting training and creating accessible resources for users and healthcare professionals, including those available online (https://abcd.care/dtn/education).

The National Institute for Health and Care Excellence (NICE) are undertaking a Multiple Technology Appraisal process on closed-loop technologies which will report in early 2023. NHS England sponsored a pilot of the use of closed closed-loop technologies in 2021-2022;[30] the Association of British Clinical Diabetologists (ABCD) Diabetes Technology Network (DTN) gathered the data from this,[31] and undertook an analysis of the outcomes, and this analysis has been submitted to NICE to help with the appraisal. The NHS is legally obliged to fund and resource medicines and treatments recommended by NICE's Technology Appraisals. It is anticipated that this will transform and facilitate equitable access to closed-loop technology and routine clinical care for people living with T1DM in the UK.

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Gazing into the future – what will the next 100 years of diabetes innovation look like? A perspective from industry

ZOE CHOLEWA

Br J Diabetes 2022;**22**(Supp1):S90-S91

Key words: Real time Continuous Glucose Monitoring, CGM, rt-CGM, Dexcom,

Great leaps of understanding and improvement have been made in the past 100 years (Figure 1), but according to the 2019-2020 national diabetes audit, fewer than 15% of people with diabetes are able to achieve target glucose levels.[1]

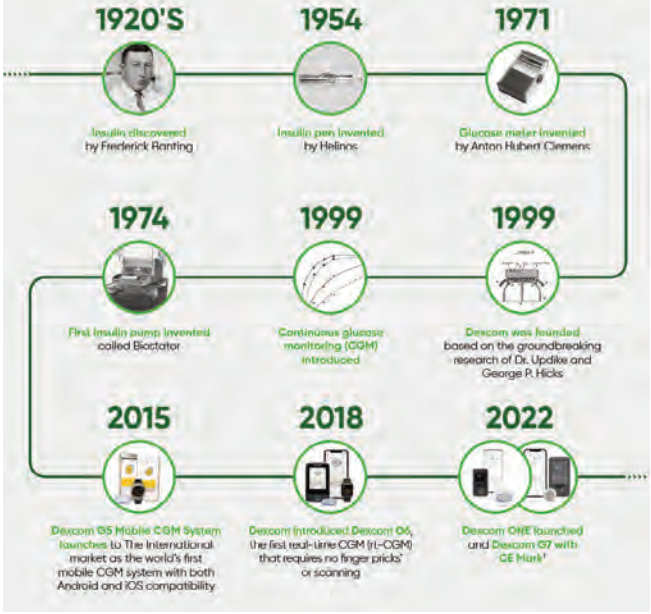
Fortunately, a new standard of care emerged with real-time continuous glucose monitoring (rt-CGM) from Dexcom (Figure 2). Dexcom rt-CGM works continuously to measure glucose levels without intervention and helps to minimise guesswork derived from making diabetes treatment decisions based on a blood glucose meter (BGM) reading alone - with no fingerpricks or scanning.

NICE now recommends that people with T1DM are offered a choice of glucose sensor, including rt-CGM.[3,4] For people with insulin-treated T2DM, NICE now recommends that rt-CGM can be considered as an alternative to intermittent scanning.[5]

Dexcom is increasing access to rt-CGM for people with diabetes with a range of products (Figure 3).

Ultimately, the aim is to offer continuity and reliability for

Figure 1. History of technology timeline.



If your glucose alerts and reading from the CGM system do not match symptoms or expectations, please use a blood glucose monitor to make diabetes treatment decisions

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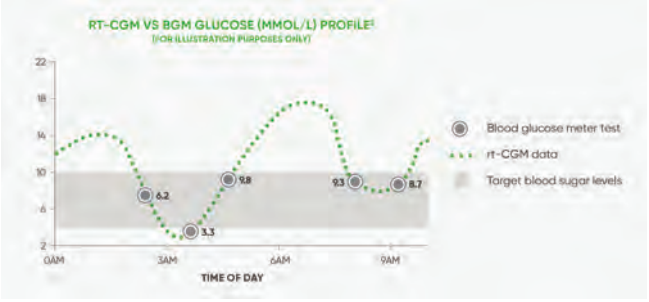
Figure 2. Real-time CGM versus BGM reading profile.[2]



