Warningless hypoglycaemia

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Today's diabetes world is fast-moving and exciting; knowledge is accumulating at an astonishing rate. To help understand the present, however, it sometimes helps to examine the past.

In this installment of *Tattersall's Tales*, Robert Tattersall looks back at the historical timeline that underpins our knowledge base regarding the development of acute hypoglycaemia, exploring the often warningless onset of this severe condition.

In 2007 during the trial of a nurse for the murder of five non-diabetic elderly women who developed severe hypoglycaemia on an orthopaedic ward, a barrister asked me how much glibenclamide would constitute a fatal dose, how quickly it would act, and whether the symptoms would be different from those of hypoglycaemia produced by insulin.

I did not feel confident of the answer to any of these questions either from my own experience or from the literature. I was therefore intrigued by a recent article in *Diabetic Medicine* that described a mini epidemic of "spontaneous" hypoglycaemia in 15 men in Singapore between the ages of 25 and 73 years (Dalan et al, 2009). It transpired that most of the men had taken aphrodisiac pills called "Power-1 Walnut", which were found to contain 98 mg glibenclamide and 1 mg sildenafil. Another aphrodisiac in Singapore, the wonderfully named "Santi Bovine Penis Erecting Capsules", contained between 14 and 100 mg of glibenclamide per capsule. The point of the article was that most of these men did not have (or remember having) autonomic warning symptoms before developing hypoglycaemic coma. It was suggested that hypoglycaemia unawareness on high doses of glibenclamide "deserved further research", although how this could be done was beyond me. Nevertheless, it got me thinking about the history of hypoglycaemia and the warning symptoms.

A history of hypoglycaemia

Before the first use of insulin in 1922, hypoglycaemia was not recognised as a disease state. The only way to make an animal hypoglycaemic was to remove, exclude or poison its liver, and whether low blood glucose caused specific symptoms was unknown because it was impossible to disentangle them from those of the operations or poisons used to produce hypoglycaemia. Before 1922 low blood sugar had been described in a few people with Addison's disease but the symptoms, if any, could not be disentangled from those of the primary disease.

Within a year of the discovery of insulin, Russell Wilder (1885–1959) and Walter Boothby (1880–1953) at the Mayo Clinic reported experimental hypoglycaemia in three diabetic patients and one normal subject, the latter being Wilder himself. In earlier work Boothby had found that an injection of adrenaline (first marketed in 1901) produced a 30–40% increase in basal metabolic rate. Insulin also produced a transient increase in metabolic rate but only when blood sugar fell below the fasting level. Wilder had hay fever that he treated with adrenaline, so he knew it caused palpitations, sweating and a feeling of anxiety. When he got the same symptoms after an injection of insulin, he suggested that "this may have been caused by a spontaneous discharge of the patient's own epinephrine and that herein we may be dealing with an automatic protection mechanism against hypoglycaemia" (Wilder et al, 1922). Wilder recounted these findings in a lecture in Boston where the physiologist Walter Cannon (1871–1945), originator of the concept of the "fight or flight" reaction, was sitting in the front row. Cannon had also noted that the symptoms of hypoglycaemia – particularly pallor, sweating, tremor, dilatation of the pupils and palpitations – were similar to those which followed an injection of adrenaline. As part of his theory of homeostasis, Cannon (1932) described the bodily reaction to hypoglycaemia as "another remarkable example of automatic adjustment within the organism when there is a disturbance endangering the equilibrium."

Silent symptoms

For several years after the introduction of insulin, the threat of hypoglycaemia was downplayed because of a belief in an orderly march of symptoms that gave the patient plenty of time to take action. George Harrop of New York was one of the first to challenge this (Harrop, 1927). He pointed out that unconsciousness could come on rapidly with few or negligible prodromes and, often without warning, during sleep. Warningless hypoglycaemia was more clearly described the next year by Stephen Maddock and Harry Trimble of Harvard (Maddock and Trimble, 1928). They measured blood sugar every hour, day and night, in a 22-year-old lab technician with diabetes for 6 years. From 8pm to 4am his sugars were in the range 2.2–3.3 mmol/L but he slept well and did not appear in any way abnormal. Nevertheless, he had had a number of severe reactions and one is described in detail:

> *"He went to a gym after his usual evening meal and exercised there from 7.30 to 8.30pm. He stayed for another hour but from the moment of leaving the building at 9.30pm until the following morning at 2 o'clock he had no memory of anything. He was heard stumbling up the steps to his room at 11pm, but was not seen by any member of the household at that time. At 2am the noise of a convulsive seizure wakened the family and he was given epinephrine [adrenaline] and sugar. His journey home should have taken 20 minutes but in fact took 1½ hours. There were several bruises on his body and tears in the knees of his trousers but no indication of how they had happened."*

Warningless hypoglycaemia with long-acting insulins

Lack of warning symptoms seems to have become more common after the introduction of long-acting insulins in 1936. Harold Himsworth suggested that "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" (Himsworth, 1937).

