THE FOX GOT YOU

Art and science project by photography artist Françoise Sergy

The drug METFORMIN

The drug Metformin (dimethylbiguanide) is currently the first line of treatment for type 2 diabetes. Its main action is to reduce insulin resistance within cells and to regulate glucose production by the liver. It is also used to treat Polycystic Ovary Syndrome, a condition that can cause infertility and is characterised by insulin resistance. Scientists are still researching the drug's precise mechanisms of action but it is known to affect several metabolic pathways, as well as energy production in mitochondria.

Metformin has been used as an anti-diabetic drug for over 50 years. During this time, many long-term studies on diabetes have shown that the drug has other positive effects: Diabetics treated with Metformin have a lower risk of cardiovascular diseases and strokes than those treated with other drugs. Their risk of developing certain cancers is also reduced. This has lead to a renewed interest in the drug - this small molecule which originally came from a plant is proving to be truly fascinating.

Metformin does have side effects: It can cause nausea, abdominal discomfort and diarrhoea and so is not suited to everyone. Separately, Metformin's reputation has been damaged through its early days association with related drugs, later withdrawn, which cause lactic acidosis: a build-up of lactic acid in the blood which lowers its pH to unhealthy levels. Metformin, which does not cause lactic acidosis when prescribed properly, was viewed with suspicion for a long time after that.

Diabetes was recognised as a condition as long ago as 1500 BC, when Hindu scholars described its main clinical features and the Egyptian medical Ebers Papyrus recommended certain treatments for it. Worldwide, more than 400 plant-based products have been recommended for diabetes over the centuries. One of the most important turned out to be the substance galegine, which comes from Galega officinalis, variously named as Goat's Rue, French Lilac, Spanish Sanfoin, Italian Fitch, False Indigo and Professor Weed. The name Galega is derived from the Greek terms for milk (gala) and goat (aigos), because it can stimulate lactation in livestock. Native of southern Europe and western Asia, it was introduced in England in 1568 and as a forage plant in the USA in the 1800s. It is now classified as a noxious weed in the States because of its toxic effects on grazing animals. Its habitat in the UK has spread northwards, particularly since the 1960s, in my view as a result of the building of motorways: The plant is found growing profusely alongside the M25 and other major roads.

In the Middle Ages Galega officinalis was used in folklore medicine to treat various ailments. In the 17th century, English physicians were becoming aware of diabetes and Nicholas Culpeper's herbal treatise suggested the plant had anti-diabetic properties. Galega officinalis was used in this way in France up to the 1930s. The plant contains several related molecules, including guanidine and galegine. From the late 1800s scientific studies were done which showed that both substances lowered blood glucose in animals but that guanidine was too toxic for clinical use. In the 1920s galegine was used briefly as an antidiabetic agent. At that time, several biguanides were synthesised, including Metformin by Werner and Bell at Trinity College, Dublin, in 1922. Chemically speaking, biguanides are two linked guanidine rings. They have similar blood glucose lowering effects to galegine whilst being safer than guanidine. However, another field of research was taking place at the same time and a major breakthrough in the treatment of diabetes happened, also in 1922: Insulin was discovered. It was decided that this was the best treatment possible for diabetes (a view no longer shared by specialists for type 2) and research on the biguanides blood glucose lowering role was more or less abandoned.

However, the biguanides group continued to be studied for their antimicrobial and antimalerial properties: Proguanil has been a very important prophylactic antimalerial drug for many years. Studies of these drugs had shown weak glucose lowering effects and this prompted Jean Sterne, a French physician, clinical pharmacologist and diabetes specialist to investigate further. He conducted rigorous and systematic research which lead to the commercial development of the drug Metformin under its brand name “Glucophage” (glucose eater) in 1957.

At the same time pharmaceutical companies in the States and Germany were developing other biguanides, including Phenformin, which were initially favoured because of their higher potency. It soon became known that Phenformin induced lactic acidosis. This resulted in several deaths and the drug was withdrawn in most countries by the end of the 1970s.

Glucophage was produced in France by a very small pharmaceutical company, Aron Laboratories, which promoted the product through direct contact with clinicians, free offers and word of mouth. It encouraged clinicians to do their own trials on its efficacy and to report the findings. This type of personalised marketing would be very much frowned upon today. Over the next few decades, studies trickled in, but it wasn't until the landmark UK Prospective Diabetes Study (1977 to 1997) that Metformin gained the positive reputation it enjoys today. In the study, overweight diabetics on Metformin lived longer and had fewer heart attacks than those with the same blood glucose levels achieved by using insulin or other drugs. Metformin not only is effective at controlling diabetes but it also helps to prevent some of its long term complications.

The drug has been used in Europe since the late 1950s. However, in the USA, the Food and Drug Administration only approved of the use of the brand name Glucophage in 1994 and the generic Metformin drug finally became available to Americans in 2002.

Visit the project’s website: www.foxgotyou.uk