

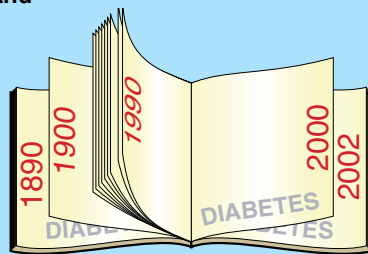
From multiple injections of insulin... to multiple injections of insulin



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Today's diabetes world is fast-moving and exciting; knowledge is accumulating at an astonishing rate, new discoveries and understanding lead to new ideas and innovations in treating, managing and preventing diabetes.

However, there's nothing new under the sun. To help understand the present, it sometimes helps to examine the past.



Tattersall's Tales will enable readers to do just that. In every issue, Robert Tattersall, renowned diabetes sage and guru, will consider an aspect of diabetes and place it in a suitable historical context. Research, treatment, people and products will all feature. In this instalment, Robert Tattersall discusses the various insulin regimens that have been recommended since the first depot insulin was introduced – from multiple daily injections to once daily... and back again.

Until the introduction of the first depot insulin in 1935, patients with 'severe' (now called C-peptide negative) diabetes were treated with three or four injections of soluble (regular) insulin. During the 1930s a paediatrician, Robert Jackson (b.1909), recommended four doses of regular insulin: one before each meal and one during the night. The split was 35, 22, 28 and 15% of the total daily dose. Under standard conditions in hospital, this produced 'normoglycaemic diurnal curves' and Jackson thought that:

'The use of more frequent small injections of insulin allows a greater degree of safety and produces a feeling of security on the part of the mother that she can control the situation. It is our impression that it is a tendency of others to place too much emphasis on the desirability of reducing the number of injections of insulin. The fact that many of the families in this study [in 1945] were hesitant to eliminate the night dose of regular insulin because of their complete satisfaction with the child's condition is evidence that the physician may be more concerned about the number of injections than the parent.'

(Jackson and McIntosh, 1945)

This might have been true when the parent was in charge but after the introduction of modified insulins in the mid-1930s many switched to a more convenient twice-

daily regimen, commonly a 2:1 mixture of soluble and protamine zinc insulin (PZI; Colwell et al, 1942). Some adult patients did reject the new long-acting insulins. One was the chest physician Charles Fletcher (1911–1995) who developed diabetes in 1940, an eventful year in which he also got married and gave the world's first penicillin injection! As he described it:

'I found [PZI] socially intolerable. It demands an evening meal at a fixed time which is often impracticable, especially after going to a theatre or in foreign countries where dinner may be very late. Twice daily soluble insulin led to frequent late morning hypoglycaemia. At my wife's suggestion I started doing what the normal pancreas does and went over to three injections of soluble insulin daily before my main meals, supplementing the evening dose with a little isophane to cover the next early morning.'

(Fletcher, 1980)

Nevertheless, Charles Fletcher was one of a minority who bucked the trend towards the minimum number of injections. In the days of glass syringes, a single daily injection meant patients could forget diabetes when they left home in the morning. It was also more convenient for their physicians, many of whom did not believe that hyperglycaemia was harmful and explicitly forbade the

changing of insulin doses (Tattersall, 1994). Thus, by the 1960s, most patients in Europe and the USA were either on one injection of PZI daily (70%) or a twice-daily mixture of soluble and isophane insulin (30%). There were a few dissenters, notably the Philadelphia physician Francis Lukens (1899–1978), who in 1965 suggested that insulin regimens should be based on physiological principles, with an attempt to mimic the normal pattern of insulin secretion (Lukens, 1965). One of the first people to try this in Europe was the Paris physician Georges Tchobroutsky, who in 1968 assigned patients randomly to either a single injection of long-acting insulin or two or three daily injections. His aim was to see if better glycaemic control with multiple injections reduced the rate of progression of retinopathy (Tchobroutsky, 1974).

Multiple injections, as used in the French study, were regarded as experimental by most physicians and it is difficult to say what the typical insulin regimen was in 1976. The probable answer is that, as with views on control, it varied from country to country and clinic to clinic. The late Michael Berger (1944–2002) told me that when he came back to Germany from the USA in 1978, 90% of people in Germany who had diabetes were on once-daily Surfen insulin. When I worked at King's College Hospital, London, in the early 1970s most patients were on one daily injection of PZI or twice-daily mixtures of soluble and isophane insulin. The exceptions were 'old stagers' who had stayed on soluble insulin for up to 40 years. Of 92 patients we studied in 1973 whose diabetes had been diagnosed before 1930, only 12 had been treated with a single daily injection for as long as 25 years (Oakley et al, 1974).

In England twice-daily soluble and isophane insulin had increased in popularity by the late 1970s. The problem was that the NPH insulin, especially if given with the evening meal, peaked too early and then ran out during the night leading to hyperglycaemia before breakfast. Increasing the dose to overcome this simply resulted in hypoglycaemia in the early hours of the morning (Tattersall and Gale, 1981). An alternative strategy promoted by Robert Turner (1939–1999) in Oxford was to give a morning injection of bovine Ultratard insulin which, as indicated by mathematical simulations in his papers, built

up to maintain constant basal insulin levels, especially at night (Phillips et al, 1979). It worked quite well with bovine Ultratard (as a similar scheme had 20 years earlier with PZI); however, when porcine and later human Ultratard replaced the bovine product, the very long action was lost and the regimen was no better than twice-daily soluble and isophane insulin.

What caused multiple injections to take off was the invention of the insulin pen (Penject) by the Glasgow physician John Ireland (1933–1988) who, as befits an inventor, was said to have been as much at home under the bonnet of a car as at the bedside. It is my impression that most of his colleagues, myself included, regarded this as a frill but it was taken on board by the Novo company who in 1985 launched the first NovoPen. This was a sleek metallic device which was then to patients with diabetes what the iPod is to music lovers today – a must-have item. The NovoPen came as part of a package of multiple injections and, although it clearly offered a competitive advantage for Novo, the company promoted the basal bolus regimen we take for granted today.

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