Simon-Kucher & Partners. HCP discussions Nov 2021

Figure 3. The Dexcom portfolio of real-time CGM systems

† For a list of compatible smart devices, please visit www.dexcom.com/compatibility. Smart device required to display readings on watch.
‡ CE2797.
§ Compatible insulin-delivery device sold separately.

people with diabetes while delivering clinical and quality-of-life outcomes with lower HbA_{1c}, decreased episodes of hypoglycaemia,[6] and more efficient clinic visits. The future is looking very exciting for diabetes care. Where will the next 100 years take us?

Conflict of interest None.
Funding None.

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Key messages

- NICE now recommends that people with T1DM are offered a choice of glucose sensor, including rt-CGM.[3,4]
- For people with insulin-treated T2DM, NICE now recommends that rt-CGM can be considered as an alternative to intermittent scanning.[5]
- Dexcom is increasing access to rt-CGM for people with diabetes with a range of products, Dexcom ONE, Dexcom G6 and Dexcom G7.

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Gazing into the future. The next 100 years: the Medtronic perspective

DAVID TURNER

Br J Diabetes 2022;**22**(Supp1):S92

Key words: MiniMed™ 780G Hybrid closed loop, SMART MDI System, Extended Wear Infusion Set

While it is difficult to predict the next 100 years of development, the current Medtronic product innovation pipeline is changing the lives of people with diabetes.

The MiniMed™ 780G system with Guardian™ 4 sensor and extended wear infusion set is the advanced hybrid closed-loop pump system currently available in the UK from Medtronic. It has been clinically proven to achieve >70% time in range and to lower HbA_{1c} levels in people with diabetes. Medtronic continues to innovate in the hybrid closed-loop and insulin pump and sensor area. The company is developing new sensor technology and personalised closed-loop options for future patients.

Medtronic recognises that not all people with diabetes will want to use an insulin pump and therefore is launching a Smart MDI system for people looking for more from MDI therapy. The Smart MDI system brings together a collection of tools that provides real-time insights and comprehensive reports. These make it easier for people with diabetes to manage life on multiple daily injections. The system combines predictive glucose management with the Guardian™ 4 sensor, with no finger pricks and personalised high and low alerts up to 60 minutes in advance. Personalised insulin management with the inpen device allows informed insulin dosing with integrated real-time glucose data trends and shareable insight reports.

The Medtronic extended-wear infusion set is due to launch in the UK soon. It is focused on improving user experience. It is the only infusion set approved for longer wear (with a wear twice as long as standard infusion sets) without compromising comfort, safety or insulin delivery. This new set will also reduce traditional infusion set plastic waste by half.

Conflict of interest Employed by Medtronic Ltd.
Funding None.

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Key messages

- Hybrid closed loop with the MiniMed™ 780G system is clinically proven to deliver a time in range of >70% and lower HbA_{1c} in people with Type 1 diabetes
- Smart MDI system from Medtronic offers more to MDI patients by combing predictive glucose management with the Guardian™ 4 Sensor and personalised insulin management with the inpen insulin delivery device and app.
- The extended wear infusion set due to launch in the UK soon will double length of wear of traditional infusion sets without compromising comfort, safety or insulin delivery.

Insulet's technology perspective: past, present and future

SEVERINE LIABAT

Br J Diabetes 2022;**22**(Supp1):S93-S94

Key words: automated insulin delivery, tubeless insulin pump therapy, innovation

At Insulet, we are driven by a mission to improve the lives of people living with diabetes through simplicity and flexibility in the management of insulin delivery. It started in 2000 when John Brooks, the father of a three-year-old boy who had just been diagnosed with diabetes, was not happy with the existing technological solutions to manage his son's diabetes.[1] He believed there must be a better way. Connecting with engineers from the life sciences industry, together they developed the first on-body, tubeless insulin pump and the Omnipod® Insulin Management System was born.

