Evolution of diabetes care over half a century

Peter Watkins

Introduction

Patients with 'big stomachs, skin-and-bone necks, skull-like faces, feeble movements' were beginning to stir in desperate anticipation of the new insulin treatment. Dr Allen arrived as it was growing dark and in just a few words gave them hope: 'I think I have something for you'.[1] Soon afterwards, Elizabeth Hughes was to write of her insulin treatment: 'It is simply too wonderful for words, this stuff'.[1] That was in 1922, and so it is still today, on every occasion when an acutely ill type 1 diabetic patient starts insulin treatment. Dr RD Lawrence, while working in Florence in 1923, described his own experience:

> *I lost weight; got so weak that I couldn't walk upstairs and I would fall down; I got peripheral neuritis, and that wasn't good for doing medicine. And even my cigarettes, I couldn't get the matches out of the box. . .so when he* [Dr Harrison, biochemist at King's College Hospital] *cabled me and said 'I've got insulin – it works – come back quickly', I bundled into my car.*[2]

And so the medical specialty of diabetes was born, and during the 1920s, the earliest diabetic clinics – Wolverhampton and Liverpool, followed by King's College Hospital, London, under the direction of Lawrence – rapidly evolved in order to manage the use of the new insulin. Patient numbers and effective treatments have increased ever since.

Working in the diabetic clinic

The diabetic clinic was an early model for life-long management of a chronic disease, administered with the expertise of hospital specialist doctors. General practitioners almost universally referred all their diabetic patients to hospital and normally took little or no part in their care. Specialist nurses, introduced into diabetes care and education in Leicester during the 1950s, were to be found in very few centres, and their key role was not fully appreciated until the 1980s.

I was introduced to the diabetic clinic by Professor John Malins at the General Hospital Birmingham during the 1960s. Clinics were characteristically overcrowded and lacking in privacy, but the reassuring presence of the chief was visible and available to all, giving confidence to the vast number of patients passing through the outpatient halls. Confidence in their care was crucial, first in understanding and managing their own condition, and later guiding them through the inexorable progression of the many complications for which there were neither preventive nor therapeutic measures. This moved Malins to write in 1968 of the all-too-frequent need 'to ease the last years of those whose health is slowly failing which calls for all the resources of the general physician'.[3] It was in this environment that generations of registrars learned the clinical skills of the consultation, learned how to make clinical judgements and offer advice to those with failing health and an uncertain future – key skills for a lifetime in clinical practice, finely expressed even in 2006 by an Australian physician also working in an overcrowded diabetic clinic in Sydney.[4] Yet in the 1960s, amputations were rife, perinatal mortality was high, death in renal failure a terrible experience, and blindness in some patients with retinopathy inevitable. It was in these areas in particular that tremendous advances were made during the last decades of the 20th century.

Fetal survival in diabetic pregnancy

One of the triumphs in medicine during the 20th century was the improvement in outlook for diabetic pregnancies. More than 20 years after the introduction of insulin, perinatal mortality in Britain reported in 1949 was as high as 40%,[5] with still poorer results among unsupervised women. This terrible plight for diabetic women was widely known and many were discouraged from ever attempting to start a family. My strong impression was that many women with diabetes in that era were either childless or perhaps risked just one pregnancy. One of my patients, Mrs B-J, whose diabetes was diagnosed when she was ten years old in 1932, vividly described this tragic situation: 'I had heard many tales about

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the trauma of diabetics who had babies, and I made up my mind I would never have any, even if I did get married. . . Dr Pyke told me a few years ago that things have changed now'.[6] And indeed they have.