Russell Wilder had personal experience of the problem of warningless hypoglycaemia on long-acting insulins. In May 1936 he went to the annual meeting of the American Medical Association in Kansas City with his assistant

Dr Randall Sprague and dietitian Miss Nelson, both of whom had diabetes. On the second evening Dr Sprague could not be found and Wilder eventually found him wandering the streets distractedly "in a delayed reaction from protamine insulin". On the drive home they stopped at a hotel where Miss Nelson, also on protamine insulin, was unable to write her name in the register because of hypoglycaemia, and it was difficult to convince the manager that she was not drunk (Wilder, 1958).

So what was happening?

In 1953, Robert Maddock and Leo Krall of the Joslin Clinic divided hypoglycaemic reactions into "adrenalin-like" and "central-nervous-system-like" – what we now call adrenergic and neuroglycopaenic (Maddock and Krall, 1953). Adrenaline-like reactions were associated with rapid falls in blood sugar and associated with the use of fast-acting (bovine soluble) insulin. They believed that slowly developing hypoglycaemia produced by long-acting insulins did not provoke an increase in circulating adrenaline, which "explains the absence of the 'adrenalin-like' symptoms as well as the failure of the blood sugar to rise and correct the hypoglycemic state." The result was malfunction of the brain.

A study devised by Karl Sussman (1929–2005) at the Joslin Clinic in 1963 was one of the first attempts to explain the physiology (Sussman et al, 1963). He enrolled 44 patients with diabetes, all of whom, he told me, were keen to take part, and five "normals". They were given small doses of insulin (0.1 units/kg) intravenously every 20 minutes until "thought to be profoundly hypoglycemic" – some actually became comatose or had convulsions!

Three types of response were noted. Twenty-three had symptoms such as sweating and palpitations and knew they were having a hypoglycaemic episode. In the words of the authors, "the manifestations of sympathetic nervous system hyperactivity served as a warning signal". The second group of 16 had a sympathetic response, but by the time it had developed, they were confused and unable to realise the significance of their symptoms. The third group of five had no sympathetic response and four of them had a generalised seizure during the experiment.

Measuring catecholamines was difficult so Sussman measured free fatty acids as a surrogate, but also took 25–50 mL blood for Dick Crout, a pharmacologist (later director of the US Food and Drug Administration's Bureau of Drugs) who had a method for measuring catecholamines. There were substantial increases in plasma free fatty acids in the first two groups in whom Sussman had observed sweating and increased pulse rate. There was no increase in the five whose hypoglycaemia was warningless and, in comparison with the other two groups, their blood glucose showed no tendency to stabilise or rise; rather it fell relentlessly.

This paper was more or less forgotten and for the next 15 years there was very little scientific interest in hypoglycaemia. I got into it because I was interested in finding out why some patients with type 1 diabetes were poorly controlled. When I worked in Ann Arbor in 1973/4 the standard explanation for patients who had high fasting blood sugars was that they had "Somogyied", or in other words, become hypoglycaemic during the night with a hyperglycaemic rebound caused by counter-regulatory hormone secretion. I suggested to my research fellow Edwin Gale that we (i.e. he) should investigate this. He measured the blood sugar every hour during the night in 39 poorly controlled patients, most of whom were on twice-daily soluble and isophane insulin. To our surprise 22 people became hypoglycaemic during the night and hypoglycaemia persisted for more than 3 hours in 17 patients (Gale and Tattersall, 1979) – we had rediscovered Maddock and Trimble's findings 50 years later! Some patients did have "rebounds" but we found that this was because their insulin ran out in the dawn hours. The situation could be greatly improved by giving the isophane insulin before bed rather than before tea, which in Nottingham was usually taken around 6pm (Gale et al, 1980).

A final thought

Edwin's overnight study was essentially unfunded. It was done in the neurology ward by arrangement with the senior registrar and the bloods were sent to the hospital laboratory. Edwin's salary was paid by an RD Lawrence fellowship from the British Diabetic Association (BDA) to do something entirely different. The "something entirely different" was never done but the BDA got their money's worth …

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