Reducing the burden of diabetes is at the core of everything we do. We are continuously innovating and updating the tubeless delivery platform to make it smaller, lighter and more intuitive, leading us to the version called the Omnipod DASH® Insulin Management System. When designing our products, we listen to and integrate the input from hundreds of users who provide important insights into what will improve their experience and meet their specific needs.[2] Driven to bring consumer-centric technology to more people with diabetes, Insulet expanded with international distribution outside the United States in 2010 and direct international distribution in 2018.

The Omnipod Insulin Management System has been studied in large real-world and controlled studies, which demonstrated reductions in HbA_{1c}, DKA and severe hypoglycemia, and improvements in time in range (TIR) and quality of life for people with diabetes. Beneficial effects on HbA_{1c} levels or severe hypoglycaemia are seen in populations with different starting levels of control, in people were previously using multiple daily injections (MDI) or other insulin pumps, and across all age groups.[3-9]

In our quest to provide more simplicity and freedom, we are now introducing the next generation of Omnipod products: an on-body, tubeless automated insulin delivery system, the Omnipod® 5 Automated Insulin Delivery System. The system consists of three components: 1) an Omnipod 5 App (on a handheld controller or compatible smartphone depending on the country); 2) a wearable Pod that includes an algorithm, communicating via Bluetooth® wireless technology with; 3) the Dexcom G6 continuous glucose monitor (CGM). The algorithm automatically adjusts insulin delivery using a set target glucose, based on current and predicted glucose values, as well as historical insulin dosage values. The system is FDA-cleared and CE-marked, currently commercialised in the USA and pending commercialisation in Europe in 2023.

Key messages

- Reducing the burden of diabetes is the driver for innovation at Insulet
- Tubeless insulin delivery is clinically proven to be safe and effective
- Innovation at Insulet will drive more simplicity and freedom for people with diabetes

The Omnipod 5 System was shown to be safe and effective in pivotal trials in subjects ranging in age from 2 to 70 years, with observed improvements in HbA_{1c} and TIR and minimal time below range (TBR). [10,11] Improvements in HbA_{1c} were seen across all age groups regardless of baseline HbA_{1c} .[10,11] Randomised controlled clinical trials are underway to provide additional evidence supporting the benefits of the system.

We are excited about what the future holds as this field is evolving so rapidly. We will continue innovating to drive more simplicity. We will do that through multiple iterations of the Omnipod 5 System, with integration with consumer technology, with artificial intelligence eliminating the number of interactions the user must have with their technology, and becoming even more intuitive. We want to take away the burden as much as possible, so people can focus more on the things they love and less on managing their diabetes.

Conflict of interest Severine Liabat is an employee of Insulet International Ltd
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Gazing into the future: the next 100 years of training from the YDEF perspective

GIULIA ARGENTESI

Br J Diabetes 2022;**22**(Supp1):S95

Key words: YDEF, The future of training, specialist training

The Young Diabetes and Endocrine Forum (YDEF) was founded a little over 20 years ago by a group of dynamic and enthusiastic registrars. Now, in their consultant adventures, they continue to lead us fearlessly within this field. They built and have left a legacy within this organisation based on three key principles: education, support and, most importantly, advocacy for trainees. Over the last year I have had the immense privilege to chair YDEF. My committee is composed of a wonderful diverse group of diabetes and endocrine trainees from all over the country. Some of us have a penchant for research (most of us are currently out of programme doing PhDs) but the commitment to YDEF and supporting trainees and training is unwavering.

This year has been a momentous year with the centenary of the discovery of insulin. I was asked by ABCD to share some thoughts on what the next 100 years of training might look like. The next 100 years seems too far off to contemplate so I thought I would focus on the next few years.

Progress in training is happening day to day and the future of training looks bright. However, there are some small points for improvement and some ideas about what we would like to see the shape of training to be.

Influence of the pandemic

As diabetes and endocrinology (D and E) trainees we have had a difficult two years. D and E contributed one third of the general internal medicine (GIM) acute medicine workforce during the pandemic. This is something to be immensely proud of this but it has naturally impacted training. Answers to a survey conducted by YDEF revealed that 51% of trainees feel GIM is an integral part of D and E training but, sadly, that 81% of trainees believe that GIM took them away from speciality. It is essential to strive for structured protected GIM-free time and to ensure this is equal for all trainees in all deaneries.

