

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

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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.

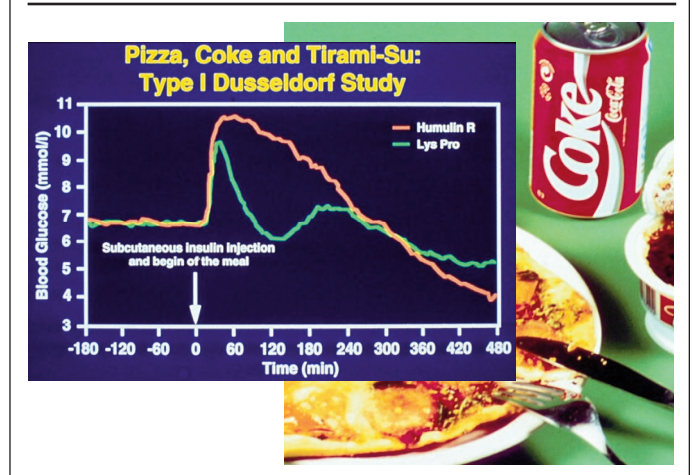
It was not just the type of insulin that was causing uncertainties in the 1980s. We also had to confront a change in insulin strength as a result of increasing confusion over marks on the syringe and units of insulin prescribed. Misunderstanding of these was leading to mishaps and the potential hazard 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

Figure 1. Düsseldorf Carbohydrate rich diet study (1996)

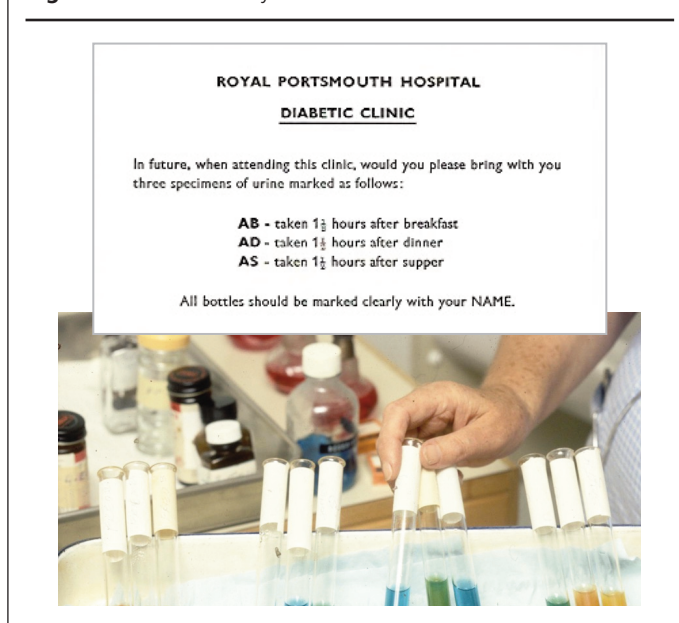


injection of insulin Lispro, blood glucose excursions after this meal were significantly lessened, with a 78% reduction under the blood glucose curve in comparison to human regular insulin.

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 Gargine'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 spoiled 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

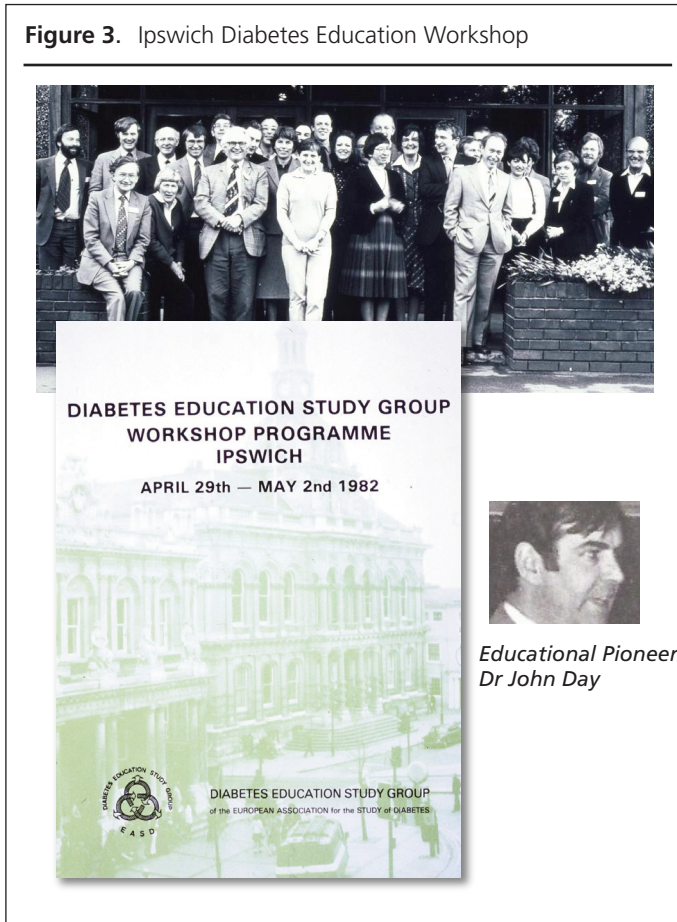
closely with glucose regulation over the red cell lifetime span of approximately 120 days. As a result of their studies, Anthony Cerami and colleagues (Rockefeller University) commented that "periodic monitoring of HbA_{1c} levels might provide a useful way of documenting the degree of control of glucose 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 the 1970s 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

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.

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