Diabetic ketoacidosis 1850–1970

Professor Robert Tattersall

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 explores the history behind our understanding of the acute complication diabetic ketoacidosis, looking back at key developments with regard to its presentation, diagnosis, treatment and prevention.

The clinical picture of fully developed diabetic ketoacidosis (DKA) is so distinctive that it is surprising that it was not described until the later part of the 19th century. In the 1850s many writers commented on the curious odour of the breath and urine of people with diabetes, which was variously compared to vinegar, chloroform, rotting apples and beer. It was assumed to be the result of some sort of fermentation and it seemed likely that it was the cause of the coma in which these people died.

In 1857, after a colleague said that the smell reminded him of acetone, Wilhelm Petters (1824–1889) of Prague isolated acetone from the urine of a 30-year-old woman with diabetes who appeared terminally ill. "Next morning," according to Petters, "she was found in a state resembling narcosis and her vicinity was pervaded by a chloroform-like odour which was so strong that the other patients noticed it." His assistant even suggested that the patient had been chloroformed during the night! (Petters, 1857).

In 1874 Adolf Kussmaul (1822–1902) gave a detailed clinical description and emphasised the characteristic breathing of acidosis, which has since then borne his name. He was particularly struck by "the contrast between the power of the respiratory movements and the general weakness" (Kussmaul, 1874). In 1877 another German physician, Friedrich Walter, replicated Kussmaul respiration by poisoning a rabbit with hydrochloric acid and suggested that patients with DKA were poisoned by an endogenously generated acid, which in 1884 Oskar Minkowski identified as beta hydroxybutyric.

The literature at the end of the 19th and beginning of the 20th century was replete with suggestions about treatment, but despite heroic measures such as purgation, alkaline enemas, intravenous injections of sodium bicarbonate, and hypodermic injections of strychnine and other stimulants, coma was always fatal.

The introduction of insulin in 1922 led, miraculously to the physicians who first used it, to recoveries. However, the benefit was not as dramatic as is sometimes portrayed since the chance of survival in many hospitals during the next 25 years was little better than 50:50. Joslin and colleagues reviewed their first 33 cases treated with insulin between 1 January 1923 and 1 April 1925 (Joslin et al, 1925). The most important statistic was that 31 survived and these results were attributed to:

> *"Promptly applied medical care. Rest in bed, special nursing attendance, warmth, evacuation of the bowels by enema, the introduction of liquids into the body, lavage of the stomach, cardiac stimulants, and above all the exclusion of alkalis."*

Joslin was at pains to play down the idea that since insulin had been available, DKA no longer needed to be taken seriously, writing that, "patients recover as the result of hard work by day and night of doctors, usually young, who apply the most modern methods of medical practice". While accepting that sufferers were seriously dehydrated, as shown by sunken eyeballs and lack of skin turgor, he cautioned against intravenous rehydration which was "too risky. Too sudden a burden is thrown on a weak heart, and, furthermore, it is difficult to carry out because of the low blood pressure and small veins". Fluid was given rectally or more often subcutaneously, subpectorally or into the thighs.

Between 1930 and 1945 the mortality rate of DKA in many American hospitals was between 20 and 40% compared with less than 5% in Joslin's. Some suggested that this was because Joslin treated a better class of patient but the real reason had to do with organisation. In a nearby hospital, the Mass General, laboratory support was not available at night, weekends or holidays. In 1944, after "some chiding from Dr Joslin", services were reorganised so that each case was treated as an acute medical emergency, a house officer remained in constant attendance during the first 24 hours and a lab technician was kept on duty until the patient was thought to be out of danger. A treatment record ("coma sheet") was pinned to the wall next to the bed and on this, pulse, blood pressure, fluid intake and output, and urine tests for sugar and acetone were recorded every 30–60 minutes. This package led to a dramatic improvement in outcomes (Harwood, 1951).

In 1948, in correspondence about how high doses of insulin should be, Joslin wrote to the *British Medical Journal* explaining his principles of treatment (Joslin, 1948). Alexander Cooke (1899–1999) wrote that since adopting the Joslin

method, the death rate from DKA in the Radcliffe Infirmary had been reduced to a third of its previous level. However, he quoted the case of a woman with previously undiagnosed diabetes and DKA who seemed to be making a good recovery until the second day when "she asked for a drink and on being sat up to receive it fell back dead". Autopsy did not show a cause of death and Cooke suggested adding the following paragraph to Joslin's protocol (Cooke, 1948):

> *"Aftercare. It is important to realise that a patient who has come round from diabetic coma has recently been in a condition of profound circulatory failure and is still ill. The patient should not be allowed to sit up in bed, and should be nursed as a cardiac case for at least a week."*

