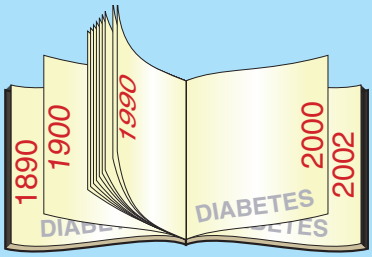
Pitfalls of changing the type of insulin

Professor Robert Tattersall

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 progression from soluble insulin, through protamine zinc insulin, to human insulin – and back again – and what this has taught us about changing insulin type.

Until 1936 there was only one insulin, an unmodified preparation called 'ordinary', 'regular' or 'soluble'. Unfortunately, even three or four injections during the day failed to control glycaemia at night so that many patients, unless they gave a 3 am supplement, woke with thirst and ketonuria. The 3 am injection was highly inconvenient, and doctors and patients welcomed the intermediate-acting protamine insulinate in 1936, and the next year the longer-acting protamine zinc insulin (PZI). This offered the dual prospect of a good night's sleep and, for those with type 2 diabetes, giving the whole day's ration in the morning and then forgetting about diabetes for the rest of the day (Tattersall, 1994).

It was soon discovered that PZI could cause severe warningless hypoglycaemia, especially at night. In 1937, Harold Himsworth (1905–1993), Professor of Medicine at University College Hospital and later secretary of the Medical Research Council, wrote:

> *'A further unpleasant feature is the suddenness with which severe attacks burst on the patient. The fall of blood sugar produced by the new insulins appears to be so gentle that the warning symptoms of hypoglycaemia are not evoked and the blood sugar slides unchecked to lower levels, where a severe attack is inevitable.'*
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> (Himsworth, 1937)

Russell Wilder (1885–1959), of the Mayo Clinic, had personal experience of this problem. In May 1936 he went to the annual convention of the American Medical Association in Kansas City with his assistant Dr Randall Sprague and dietitian Miss Nelson, both of whom had diabetes. One evening Sprague disappeared and Wilder eventually found him wandering the streets like a zombie 'in a delayed reaction from protamine insulin'. On the drive home to Minnesota, Miss Nelson was unable to write her name in the hotel register because of hypoglycaemia. It took some explaining to persuade the hotelier that she was not drunk. This made a big impression on Wilder, one of whose patients said, after going onto PZI, 'I don't have diabetes any more; I have insulin reactions'. Wilder went so far as to advise patients on PZI not to sleep alone. Many patients also rejected the new long-acting insulins. One was the English 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! He wrote:

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'At first I took long-acting insulin (protamine zinc), but I found this 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. I take extra insulin supplements to control unusual hyperglycaemia.'

(Fletcher, 1980)

In some ways, history repeated itself between 1983 and 1989, when 80 % of patients with diabetes in England were switched to recombinant human insulin. This time there was no overwhelming medical advantage from the new insulin, and the changeover was driven by the manufacturers, who had been working for years towards what they saw as the holy grail of diabetes research. Certainly it was a marketing man's dream. Advertisements described it as 'identical to the body's own insulin and therefore the logical choice' or 'outstandingly pure and less immunogenic than that which comes from the pancreas of pigs or cattle'.

These were half-truths. Clinical trials had shown that on changing from porcine to human insulin the only difference was a slightly higher fasting blood sugar on human insulin. Furthermore, the immunogenicities of human and porcine insulins were essentially the same. I was chairman of the medical advisory committee of the British Diabetic Association at that time, and what was disturbing was that many patients were changed to human insulin with little explanation, or even by accident when the pharmacist or GP simply substituted human insulin, with the comment: 'Your old insulin has been discontinued; this is the new one'.

How many patients suffered from the change to human insulin is unknown, but like those changed to PZI in the 1930s, many complained bitterly about altered symptoms of hypoglycaemia. The most common problem was that their usual autonomic warning symptoms were replaced by neuroglycopenia. This happened particularly in those with long-duration diabetes who were switched from bovine to human insulin. The role of the species of insulin was never conclusively determined, and it may be that the better glycaemic control reduced the counter-regulatory response (Simonson et al, 1985) or that hypoglycaemia during the changeover begat subsequent unawareness (Heller and Cryer, 1991). Nevertheless, I vividly remember one case where an exceptionally difficult patient was miraculously stabilised after being switched, much against his inclinations, from the 'modern' human to the 'prehistoric' beef insulin (Kerr et al, 1989).

What lessons can we learn about changing the type of insulin?

- Patients should be told exactly why it is being done.
- People who have been on a particular type of insulin for many years become attached to it like an old pair of slippers. In other words, 'If it ain't broke, don't fix it'.
- A change of insulin will hardy ever stabilise a difficult patient. The answer to their problem is most likely to be found in their personal or family life.

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