Early history of oral hypoglycaemic agents

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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 describes the history of oral hypoglycaemic agents, beginning with nostrums like 'Dill's Diabetic Mixture' in the early 1900s, to the development of the synthalins with fatal side-effects.

In 1904 William Osler suggested that, "the desire to take medicine is one feature which distinguishes man, the animal, from his fellow creatures". As a result there has always been a ready market for anti-diabetic remedies. In 1894 the US National Dispensatory (an early formulary) listed no less than 42 such drugs and in 1911 Forscheimer claimed to be able to add another 45 (Forscheimer, 1911). On the whole the use of drugs was disdained by experts who believed that if you gave a person with diabetes an inch he would take a mile and abandon all pretence of dietary restriction. In the 1909 edition of his famous textbook Osler claimed that "opium alone stands the test of experience as a remedy capable of limiting the progress of the disease" although he did qualify this by saying that not much effect would be noted until the patient was on a rigid diet. Apart from approved remedies there were the nostrums of the patent medicine men (These are described in detail by James Harvey Young, 1961). ie. James Harvey Young described the nostrums of the patent medicine men not strychnine and creosote.

Apart from approved remedies there were the nostrums of the patent medicine men. (The word 'patent' in this context is a misnomer since to be patented the composition would have had to have been divulged). Secret remedies, as the British and American medical associations more accurately called them were marketed with alliterative titles such as 'Pink Pills for Pale People', 'Hoffman's Harmless Headache Powders' etc. Extravagant claims were made for the number of conditions they could cure, none quite as all-embracing as 'Somos' which was said to work in 158 diseases from hallucinations to hydrophobia (rabies).

The British and American medical associations waged long campaigns against secret remedies. In 1908 the British Medical Journal published the compositions of popular diabetes and obesity cures (British Medical Journal, 1908). One was Vin Urane Pesqui, a small amount of uranium nitrate in old Bordeaux wine - uranium nitrate was widely used to treat diabetes and approved by main stream physicians. According to the advertising blurb, Vin Urane Pesqui "positively cures sugared diabetes, provided it is resorted to at an early stage and used during a sufficient length of time… as soon as the patient has made use of this wine, his thirst is allayed almost instantaneously; his strength reappears; all his functions are gradually restored." Another nostrum was Dill's Diabetic Mixture advertised as "The only known remedy for this deadly disease. No dieting is necessary." One third of it was alcohol, a common feature of secret remedies and one which presumably made the patient feel better. A preparation called 'Expurgo Anti-Diabetes' was described by the Journal of the American Medical Association as such an evident nostrum that even intelligent laymen could not be deceived by it. Nevertheless some medical journals had accepted adverts for it and physicians 'of a certain type' supplied testimonials which appeared prominently in the adverts – later in the 20th century such physicians would be known as drug company whores!

After the discovery of insulin in 1921, there was an intensive search for orally active compounds since it seemed likely that substances with insulin-like activity would be present wherever carbohydrates were broken down or synthesised, especially in lower organisms or plants. JB Collip, who worked with Banting, Best and MacLeod on the purification of insulin, thought that because plants contained glycogen, they must also have something like insulin. He made extracts from yeast, onion tips, lettuce, sprouted grains of barley and even lawn grass. In some of his experiments these did appear to lower the blood sugar of rabbits and he called the active ingredient 'glucokinin'. Because of Collip's reputation in relation to insulin, his work led to a plethora of experiments by others on a variety of plants and seeds. These products were often claimed to be active but the claims, as for glucokinin, could rarely be replicated.

The first synthetic oral hypoglycaemic agents, the synthalins, were introduced in 1926. Their discovery was based on experiments which showed that parathyroidectomy in animals caused hypoglycaemia and that *pari passu* there was a large increase in guanidine in the blood. Furthermore, injection of guanidine into rabbits caused hypoglycaemia and convulsions (Watanabe, 1917). Interestingly, a guanidine compound had long been used as a folk remedy for diabetes in the form of the perennial herb Galega officianalis also known as goat's rue, French lilac, Spanish sanfoin, Italian fitch or false indigo (Bailey et al, 2004). In addition to its medieval use for diabetes, it was also used to promote sweating and as a galactagogue in cows. Later studies showed that G. officianalis was rich in guanidine and extracts of it were used to treat diabetes in France until the

1930s. Attempts were made to modify the guanidine molecule to increase its hypoglycaemic action and dissociate it from the toxic effect. Eventually Synthalin A (decamethylene diguanide) and Synthalin B (dodecamethylene diguanide) were tested on patients in Berlin. They were discussed at the German Medical Association meeting in 1926 amid great enthusiasm. Oskar Minkowski wrote "it is a momentous fact that the practical results exceeded all hopes…now an insulin-like substance has actually been obtained that could help the great army of mild and medium severe diabetics." The main selling point of the synthalins, apart from the fact they could be given by mouth, was that their action lasted more than 24 hours, much longer than that of [soluble] insulin. The side effects of anorexia, abdominal distress, nausea and diarrhoea were downplayed or treated with antacids (Thomson, 1932). Samples were sent to the British Medical Research Council and their opinion was distinctly unfavourable (Anon, 1927). Reports of hepatic toxicity began within a few months and when it was clear that this was unacceptably frequent and severe the drug was withdrawn in England in 1928. German opinion leaders did not believe that there was conclusive evidence of hepatotoxicity and continued to use it until the mid 1930s. Surprisingly it was still being used at Birmingham General Hospital as late as 1932. Retrospectively, it is possible to argue that synthalin was not as toxic as later generations have assumed and that, because of lack of understanding of the pathophysiology of diabetes in the 1920s, it was used in excessive doses in inappropriate patients. Nevertheless, the prejudice against guanidine derivatives was so great that when biguanides were introduced in the late 1950s, their true chemical nature was concealed by calling them 'formamidinyliminoureas'. Happily, after they were shown to be effective, they were renamed!

In May 1927, the highly respected German diabetes specialist Carl von Noorden published an account of an oral pancreatic preparation which was said to have been obtained by 'strong tryptic digestion of fresh pancreas' and more crucially not to contain synthalin or related guanidine compounds (Von Noorden, 1927). It was given the name 'glukhorment' and attracted a lot of attention – the 1928 Index Medicus contains 17 references to it compared to 44 for synthalin. The Horment company sent samples to Henry Dale at the National Institute for Medical Research in London but when analysed it was found to contain 1% of something which was chemically indistinguishable from synthalin (Dale et al, 1927). A similar conclusion was reached independently in Prague. When he heard these results, von Noorden considered the only two explanations; that synthalin had somehow been synthesised during the process of tryptic digestion or that it had been dishonestly added. The latter was obviously more probable and foreshadowed scandals in the 1990s when 'natural diabetes cures' turned out to be laced with glibenclamide.

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