YDEF have been fortunate enough to sit on the specialist advisory committee (SAC) at the Royal College of Physicians for Diabetes and Endocrinology. During our time on the SAC, we have gained real insight into the care and thoughtfulness taken by training programme directors in shaping the next generation of diabetologists and endocrinologists. In the YDEF survey conducted during the pandemic, 95% of trainees felt tertiary centre experience was important in their training. YDEF agree. With the introduction of internal medicine training (IMT), concerns were raised that tertiary centre experience would be removed from senior trainees to accommodate IMT. Whilst this has been encountered in some centres, we have also found in some hospitals they have doctors in speciality training, allowing trainees to go to specialist clinics and MDTs whilst the general medical wards are covered. We must not become complacent and allow changes in other training pathways to take precedence over our own.

Key messages

- Improvements in training ongoing but there is still work to be done.
- Frontline and GIM work should not come before D and E training but alongside.
- Support for trainees is imperative and more is to be done for mental health wellbeing.
- Equal opportunities should be given throughout the whole specialty.

Health technology and diabetes

Our specialty is a keen proponent of health technology within diabetes. With the rise in digitalisation of the NHS and patient consultations, our training needs to rise to the challenge and prepare us to adapt our skills for diagnosis and management in the digital forum as well as becoming familiar with novel health technology in diabetes.

Trainees are so very important to us at YDEF and we would like to see support for trainees at difficult times improve. Over the next few years, with ongoing geopolitical uncertainty and strain upon our health services, mental health problems will almost certainly continue to rise. We must ensure that we work collectively to look after one another.

Finally, at YDEF representation matters. As training continues we must ensure that opportunities of professional development are offered equally to all trainees.

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Conflict of interest None.
Funding None.

100 years of insulin; 50 years of diabetic life*

MAGGIE LOUGHRAN

Br J Diabetes 2022;**22**(Supp1):S96-S98

Key words: patient experience, 50 years, type 1 diabetes, living with diabetes

> *'With insulin the stone was rolled away and diabetes became about the quality of life rather than the avoidance of death.'* Bliss M. *The Discovery of Insulin*, (utoronto press.com, Toronto, 2021.)

A juvenile-onset type 1 insulin-dependent diabetic living for 50 years only because of and in spite of injecting the purified hormone insulin, living with diabetes means existing on a battlefield for quality of life while coping with the avoidance of death.

The insidious nature of diabetes changes and threatens in a deteriorating constant state of flux. Diabetes is unpredictable and remains an insurmountable foe.

I recall vividly what still is assumed to be the beginning of my life with diabetes. In fact, it marks the first time my life was saved by using injected insulin. Assumptions and guesses become part of life for a diabetic child, adult and healthcare professional too when faced with diabetes. Despite the enormously negative impact of incorrectly made judgements by all parties for the assumed reasons behind diabetic disease progression, diabetes and its treatments remain an inexact science.

Following an interminable bout of flu, a determined set of two worried parents took a pale, thin and fainting, thirsty and lethargic 10-year-old daughter on a third repeat visit to their family doctor. Contrary to the excess of loving care and extra glasses of glucose-laden cellophane-wrapped Lucozade, sold solely in a chemist and given to build her strength, their child was still losing weight. It was 1972, and I was that child.

This is a brief outline of my story

Over a fizzing tablet in a test tube in a kit similar to one that would later adorn, like a mini laboratory, our family bathroom windowsill for years to follow, the doctor pronounced in hushed tones in case I overheard (which I did) to my shocked parents that I was 'a diabetic'.

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They were instructed to take me straight to hospital. Mustering all that 10-year-old child's polite manners I responded unasked with a flat, "No thank you. I don't want to be a diabetic." The doctor ignored me. It was not the last communication with a health professional that would be ignored, difficult, mismatched or just not great.

First hospital admission

Torn from my family at the doors of the then modern ward 1 in East Birmingham Hospital, I was reluctantly left – frightened distressed and very unwell – in the care of my first diabetes hero. Many incredibly talented and dedicated professionals would, fortunately for me, follow in the wake of this particular male nurse.