Dr Wilfred Oakley, diabetologist, and Sir John Peel, obstetrician, later joined by Dr David Pyke, started work together during the 1940s at King's College Hospital and began to set new standards for the management of diabetic pregnancies, eventually with dramatic results. They established team working in its best sense, developing a model now extending to clinical practice across many specialties including other areas of diabetes itself. The subsequent joint diabetes-obstetric clinics (later joined by paediatricians) enhanced clinical care and promoted research collaboration. They demonstrated that spontaneous unexplained intrauterine and neonatal deaths occurred in oversized babies allowed to proceed to full term. They therefore proposed delivery by caesarean section between the 36th and 38th week: as a result of their work, and that in many other centres, outcomes steadily improved. Subsequently, the benefits of tight diabetes control were recognised, reducing both the incidence of congenital malformations as well as perinatal mortality. To achieve the best results, women were for some years confined to hospital after the 32nd week until delivery, a practice only rescinded after the introduction of home blood glucose monitoring which enabled them to achieve good control at home.

Perinatal mortality plummeted decade by decade through the second half of the 20th century, falling dramatically from around 40% in the 1940s to 3.2% in 2003 and even below 2% in at least one centre.[7] The late Ivo Drury, distinguished Dublin physician writing in 1984, observed that the key to success has been that 'the physician and obstetrician should see the patient together at weekly intervals…. Successful application of this programme demands considerable commitment from both patient and caring team'.[8]

Gradual decline of diabetic nephropathy and blindness

'There is no way of preventing or modifying the progression of nephropathy,' wrote Malins in 1968.[3] The symptomless appearance of protein in the urine, the clinical hallmark of diabetic nephropathy, pointed to premature demise from renal failure (the fate of 20% of young type 1 diabetic patients diagnosed under 30 years of age). Most of those in advanced renal failure were also beset with other diabetic complications as well, including blindness. Renal replacement treatments, dialysis and transplantation were, during the early 1970s, still in their infancy, and because of limited resources, were generally withheld from those with diabetes because of the perceived poor prognosis for this group of patients.[9]

The turning point came with the demonstration by research groups in Denmark, followed by groups at Guy's Hospital, London, that vigorous antihypertensive treatment slowed the decline of glomerular filtration (Fig 1),[10] which for the first time could be stabilised, thus delaying, sometimes by several years, the development of renal failure. At the same time, there was a striking decrease in proteinuria, which on occasions disappeared altogether – never previously possible. Subsequently, two further developments enabled early prevention of this terrible complication, namely reduction of the predictive marker microalbuminuria by the use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers; and the effectiveness of tight diabetic control demonstrated by two remarkable studies in both type 1 diabetes (Diabetes Control and Complications Trial conducted in the USA),[11] and type 2 diabetes (the Oxford-based United Kingdom Prospective Diabetes Study.[12]

Taken together, these measures have resulted in a dramatic decrease in the incidence of nephropathy at least in type 1 diabetes (Fig 2).[13] While 50 years ago, end-stage renal disease

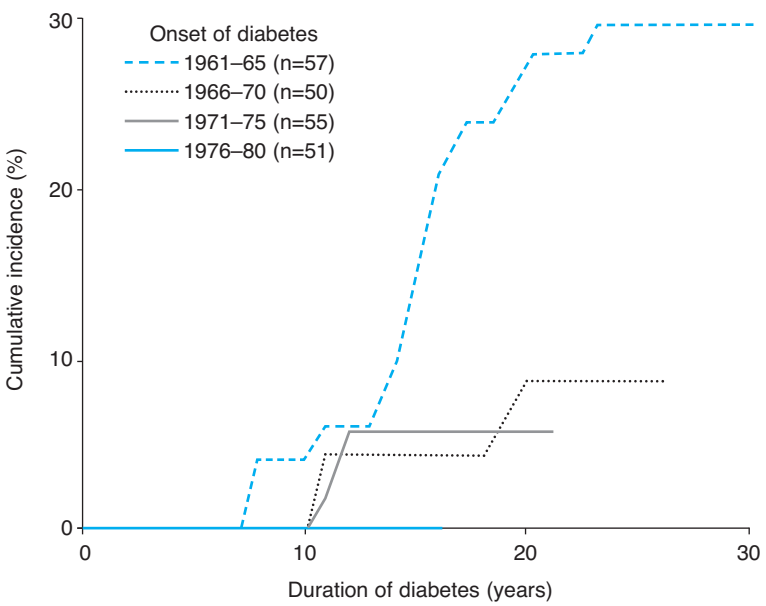

Fig 1. Cumulative incidence of persistant albuminuria among patients in whom insulin-dependent diabetes began before the age of fifteen, according to year of onset. [13]

developed in between 30–40% of these patients, recent observations have shown the cumulative prevalence after 30 years of diabetes to be just 7.7%.[14] Treatment with both dialysis and transplantation is now available and successful, albeit still somewhat less so than among the nondiabetic population.

