Insulin and the mind: Coma therapy in schizophrenia

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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 takes us back to the 1930s, recounting the fascinating history of insulin coma therapy, a then new and exciting treatment for schizophrenia, until it was gradually phased out in the late 1950s.

I have just read a news article entitled "Insulin protects the brain from Alzheimer's – US study". It explained that insulin shielded the brain from toxic proteins, thus, in the words of the article, "supporting the theory that Alzheimer's may be a third form of diabetes" (Steenhuysen, 2009). I didn't know what to make of this but it reminded me of the remarkable story of insulin coma therapy (ICT), which may not be familiar to some readers.

Around 1930 a young Austrian, Manfred Sakel (1900–1957), was working in a private clinic in Berlin that catered for rich morphine addicts. He found that withdrawal symptoms, such as tremors, vomiting and agitation, could be abolished by injections of insulin, which caused sufferers to gain weight and become more cooperative. Sometimes he gave too much insulin and the patient went into a coma, but this seemed to be even better and abolished the craving for morphine. After animal experiments, allegedly in his own kitchen, he satisfied himself that hypoglycaemia could be reversed safely and that deep levels of coma were possible. In 1933, Sakel returned to Vienna to work in the university psychiatric clinic and, after convincing his reluctant boss, began testing his theory that ICT might cure schizophrenia (Jones, 2000).

When he published his first results in 1934, Sakel claimed that 70% of patients had had a full remission and a further 18% a "social remission". His colleagues were impressed, as well they might be, because in the 2 years before his arrival only 20% of people with schizophrenia recovered sufficiently to be discharged, whereas during his first 2 years 68% were discharged. In 1939, the English Board of Control (which oversaw psychiatric hospitals) commissioned Dr Isobel Wilson to visit Vienna and report on the new treatment. Her 61-page booklet, *A Study of Hypoglycaemic Shock Treatment*, was extremely enthusiastic and psychiatrists were quick (with official encouragement) to jump on the bandwagon, so that by the late 1930s virtually all psychiatric hospitals in England and the USA had an insulin coma unit. These were dedicated units with a permanent staff who regarded themselves as an elite – they treated and "cured" people whereas staff in the rest of the hospital were little more than custodians. Descriptions of the insulin units stress how well appointed and quiet they were – an environment of peace and safety in contrast to the chaos and noise that characterised the rest of the hospital (Doroshow, 2006).

In large units up to 20 patients would be treated simultaneously. Sakel's technique was for:

> *"The patient [to] be given increasing doses of insulin until the so-called 'shock dose' is reached; the size of the shock dose varies considerably in different individuals and may be anything from 15 to 450 units. The initial dose varies from 15 to 50 units a day depending on the physical condition of the patient and the duration of the illness, and doses are increased by 5 to 20 units daily until the shock dose is reached (by shock dose we understand as that amount of insulin which in any individual produces deep coma with areflexia within 4 or 5 hours after one injection). A shock dose is given 3 to 6 times a week until the desired result is attained, but if the patient does not respond no more than 50 injections [treatments] need be given." (Sakel, 1937)*

Coma – defined by absence of pupillary and deep tendon reflexes – would be maintained for anything between 20 minutes and 2 hours. It was most commonly ended by giving 50% glucose through a stomach tube. Less commonly glucose was given intravenously (Shorter, 1997). Comas would be repeated for 5 days a week for several weeks. Patients were often kept in the insulin unit for the rest of the day where nurses hovered around with glasses of orange juice in case hypoglycaemia recurred – either because of the depot left by several hundred units administered intramuscularly (the usual route) or because insulin dissociated from the antibodies which had formed during the weeks of treatment.