Few would know it was that male nurse who taught me to take control, to question and understand, and to insist on involving myself in decisions about my health. Performing or directing my own care wherever possible. A shy well-behaved child, I had an innate independent streak and from a very early age my favoured phrase was 'Me do it!'

The second morning in hospital at 6 a.m. my parents were not allowed to see me straight away. They were kept waiting in the chairs at one end of the corridor while another soon-to-be-ritualistic fizzing tablet test was done in the urine-smelling sluice room. Returning to bed with a nurse I'd never met, accompanied by a larger than necessary glass and metal syringe in a blue and white enamel tray (amusingly those now used for chips in trendy bars), I was less than impressed. My parents appeared when permitted in my room, just in time to see the needle being pushed into my tightly gripped, unwilling but acquiescent arm. This syringe was daily filled up with an opaque fluid from a little dense rubber-topped bottle which was placed upside down on top of those thick needles and helped to blunt them. This equipment I was to continue to use at home. It would in a matter of a few months be responsible for removing muscle from my thin shoestring thighs by inflicting fat atrophy, huge craters of well...of just 'missing'.

It was that same male nurse who, after that horrific first experience of an insulin injection, encouraged me to take the syringe off my visibly nervous and suffering mother at 6 a.m. on my second week in hospital. My mum, learning to hurt her own child for the first time ever, looking pale and perceptibly shaking, was overtaken by her 10-year-old's hand relieving her of that needle and perform-

* The editors deliberately refrained from editing text because whilst some health beliefs referred to may not concur with current scientific understanding it is important for readers to hear an authentic account of the experiences and thoughts of someone who has lived in the shadow of diabetes.

ing the injection herself. It hurt a lot less. In my head was a vision of adult independence and freedom. I had already understood this was for life. Determined self-care began.

The fizzing of Clinitest colour-changing tablets and later Clinistix testing strips was the only inaccurate and imperfect guide to judge the amount of insulin required in those once-a-day insulin injections. A doctor was required to adjust those large doses. Autonomy and understanding were neither requested nor required from a child. What followed was a true rollercoaster.

Standard measures of doses of insulin given once only daily at 6 a.m. were injected into my arm and thighs; that load of insulin required a huge carbohydrate intake for me to stay upright. I did not stay conscious long in any day that first week. I have scant recollection as a result. Doses crept downwards but hypoglycaemic attacks increased.

Discharge home

I was spewed out of hospital and found a house full of strangely holed and water-filled oranges used to try out injecting technique. This amused me, as by then I routinely administered my own insulin injections unless very unwell.

Our kitchen was ruled by a tiny weighing scale upon which sections of Nimble white sliced bread or half a semi sweet biscuit were weighed to the correct carbohydrate allowance. What I ate was dictated by 'anorexic looking' dieticians who controlled my restricted diet selected from lists of a tiny number of incorrectly named 'good' and 'bad' foods. 'Diets' were turned rapidly on their heads by new fads and theories. A straitjacket nowadays alien to the majority of young people with diabetes, adjusting flexible treatment to more accurately responsive data to fit their socially acceptable lives.

Attaining level blood sugars despite concerted efforts and adherence remained throughout the years almost ethereal, and sadly frequently short-lived, events. Largely unsupported other than through a once-weekly hospital clinic visit with interminable waits, always on Thursdays so I missed my clubs after school, my parents juggled full-time work and the busy demands of family life with four children just for three minutes each week with a consultant or registrar. Difficult to answer questions about why control was so elusive for us to achieve were met with a dismissive, 'We will see you again next week.'

Transferring from primary to secondary school after one year of diabetes, I was the only type 1 diabetic at my secondary school of 1,000 pupils and staff. There were only three diagnosed type 1 diabetics on insulin when I left in 1979.

Soon came disposable needles and then disposable syringes, then combinations of attached needle and syringe. In six months, fat atrophy improved until in 1979 the government decided that those syringes and needles 'if preferred' should now be purchased by people with diabetes. Prescriptions from the diabetic clinic were grudgingly provided to cater for my need for disposable needles. Gladly I let go of the glass and metal syringe; no longer did I need to spend time sterilising syringes and blunt metal-based needles in stinking methylated spirits after boiling them in an enamel saucepan.