During the same period, the potentially devastating impact of diabetic retinopathy has also diminished substantially. The empirical observation during the 1970s that photocoagulation might alter the course of retinopathy was indeed substantiated. Now, combined with tight control of both blood pressure and blood glucose, laser photocoagulation and vitrectomy have resulted in considerable preservation of vision, and reduction of blindness by up to one-third.[15]

Malins would have been both surprised and delighted that by the end of the 20th century, the onset of both nephropathy and retinopathy could be delayed, their course modified, and successful treatments had become available.

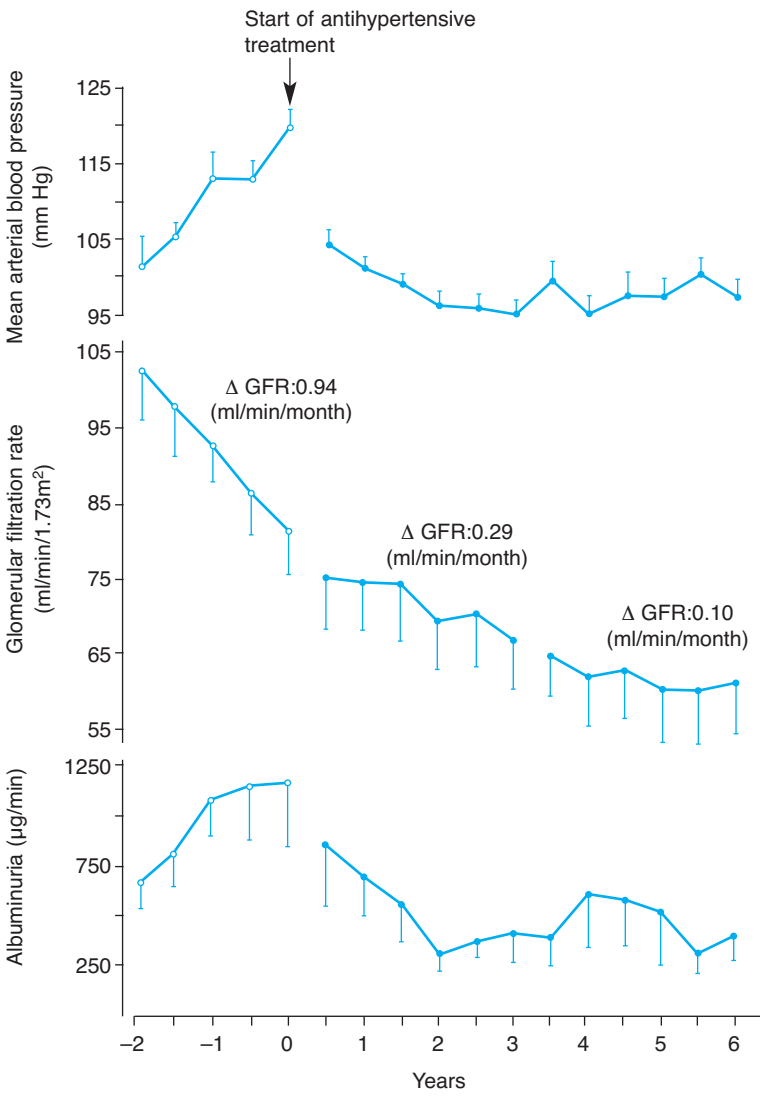

Fig 2. Antihypertensive treatment reduces the decline of glomerular filtration rate and the amount of proteinuria in patients with type 1 diabetes. With permission from the BMJ Publishing Group.[10]

The diabetic foot: halving the amputation rate

A common perception of the patient with diabetes was once that of a blind amputee. While successful measures to reduce blindness were introduced, amputations continued unabated in young and old alike, with little attention to the antecedent foot problems.