Cooke did not know but a case report in 1946 by an American Jacob Holler had drawn attention to the lethal effects of hypokalaemia (Holler, 1946). His patient was an 18-year-old woman who had not taken any insulin for 5 days and was admitted in coma. After 4 hours of treatment she was conscious but drowsy. After 12 hours she was having increasing difficulty breathing but examination of the heart and lungs was normal. Twenty-one hours after starting treatment she could hardly breathe or move. Since she was obviously dying, she was put in an iron lung. After she had been in it for 3 hours, Holler decided that the respiratory paralysis might be due to potassium deficiency. She was given 1.5 g of potassium chloride intravenously over 35 minutes – a major logistical problem since it involved opening the respirator and resuming artificial respiration; also, potassium chloride was not a staple item and had to be made up specially by the pharmacy. Twenty minutes after the infusion the respirator was opened and she was breathing normally.

Holler and his fellow physicians did not measure serum potassium routinely because the chemical method used before the introduction of flame photometry in 1950 took 2 hours or more. Neither does he say what made him think of hypokalaemia, but over the previous decade there had been a few reports of low potassium leading to paralysis in non-diabetic patients.

In his article Holler describes what we would now regard as the typical ECG changes of hypokalaemia. Similar findings had been reported in a 1937 article, where the authors had studied 17 cases of coma and six of pre-coma and found abnormalities in all (Bellet and Dyer, 1937). The changes were lengthening of the QT interval, depression of the ST segment and inversion of T waves. What was surprising to the authors was that the most striking changes were seen, not at the height of the acidosis, but 24 hours later when the patient seemed fully recovered. Since the changes were reversible, they were regarded as "functional" rather than due to structural myocardial damage, which was thought to be common and the explanation of unexpected deaths.

Joslin believed that DKA was preventable and that when it occurred it was someone's fault – the doctor's, the patient's or the system. He cited the work of Alfred Gottschalck (1894–1973) in Stettin, a city of 270 000 where there was only one case of DKA in 1928–30 (0.3%) compared with incidences of 3.6–16% in other major German cities. This was achieved by systematic education of patients and doctors, follow-up of all patients who had been in hospital with an insistence that they keep in close contact with their GP and social assistance with nursing, food and insulin.

A good example of system failure 40 years later was the chaotic system in California described by Leona Miller (Miller and Goldstein, 1972). A survey of admissions to the diabetes wards for 1962–7 (including an average of 300/year for DKA) indicated that as many as 50% could have been prevented if medical care had been easily available. At the time, patients could only get advice during a hospital stay, visit to the clinic or emergency room (ER), or by going to a private physician – the latter was generally too expensive.

In 1969 several changes were made: a telephone answering service was instituted for clinic patients, and nurse practitioners or diabetes service residents assigned to screen all patients being considered for admission, rather than allowing the decision to be made by ER staff. Patients could now be "held" on the diabetes ward until the results of tests were available. The phone was manned 24 hours a day, 7 days a week and, if a patient turned up at the ER, they were told to use it. These changes halved the number of admissions, reduced cases of DKA by two thirds and reduction of hospital bed days/patient/year from 5.6 to 1.7 (Miller and Goldstein, 1972).

This article has often been cited to support the importance of education, although it is actually about organisation of a diabetes service. It probably had little effect nationwide because changing the system in Los Angeles depended on the dynamism of one person, Leona Miller.

Bellet S, Dyer WE (1937) The electrocardiogram during and after emergence from diabetic coma. *Am Heart J* **13**: 72–87

Cooke AM (1948) Diabetic coma. *Br Med J* **2**: 799

Harwood R (1951) Diabetic acidosis: results of treatment in 67 consecutive cases. *N Engl J Med* **245**: 1–9

Holler JW (1946) Potassium deficiency occurring during the treatment of diabetic acidosis. *JAMA* **131**: 1186–8 (This is discussed in more detail in: Tattersall RB [1999] A paper which changed clinical practice [slowly]. Jacob Holler on potassium deficiency in diabetic acidosis [1946]. *Diabet Med* **16**: 978–84)

Joslin EP (1948) Diabetic coma. *Br Med J* **2**: 657–8

Joslin EP, Root HF, White P (1925) Diabetic coma and its treatment. *Med Clin N Amer* **8**: 1873–919

Kussmaul A (1874) Zur lehre vom diabetes mellitus. *Dtsch Arch Klin Med* **14**: 1–46

Miller LV, Goldstein G (1972) More efficient care of diabetic patients in a county hospital setting. *N Engl J Med* **286**: 1388–91

Petters W (1857) Untersuchungen über die Honigharnruhr. *Prager Vjschr Prakt Heilk* **3**: 81–94