Tiny square swabs made stinging red rashes a norm of course and still the peaks and deep troughs remained. Insulin now sat on a shelf in the fridge door in a repurposed Tupperware box. Joined by Lente, a long-acting insulin, two injections daily began. A steady baseline was the aim, and severe hypos kicked back in as doses and evening snacks were adjusted to suit.

Synthetic insulins arrived, the holy grail at the time in the name of added control and avoiding complications. For me and many others this caused or coincided with a loss of symptoms of hypoglycaemic attacks. Another heroic figure of a most uniquely knowledgeable consultant began the use of an old-fashioned bovine-derived insulin, saving my life and facilitating independent living.

Complications

From those early and continually erratic blood sugars complications of diabetes loomed. They duly arrived in spite of consistent monitoring and continual hospital care. Diabetic retinopathy was diagnosed when I was aged 21, a few weeks into a teacher training year.

Due in part to the severe overuse of very early laser treatment by inexperienced hands on such a relatively young eye I developed burning and a retinal detachment. Obtaining a consultation urgently at Moorfields eye hospital I underwent a vitrectomy and reattachment. Again dedicated staff and technological advances, saved and continue to preserve partial sight in a damaged right eye after a subretinal blister just 'happened'.

I was due to start teaching later that year. I did so by adapting, as diabetes had amply taught me to do, to the situation and this proved key to success. Blood sugar testing methods improved; control and dietary freedom advanced together. Things had begun to take on a feeling of rapid advancement. Since I was included in early trials of a 'James Bond' kit containing a stainless steel injection pen hiding a needle and insulin cartridge in a suave black case and a slim black designer digital blood test pen, I enjoyed flexible injections and meals. A stylish forerunner to the plastic injection pens used today.

Diabetes produces many paradoxes. Since insulin has been used as a lifesaving therapy rather than leading to a that elusive 'cure', its use has resulted in an explosion in the number of individuals suffering long-term complications. Any list of 'so called' diabetic complications covers most medical specialities. After 50 years I am able to tick off involvement in too many hospital departments.

Early childhood and continuing battles for 'control' coupled with many adverse reactions to synthetic insulin, possibly too that bovine-derived insulin, have all taken their toll on my physiological makeup. As has an erratic blood pressure. Is this known as insulin sensitivity? It is more correctly termed all part of suffering from diabetes. Auto-immune disease continues to attack multiple areas of my ailing systems, insidiously silent and eventually fatal.

After 27 years of insulin injecting, I believe that living a packed and high quality adventurous interdependent life was encouraged by having to live with diabetes and realising the insecurity of life. Whilst working and living in the Caribbean and travelling globally, the unpredicted rapid onset of what is presumed, but not to date

Key messages

- A life of difficulty and disability caused by type 1 diabetes which developed 50 years ago at the age of 10 has been treated with a functioning pancreatic and kidney transplant
- A life with type 1 diabetes can be demanding but with resilience and good care it can be lived to the full
- The keystone of effective diabetes care is shared knowledge and good communication with supportive professionals willing to listen and take account of each person's individual concerns and health beliefs

fully proven, to be diabetes-induced end-stage kidney failure was diagnosed in a routine hospital blood test.

Transplants: transformative treatment

Chronic kidney disease and end-stage kidney failure has now been treated for 23 eventful years, which have included dialysis and a stroke, heart surgery, vascular issues and bone disease. I received a functioning kidney and pancreas transplant in 2000, and this has transformed my diabetes and my life.

Living now for 23 years with diabetes induced kidney failure has meant 23 years of the worst of times and the best of times. A story too long to relate here. The worsening side-effects of diabetic damage, some of which are listed, have to an extent halted in their downward destructive spirals but have been replaced by those produced by 21 years of the immunosuppressive therapy needed to preserve a working double transplant. Freedom from that purified alien insulin has been miraculous although an oversensitive immune system persists.

Gazing into the future now, as Albert Camus states in an apt but roughly translated quotation: *"We must 'get on' in an attitude of constant doubt, with provisional commitment only, and a healthy questioning of authority."*

With heartfelt thanks to all who got me here, particularly my family and organ donor who still strive to keep me well.