Collaborative work between physicians, podiatrists and orthopaedic surgeons has been the key to success. The first dedicated diabetic foot clinic was established at King's College Hospital in 1981, with the dramatic result that by 1986 the amputation rate had been halved,[16] setting a widely adopted gold standard. Similar achievements were subsequently reported from other centres. For example, by the year 2000, amputations among diabetic residents from a reservation community in Minnesota (USA), decreased from 29 to just 7 per thousand patient-years during a period of less than 20 years.[17] The observation that rampant and often persistent sepsis both prevented healing and preceded tissue necrosis strengthened the judicious use of antibiotics, which, combined with skilful podiatry and other measures to reduce pressure points, has resulted in complete healing, without a major amputation, in 80–90% of neuropathic foot lesions where the peripheral circulation was intact.[17,18] Yet the outcome in those with peripheral vascular disease remained less than ideal. Collaboration with a new generation of vascular surgeons using a host of impressive new technologies (duplex Doppler vascular studies, magnetic resonance angiograms, day-case angioplasty and distal bypass surgery) show much promise for the future.

Preventive measures using simple risk assessment techniques, the education of staff and patients, combined with availability of good podiatry and orthotic services, also significantly reduces serious foot lesions in diabetic patients. This remarkable revolution of care and prevention has taken place largely as a result of astute clinical observation combined with multidisciplinary team working during just a few years. It remains tragic and unnecessary that amputation rates remain high in many countries, with gross disparity between the best and the worst.[19] World Diabetes Day in 2005 for the first time focused on the diabetic foot with the recognition that, with appropriate organisation of care, limbs can be saved.

Advances in clinical care

The burden of diabetes for the individual has been substantially eased by the introduction of many new technologies. Glass syringes with often blunt, non disposable steel needles, kept in metal spirit-filled containers, were replaced first by disposable plastic syringes with fine silicone coated needles, followed by the very practical insulin 'pen'. This technology made possible the use of multiple daily injections, and was

further aided by continuous subcutaneous insulin infusion pumps enabling achievement of tight diabetic control. The introduction of highly purified insulins resulted in the disappearance of grossly disfiguring lipoatrophy at injection sites (Fig 3), and more recently structural modifications of the insulin molecule have provided insulins enabling improvement in blood glucose control while gradually reducing the development of disabling hypoglycaemia.

Urine testing, once requiring the patient or nurse to boil the sample in a test tube, and subsequently using clinitest tablets instead, has been largely replaced by home blood glucose monitoring, introduced during the 1970s. This ingenious technology both enhanced the independence and confidence of those with diabetes, substantially reducing the need for hospital admission, sometimes required for several weeks as in the last trimester of pregnancy.

The use of insulin in the treatment of diabetic ketoacidosis was revolutionised following the demonstration, during the early 1970s, of the effectiveness of small dose intravenous insulin infusions. Until then, huge doses of insulin were used empirically: standard texts in 1968 recommended regular doses of between 100 and 300 units.[3,20] Intravenous pump infusion of insulin at six units per hour subsequently became routine[21] despite objections by US clinicians who, at the 1975 International Diabetes Federation meeting, considered small dose insulin treatment to be unethical! The use of intravenous insulin infusions not only for diabetic ketoacidosis but also at times of illness or surgery has both simplified the care of diabetes and improved safety in these situations.

