

THE FOX GOT YOU

Art and science project by photography artist Françoise Sergy

The drug DIGOXIN

Digoxin is extracted from the woolly foxglove, *Digitalis lanata*. This plant is native of Eastern Europe and although widely introduced in Britain, it is not seen as frequently as the common foxglove, *Digitalis purpurea*. Both plants are associated with the same drug: *D. purpurea* is the source of Digitoxin and *D. lanata* produces Digoxin, which is now the favoured active ingredient. Both these compounds are cardiac glycosides: molecules which contain sugars and are used for their therapeutic effect on the heart.

The story of these drugs is centered around English physician and botanist William Withering, who in 1785 published a book, "An Account of the Foxglove and Some of its Medical Uses" which is regarded as one of the first detailed clinical studies of a drug. Prior to his work, the plants were used in folk medicine but little was written about them in learned texts. Other plants with similar therapeutic effects were more well known, particularly the *Scilla* genus which contains related cardiac glycosides. In the mind of the famous 16th c. botanist John Gerard, the foxglove had no place amongst medicines. However, the plant was used by herbalists to treat all sorts of ailments for which, with hindsight, it has no use: such as fevers, tuberculosis and epilepsy. Foxgloves are highly toxic and this may have affected people's perception of them. Past medical knowledge was also inevitably very sketchy. Withering's book provides a fascinating account of the prevailing medical orthodoxy of that time. For a contemporary study of his work, I recommend "An account of the Foxglove and its Medical Uses 1785 - 1985" by J. K. Aronson.

Ten years before he published his account, Withering was shown a list of herbs, including foxglove, used for the successful treatment of the dropsy. The term dropsy described the swelling of soft tissues, which can be caused by, among other things, congestive heart failure, as the condition is now called. At the time, the dropsy was not understood to be a heart problem and diuretics were the only treatment. As foxglove worked for the dropsy, Withering assumed the plant was a diuretic. Today, we know that the drug works on the heart itself.

This is how he describes the event: "I was told that it had long been kept a secret by an old woman in Shropshire, who had sometimes made cures after the more regular practitioners had failed. I was informed also, that the effects produced were violent vomiting and purging; for the diuretic effects seemed to have been overlooked. This medicine was composed of twenty or more different herbs; but it was not difficult for one conversant in these subjects, to perceive, that the active herb could be no other than the Foxglove."

This account shows how valuable the relationship between botanical and medical knowledge was at the time, with Withering the physician able to solve a problem thanks to his skills as a herbalist. After this event, he increased his prescribing of foxglove, particularly when he learned of another successful story, again coming from a lay person who used foxglove to treat the dropsy. Withering prescribed the plant for a range of conditions, with much success in case of the dropsy. Over the years he became an expert on how to administer the drug and his book describes in detail his trials and errors looking for the best therapeutic effects. He aimed for uniformity of dosage by picking only the leaves and always at the same time of year. He tried various formulations until he settled for dried powdered leaf. He used only short-term treatment to avoid toxicity: He had realised the drug easily becomes toxic when allowed to accumulate in the body. This pharmacological characteristic is called a narrow therapeutic index - the gap between the drug having a therapeutic effect and becoming toxic is very narrow.

After Withering's account was published, foxglove enjoyed a period of considerable success, with physicians prescribing it for the dropsy as well as for many other conditions. However, it was often used in the wrong doses and much harm was done by the plant's toxicity. Its use then decreased and in the 19th c. it was mostly prescribed for the wrong ailments and not for the dropsy, which is a shame as the plant was one of the only effective heart treatment of the time.

The *Digitalis* genus contains several cardiac glycosides. These were gradually isolated by chemists and pharmacists from the mid 19th c. onwards. In 1930 Dr Sidney Smith at Burroughs Wellcome isolated Digoxin, which is more effective than Digitoxin and is excreted from the body more rapidly, therefore safer. At the same time, medical science was progressing. Scottish cardiologist Sir James Mackenzie (1853 - 1925) studied the heart pulse and was influential in developing the use of foxglove as a treatment for heart arrhythmias. The invention of the electrocardiogram (ECG) and other techniques for measuring cardiac output allowed clinicians and scientists to further study the action of foxglove on the heart. Gradually they came to understand that the drug affects the heart in two ways: It increases the intensity of the heart muscle contractions and it slows down the rate of the heart beat.

Some of Digoxin's mechanisms of action within heart cells are now quite well understood. One mechanism is that Digoxin inhibits a pump moving sodium ions in and out of cell membranes, causing increased sodium levels within the cell. This triggers another mechanism which increases the level of calcium in the cell. A higher concentration of calcium improves the heart muscle contractions. This in turn slows the heart rate. Another separate mechanism which slows the heart rate is not completely understood.

Digoxin is now primarily used for the treatment of atrial fibrillation, a type of heart arrhythmia. ECGs are the main tool for diagnosing the condition but cardiologists have an array of techniques at their disposal these days, including ultrasound echocardiography, laser treatment and newer drugs. Today the role of Digoxin is on the wane, unlike that of other drugs studied in this project. Recent large scale studies have shown that patients treated with Digoxin are at a higher risk of dying than those on other treatment. Newer drugs have their own shortcomings but the age old drug Digoxin is not proving to be completely safe after all.

So, how poisonous are foxgloves? Very: the entire plant is toxic. There are many reported cases of poisoning, often because foxglove is confused with comfrey, which is used in herbal tea. Foxglove leaves are soft and velvety to the touch, whilst the leaves of comfrey (*Symphytum officinale*) feel rough and hairy. However, accidental deaths are very rare. Anyone suspected of foxglove poisoning or Digoxin overdose is given an antidote which is an effective treatment. Because of its toxicity, foxgloves have acquired in the past some sinister names, such as Dead Man's Bells and Bloody Fingers. The drug's most common possible side effects are nausea, vomiting, diarrhoea, dizziness and rarely skin rash. Severe toxicity can cause visual disturbances with blurred vision or yellow sight. A possible famous case of foxglove poisoning is that of Vincent van Gogh, particularly during his "Yellow Period". The plant was used at the time to control seizures and the painter made several self-portraits which included foxgloves. On the other hand, he may have been under the influence of absinthe, a popular drink then. In 2003 the American nurse Charles Cullen admitted to killing up to 40 hospital patients with medication overdoses, mainly Digoxin. He was sentenced to 18 consecutive life sentences.

When you next admire a foxglove and the bumble bees busy pollinating it, do also admire its deadly powers, which have had such an influence on the course of human medical history.

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