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What does the next 100 years hold? The perspective of a patient with T1DM

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Key words: Future, speculation, imagination, making research real is hard

Introduction

Though we have come a long way in the treatment of type 1 diabetes (T1DM) since 1922, in many senses we have not come far at all. In 1922, we had the very first insulin, and now we are on the verge of wider access to automated insulin delivery systems that can detect glucose levels and adjust insulin delivery, and automated therapies in combination. However, we have not come far enough.

A multitude of insulins are available now but there remains a significant problem since many people are unable to access them. This may be because the insulins are not available in the country in which they live, but perhaps even more so because of their cost. I would hope that the next 100 years brings much greater and easier access to treatments for T1DM.

Other than improved access to life-saving treatments, what else might we expect over the next 100 years? I'm going to look at the near term, mid-term and long term, and discuss what we might see.

The near term – making life easier

The near term is all about the technologies available now and the delivery of today's research projects into the hands of end users. It's also about improvements to interoperability in technology, instead of the "walled gardens" that we users currently face. We will see the continued development of fast-acting, and maybe targeted, insulins plus adjunct therapies that making living with T1DMeasier. Automated insulin delivery systems and algorithms will continue to be developed and made available to aid end-user decision-making and reduce the amount of effort required to live with T1DM. I'm not sure how long this period will last, but I imagine that it will be about 10 to 20 years.

The medium term – making life much easier

The key to managing T1DM does not lie in technology, however. It would be far more efficient to use biological means to manage the condition. I believe that this is the direction of travel for treatments in the medium term.

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Biotechnologies that are currently in development include provision of a gluco-responsive insulin (Smart insulin by another name) that can be injected once per month, or embedded capsules containing insulin-producing cells that are protected against the immune system. We can expect to see more of biotechnologies such as these in the medium term. We may also see broader rollout of vaccinations that extend the period before which susceptible individuals develop T1DM, and perhaps more ways of stopping the body attacking the beta cells. None of this, however, is a cure.

The longer term – "curing" type 1 diabetes?

Here, we are really gazing into the future. But let's speculate.

Extrapolating from the use of vaccines to prevent the immune system attacking the beta cells, might be possible to look at replacing or regrowing beta cells? Maybe techniques like Crispr gene editing, gene therapy and stem cell therapy could be brought into play to rebuild the missing hormone production typical of T1DM.

A cure would not be limited to stopping the autoimmune attack and replacing lost functions. It would also potentially require reversing damage done over the lifetime of someone with T1DM. It is not clear whether restoring beta cell function would enable this.

Ultimately, only stopping type 1 and repairing the damage done could be called a cure.

Final thoughts

If we have learned one thing from the journey of the past 100 years, it is that everything takes longer than we expect to arrive. Research progresses slowly and advances are hard to achieve.

Treatments come and go, but they are only of value if those who need them are able to access them and know how to use them. Those are the critical aspects of technological solutions to biological problems.

Key messages

Ultimately, a cure is:

- Hard, when we don't yet know the cause
- Not just replacing beta cells
- Not just prevention
- More than 10 years away…

Conflict of interest None.
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Gazing into the future – the next 100 years. Perspectives from diabetologists

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Key words: insulin centenary, next 100 years of diabetes, diabetes, immunotherapy in type 1 diabetes, diabetes technology, worldwide diabesity pandemic, dual hormone agonists, EndoBarrier, bariatric surgery

Gazing into the future, into the next 100 years, to consider the possibilities of what might emerge to improve the management of diabetes is a challenging task. Nevertheless, we thought that diabetologists should consider the matter alongside the contributions from industry, people living with diabetes and the outgoing YDEF chair. The task is shared here by a very senior diabetologist (REJR, #Iwasthere) who was present at the inaugural meeting of ABCD in 1997,[1] a younger but well established diabetologist who founded the ABCD Diabetes Technology Network (EGW),[2] and a trainee diabetologist, ABCD research fellow and current chair of Young Diabetologists and Endocrinologists Forum (TSJC).[3]