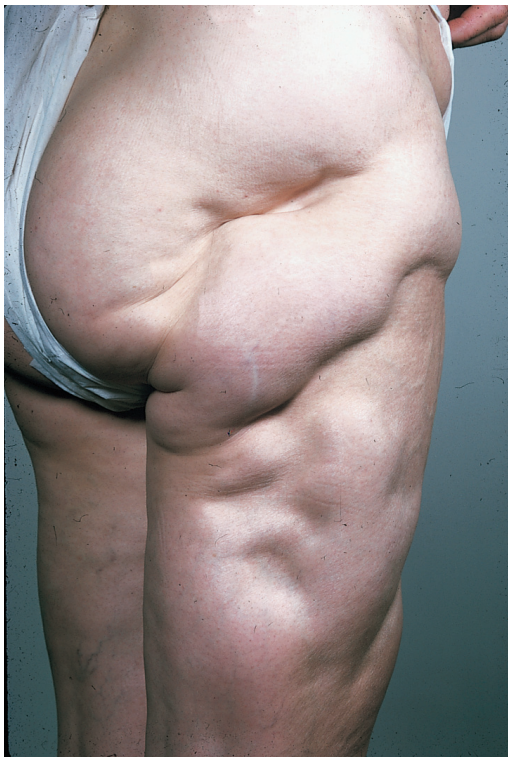

Fig 3. Disfiguring lipoatrophy occurring chiefly in women at insulin injection sites disappeared completely after the introduction of highly purified insulins.

Life without insulin injections

Life without insulin injections for patients with type 1 diabetes once seemed unachievable. The frustration of Mrs B-J was elegantly expressed:

> *I had started insulin only ten years after its discovery, but I remember meeting an elderly man in the upstairs waiting room by the pathology lab telling us that he had become diabetic before insulin, and how he thanked God for it every day. I know how he felt, but sadly his prophecy, that diabetes would be treated only like a cold in a further 10 years, was not fulfilled.*[6]

But today not entirely unfulfilled.

Tremendous advances in basic sciences, particularly immunology, cell biology and genetics have profoundly enhanced the understanding of diabetes and its causes. Successful islet transplantation now has the potential to eliminate the need for insulin injections for some type 1 diabetic patients whose lives are at risk because of limitations of conventional treatment. Eighty two per cent of transplanted patients have been reported to be free from the need for insulin injections after one year, a success still present in 50% of patients after three years.[22] The first successful islet transplants in the UK were performed at King's College Hospital, and have transformed the lives of patients not just because they may be injection free, but principally because they no longer suffer the disabling hypoglycaemic episodes which had afflicted them for long periods of time.

Withdrawal of insulin is also possible in some patients with dominantly inherited maturity onset diabetes of the young (MODY). Diagnostic precision of six genetic types of monogenic diabetes affecting 1–2% of all diabetic patients has made it possible to identify some groups who do not need insulin even when diabetes is diagnosed at a very early age.[23] The experience of withdrawal of insulin from some of these patients after as many as 30 years has been uniquely rewarding, causing at first perhaps some apprehension, and then the sense of delight and liberation from the constraints of their previous regimen.

On the other hand, it is disappointing to record that, despite the recognition during the 1970s that type 1 diabetes has an immune basis, and despite early hints of success, immunosuppression has failed to prevent its development. The search for this Holy Grail continues.

Conclusions

The astonishing improvement in the quality of life for those living with diabetes on the one hand, and in the outlook for diabetic pregnancies, nephropathy, retinopathy and foot problems on the other, has arisen first from meticulous clinical observation which both identified and then solved many of the problems. While advances in technology have played a major role, even more importantly, the seedlings for innovation have

been planted by constructive multidisciplinary teamwork in an environment pursuing high-quality clinical research backed by basic sciences and thus generating novel ideas. Centres of research excellence need to be preserved at all costs, particularly at this time of devolution of care into an environment where treatment is often protocol driven with the potential to stifle the generation of new ideas. Yet it is in the everyday routine clinics attended by so many people with diabetes where the detection of 'absorbing variations on an unchanging theme' provides the crucial seed for innovation.[24]

