150 years of subcutaneous injections

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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 a look back at the history behind the subcutaneous injection, from the invention of the syringe in the mid-1800s, subsequent innovations and adaptations, to the modern-day development of the insulin pen.

At the beginning of the 19th century the effects of snake bites and poisoned arrows clearly indicated that drugs could be introduced into the body through a hole in the skin and have a systemic effect.

In the 1830s the first attempts to imitate snakes or South American Indians involved removing a patch of epidermis with a blistering agent and then painting a drug (usually opium) on the raw surface. In France this was known as "la méthode endermique" (Howard-Jones, 1947; Mogey, 1953). Less drastic and painful was to lace the tip of a vaccination lancet with opium paste and make multiple pricks along the course of a nerve – a method first described in France in 1836.

There is some dispute about whether an Irishman, a Frenchman or a Scot should be credited with the invention of subcutaneous injections. In 1844, Francis Rynd (1811–1861) of Dublin treated a woman with trigeminal neuralgia with morphine acetate which was introduced by punctures along the course of the supraorbital nerve. Rynd's instrument, which he did not describe until 1861, was a trocar and cannula onto which he screwed a reservoir through which the morphine solution was introduced by gravity.

The Frenchman, Charles-Gabriel Pravaz (1791–1853), a vetinarian, made a metal syringe with a screw plunger and hollow needle which he used to inject iron perchloride into the arteries of horses and sheep so as to coagulate them. He suggested that this could be used in humans to treat aneurysms.

The first subcutaneous injection with what we would recognise as a syringe (as opposed to Rynd's gravity fed apparatus) was made by Dr Alexander Wood (1817–1884) of Edinburgh. Wood used a syringe made by the London instrument maker Ferguson to inject morphine along the course of a nerve. Clearly, Wood was aiming for local anaesthesia although he did note that some of his patients became extremely sleepy, which implied that the morphine must have reached the brain. Wood's original paper in the *Edinburgh Medical and Surgical Journal* in 1854 did not attract much attention, but after another in the *British Medical Journal* in 1858, he was deluged with letters from doctors asking where the equipment could be obtained (Wood, 1858). The syringe that Wood used, albeit much damaged and *sans* needle, is preserved in the Royal College of Surgeons of Edinburgh.

A young London surgeon, Charles Hunter, pointed out that analgesic injections did not have to be given in the vicinity of nerves but worked equally well when injected into any area of the body. Hunter called his injections "hypodermic", perhaps to distinguish them from those of Alexander Wood with whom he conducted a long correspondence in *The Medical Times and Gazette* about priority for recognising the remote effects following injection.

Opiates were freely available in Victorian Britain and it did not take long for opium eaters to become injectors. In 1870, George Eliot's friend, the Leeds physician Clifford Albutt (1836–1925), warned that:

> *"We are now being consulted by patients who have been injecting themselves daily or more than daily during long periods of time for neuralgias which seem nevertheless as far from cure as they were at the outset."*

In short, many middle- and upper-class women had become addicted and often used injections of morphine to get to sleep. Popularisation of self-injection was helped by such devices as mini-syringes which one could attach to one's key chain and "automatic injectors" (Anon, 1875).

The introduction of insulin in 1922–3 greatly increased the market for syringes. In spite of the fact that addicts gave themselves injections without problem, the idea that (lower class) people with diabetes should be allowed to, or would be able to, inject themselves seemed to many doctors outrageous, perhaps because it would transfer power to the patient, which, of course, it did.

The question of the practicability of self-injection of insulin was soon answered. In 1923, Joslin remarked that "intelligent patients can be taught the use of diet and insulin in a week" (Joslin, 1923), while for RD Lawrence, "one minute's practical demonstration of an injection will teach a patient more than pages of writing [since] all doctors and, indeed, many patients are quite familiar with hypodermic injections" (Lawrence, 1925). Lawrence made his patients give their own injections to free them from dependence on a nurse or doctor and claimed that few, if any, had difficulties after the first week.

By the 1920s the metal syringes with leather plungers in use before World War I had been replaced by all-glass syringes originally made by the Parisian instrument maker

H Wülfing Luer. People with diabetes were advised to boil them before each injection, a practice which led to many breakages and consequent expense. Needles had to be resharpened regularly with a stone. Proprietary metal or Bakelite cases in which to store the syringe in alcohol did not come until the 1930s.

Other innovations followed quickly as the demand for syringes grew. The Yale Luer-Lok was designed and patented by Becton Dickinson (BD) in 1925 and stopped the needle coming off or damaging the end of the syringe. Apart from breakage from boiling, other syringe problems were jamming of the plunger due to being gummed up by residue from the methylated spirits in which it was kept, and loosening of the plunger which led to inaccuracies in dosing.

In England, the first strength of insulin to be marketed was 20 U/mL (later called single strength) and syringes were made with 20 marks per mL. When 40 and 80 U/mL insulins (double and quadruple strength) were introduced the old syringe (British Standard 1619) was retained so that marks on the syringe and units no longer corresponded. This caused endless trouble because, depending on which strength of insulin was being used, a mark could be 1, 2 or 4 units. In the USA, and less commonly in Europe, syringes were made with dual scales, which caused halving or doubling of the dose if the patient inadvertently used the wrong one.

The confusion from different strengths of insulin was solved by the U 100 changeover in the early 1980s when a standard syringe was made in which units and marks again corresponded.

The first plastic syringe for venepuncture was produced by BD in 1961 and the first insulin syringe with a permanently attached needle in 1969. The debate in England as to whether plastic insulin syringes should be available on prescription was long and surreal. In the real world many, if not most, patients reused plastic syringes for a week or more, a practice which was shown to be safe. The Department of Health (DH), advised by the syringe manufacturers that reuse was hazardous, insisted that they could not go against the manufacturer's advice. This made plastic syringes too expensive and the DH only relented in 1987 (Alexander and Tattersall, 1988). By this time the days of the syringe were numbered. In 1981 the Glasgow physician John Ireland (1933–1988) had invented the first insulin pen (Penject) and the idea was taken on board by Novo Nordisk, who in 1985 launched the NovoPen. Other companies followed suit so that today few use the old fashioned syringe.

Patient handbooks had always given complicated instructions for injecting insulin, including a map of "safe sites" and instructions about cleaning the skin and maintaining sterility. Until recently, most of these practices existed in an evidence-free zone. For example, Robin Lawrence and the TV doctor Charles Fletcher injected in their calves and through their clothes. The latter was not scrutinised scientifically until 1997 when it was found to be safe (Fleming et al, 1997).

While visiting Birmingham in 1976 I asked John Malins whether he thought it was necessary to sterilize the skin before an injection and he roared with laughter at the idea and told me that he had given it up even for lumbar punctures 30 years earlier. The number of organisms on the skin is far below that needed to cause infection after an injection with a 25–27 gauge needle (Koivisto and Felig, 1978).

Abscesses at insulin injection sites always seem to have been very rare and this is almost certainly because insulin preparations contain preservatives such as phenol, metacresol or methylparaben. They are so effective that if a culture of bacteria is injected into a bottle of insulin, it is sterile again within 24 hours (Border et al, 1984).

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