Type 1 diabetes

Considering the rate at which science, medicine and technology are all advancing, there are clues from how things are now, as presented in this supplement, to where management of type 1 diabetes (T1DM) might be 10, 20 and 30 years from now and beyond. There seems to be a strong possibility, indeed likelihood, that an immunotherapeutic solution will emerge that will stop T1DM occurring, as the progress outlined by Colin Dayan evolves to safer and safer medicines that are more and more effective.[4] Alongside this, the identification of high-risk individuals is likely to become increasingly accurate as our understanding of the immunology also improves. In the meantime, and for any who do not respond to immunological therapies or who are not detected in time, closed-loop systems are also likely to improve in safety and efficacy in our extreme technological age,[5,6] with the hybrid closed loop replaced by the fully closed loop. It may be that future ultra-effective technology will involve dual-hormone fully closed loops,[7] and it is not impossible that safe and effective devices will be placed in the abdomen, in the portal system, to emulate natural physiology more closely. It is also possible that cell biology will advance to the stage where pancreatic islets that are not immunogenic to the patient can be grown in the laboratory and implanted, along the lines of current islet cell transplantation techniques.[8] The work described by Kevin Docherty concerning reprogramming pancreatic tissue might also advance considerably as medical science continually moves forward.[9] As the science of cell engineering continues to progress, there may be solutions to the abnormalities of T1DM that we cannot even imagine at this time.

Type 2 diabetes

We are in a worldwide pandemic of diabetes and obesity which seems set to worsen.[10] We can but hope that as the decades pass of the next hundred years, improving equality of living standards worldwide, abolition of poverty, universal education, improving food quality and understanding about healthy eating and lifestyle will, for the first time since the IDF started measuring, slow down the pandemic. In the meantime, we know from the ground-breaking work outlined by Roy Taylor in this supplement,[11] that we now have low-calorie diet programmes that can reverse totally the metabolic abnormalities associated with type 2 diabetes (T2DM) if applied early in the course of the disease. With regard to medications, GLP-1 receptor agonists have been increasing in effectiveness in terms of reducing weight and improving the metabolic abnormalities of T2DM,[12] and it seems probable that this trend will continue. It is already clear that tirzepatide, which binds to both the GLP-1 and GIP receptors, will soon be available to prescribe; it is an order of magnitude more effective than current GLP-1 receptor agonists, with commentators stating that the impact of tirzepatide is equivalent to that of bariatric surgery.[12] It seems likely that, with the passage of time, medical science will improve further in its understanding of the factors involved in appetite control and that increasingly effective medications will emerge. For those who continue to struggle with obesity and sub-optimal glycaemic control despite maximised medications, it seems likely that increasingly safe and effective endoscopically applied devices will emerge, learning from the already established effectiveness of EndoBarrier.[13] Barbara McGowan in this supplement describes effectiveness of current surgical interventions,[14] and it is probable that these will become increasingly safe, effective, and available.

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Key messages

- 100 years is a long time. Medical science and technology are advancing at a great and accelerating pace, so the changes in diabetes management are likely to be considerable – and are difficult to predict beyond the next decade
- An immunotherapeutic solution to type 1 diabetes seems likely, obviating the need for insulin for most patients, with advanced technology as a back-up, utilising full closed-loop technology. Dual-hormone devices are likely, perhaps implanted in the abdomen, in the portal system, to be more physiological. Cell biological solutions are also likely to develop more and more
- In type 2 diabetes, we can but hope for worldwide improvements in living standards, food production and education to slow down the worldwide diabesity pandemic. Extensive roll out of low-calorie diet regimes to reverse early-onset type 2 diabetes is likely
- Medical science will probably increase further in its understanding of the factors involved in appetite control and increasingly effective medications will likely emerge, the process starting with further development of agents which bind to both the GLP-1 and GIP receptors. It is also likely that increasingly safe and effective endoscopically applied devices will emerge, and surgical interventions will improve and become more widely available

Other types of diabetes

Precision medicine may also hold the key to optimising diabetes in future. T1DM and T2DM may become things of the past due to the recognised significant heterogeneity between people with the same type of diabetes, building on the work of such as Andrew Hattersley and Emma Ahlqvist.[15,16] Recognition of the various underlying genetics, immunology and phenotypic features may allow us to personalise the approach to managing diabetes of all types and improve the quality of life of all people with diabetes.

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