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References

1 Bliss M. *The discovery of insulin*. Edinburgh: Paul Harris Publishing, 1983.
2 Lawrence RD. Diabetes at King's. *King's College Hospital Gazette* 1961;40:220–5.
3 Malins J. *Clinical diabetes mellitus*. London: Eyre and Spottiswoode, 1968.
4 Campbell LV. Our patients remain with us: that is what experience means. *Lancet* 2006;367:1626–7.
5 Oakley WG, Peel JH. *XII British Congress of Obstetrics and Gynaecology*. London: Austral Press, 1949.
6 Watkins PJ. The personal story of Mrs B-J's diabetes. Quoted in: *ABC of diabetes*, 5th edn. London: BMJ Books, 2003.
7 Confidential enquiry into maternal and child health (CEMACH): pregnancy in women with Type 1 and Type 2 diabetes, 2002–03. www.cemach.org.uk
8 Drury MI. Diabetes in pregnancy – Matthews Duncan revisited. *Ir Med J Med Sci* 1984;153:144–51.
9 Winearls CG. In the wake of progress – ethical problems of renal failure treated by dialysis. *Clin Med* 2006;6:76–80.
10 Parving HH, Andersen AR, Smidt UM, Hommel E, Mathiesen ER, Svendsen PA. Effect of antihypertensive treatment on kidney function in diabetic nephropathy. *BMJ* 1987;294:1443–7.
11 Diabetes Control and Complications Research Group. The effect of diabetes on the development and progression of long-term complications in insulin dependent diabetes. *N Engl J Med* 1993;329:977–86.
12 United Kingdom Prospective Diabetes Study Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with Type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837–53.
13 Bojesting M, Arnqvist HJ, Hermansson G, Karlberg BE, Ludvigsson J. Declining incidence of nephropathy in insulin-dependent diabetes mellitus. *N Engl J Med* 1994;330:15–18.
14 Finne P, Reunanen A, Stenman S, Groop PH, Gronhagen-Riska C. Incidence of end-stage renal disease in patients with type 1 diabetes. *JAMA* 2005;294:1782–87.
15 Backlund LB, Algvere PV, Rosenqvist U. New blindness in diabetes reduced by more than one-third in Stockholm County. *Diab Med* 1997;14:732–40.
16 Edmonds ME, Blundell MP, Morris ME *et al.* Improved survival of the diabetic foot: the role of the specialised foot clinic. *QJM* 1986;60:763–71.
17 Reiber GE, Raugi GJ. Preventing foot ulcers and amputations in diabetes. *Lancet* 2005;366:1676–7.
18 Katz IA, Harlan A, Miranda-Palma B *et al.* A randomised trial of two irremovable offloading devices in the management of plantar neuropathic diabetic foot ulcers. *Diabetes Care* 2005;28:555–9.
19 Boulton AJM, Vileikyte I, Ragnarson-Tennvall G, Apelquist J. The global burden of diabetic foot disease. *Lancet* 2005;366:1719–24.
20 Oakley WG, Pyke DA, Taylor KW. *Clinical diabetes and its biochemical basis*. Oxford: Blackwell Scientific, 1968.
21 Page MM, Alberti KGMM, Greenwood R *et al.* Treatment of diabetic coma with continuous low-dose infusion of insulin. *BMJ* 1974;2:687–90.
22 Nanji SA, Shapiro AJM. Advances in pancreatic islet transplantation in humans. *Diabetes, Obes Metab* 2006;8:15–25.
23. Hattersley AT. Molecular genetics goes to the diabetes clinic. *Clin Med* 2005;5:476–81.
24 McEwan I. *Saturday*. London: Jonathan Cape, 2005:27.

CURRENT KEY DEVELOPMENTS

Advances in the management of painful diabetic neuropathy

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Diabetic distal symmetrical polyneuropathy (DSP) affects approximately 30–50% of all diabetic patients.[1] The two main clinical consequences of DSP are foot ulceration because of insensitivity to trauma and painful diabetic neuropathy (PDN) that can be very distressing. There is little doubt that glycaemic control and duration of diabetes are major determinants of DSP.[2] In addition, a major European prospective study has recently shown that potentially modifiable, traditional markers of macrovascular disease such as hypertension, hyperlipidaemia and smoking are also independent risk factors for DSP.[3]

Pain is the most distressing symptom of DSP and prompts the patient to seek medical advice.[4] There has been little advance in the description of PDN; the features of pain in DSP were documented by Pavy in the latter part of the 19th century, who observed that it was of burning and unremitting quality often with a nocturnal exacerbation.[5] Sufferers may be so disabled by the pain as to experience a reduction in their daily activities, profound depression and a poor quality of life.[4]