As far as I can tell, diabetes specialists were not usually asked to advise on or observe the treatment. However, in 1937 a neurologist, Dr Lewis Golden, watched comas at a mental hospital in New York and wrote an account of the signs and symptoms which, to him as a neurologist, were completely

new (Golden, 1937). Epileptic fits were frequent but he also described a distinct state where there were quick jerking movements of the limbs which could be provoked by touching or shaking the patient – my colleague Edwin Gale observed this during overnight studies and pointed out that relatives might well describe it as a fit (Gale and Tattersall, 1979).

Other patients observed by Golden had prolonged sucking movements, catatonic postures, opisthotonos, or irregular, threshing, purposeless movements. Transient hemiplegias were apparently quite common and he was told of one that had lasted 9 hours. Some manifestations were particularly frightening; patients whose coma was not terminated within 45 minutes by intravenous glucose would enter "an excited phase with convulsive movements, contortions, rigid attitudes and extremely labored breathing". This phase, which lasted 15–20 minutes, was so severe that the patient appeared to be *in extremis*. It seemed to Golden that "the whole nervous system was thrown into a frenzy of disorganised activity. There were recognisable hemiplegic attitudes, extrapyramidal manifestations of transitory cogwheel rigidity and signs of mid-brain involvement." Eventually the patient woke from his coma with "no trace of the neurologic storm through which he had passed." It was often followed by what the psychiatrists called a lucid period when "from an aloof, withdrawn, bizarre and suspicious individual, the schizophrenic is momentarily transformed into a warm, friendly, responsive, and lucid person whose symptoms are either absent or greatly diminished in intensity." As treatment progressed, these lucid periods became longer and eventually (so it was hoped) the patient would be permanently lucid.

It is difficult to know how effective ICT was. There were problems with the diagnosis of schizophrenia and often the outcome was vaguely defined in terms such as "greatly improved" or "slightly improved". It was generally agreed that treatment was most likely to be effective in the first year of illness with diminishing benefits thereafter. This led to accusations that psychiatrists exaggerated the benefits of insulin by using it on the healthiest patients who were most likely to have a spontaneous remission. Critics were also concerned about the dangers. How often the treatment produced death or permanent disability is uncertain but was estimated at between 3 and 30% (Spencer, 1948). A particular problem was irreversible coma due to hypoglycaemic brain damage (Kay, 1961). In addition, as would be expected, most patients put on large amounts of weight.

In England, prominent psychiatrists William Sargant at St Thomas' Hospital and Eliot Slater at the Maudsley were staunch supporters and claimed that ICT brought about more remissions and that these were likely to be longer lasting than spontaneous ones. This was important because, in their words, "one would wish to keep the potential lunatic sane as long as possible" (Sargant and Slater, 1944).

Some insulin therapists got better results than others. Ideally, according to Sargant and Slater (1944):

> *"The successful therapist will be gifted with enthusiasm and caution, he will have a sympathetic interest in, and a detached appreciation of the personalities of, his patients, he will have the general medical training that has accustomed him to the handling of medical emergencies, and the refined clinical judgment of the experienced psychiatrist, and he will have the facilities to give the whole of his energy to the treatment of his patients without administrative after-thought."*

The first challenge to ICT came in a paper in *The Lancet* in 1953 from Dr Harold Bourne who pointed out that it was extremely labour intensive. According to Bourne, those subjected to insulin shock had, as measured by the clock, 50–100 times as much attention as ordinary psychiatric patients. Also, they received hands-on care such as sponging to mop up the sweat. His suggestion (strongly refuted in the correspondence columns by prominent psychiatrists) was, basically, that all this care by an enthusiastic team caused a massive placebo response (Bourne, 1953). Bourne's criticisms came at the same time as the introduction of chlorpromazine, which was a much simpler and better treatment for schizophrenia. As a result, ICT was gradually phased out in most units during the late 1950s.

ICT is important in the history of diabetes and endocrinology because it provided the opportunity to study the reaction of normal subjects to repeated insulin injections. It was on samples from psychiatric patients that Berson and Yalow (1966) first showed the presence of insulin antibodies.

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