

THE FOX GOT YOU

Art and science project by photography artist Françoise Sergy

The drug COLCHICINE

The drug Colchicine is extracted from the autumn crocus (*Colchicum autumnale*). It is used mainly for the treatment of acute gout attacks. It prevents and reduces inflammation in joints caused by too much uric acid. It is understood to reduce the accumulation of neutrophils, a type of white blood cells which respond rapidly to inflammation and cause the joints to become painful. Colchicine helps to relieve pain and swelling during an acute gout attack.

The drug also inhibits the activity of microtubules fibres within cells, which are essential for cell division. Its use in cancer treatment is being studied but so far the high toxicity of the drug has proved to be a major obstacle in this field. However, Colchicine has been used in plant breeding since 1937, thanks to its action on cell division. Unlike us, plants can experience the doubling or tripling of their chromosomes without ill effects. In fact, this is often to their benefit. This is a condition known as polyploidy, which Colchicine induces. Commercial growers use it to breed cultivars larger in size, faster growing, more hardy or with seedless fruits, amongst other positive effects.

Colchicine is a highly toxic drug. It is only used as a short term treatment and even so has adverse effects which can be severe enough to stop the treatment: Patients can experience nausea, vomiting, diarrhoea and abdominal pain. An overdose can be fatal, particularly as the symptoms associated with severe toxicity are often delayed for several hours: These include cardiac arrhythmias, kidney / liver malfunction leading to multiple organ failure.

The use of the autumn crocus as a poison and in the treatment of gout can be traced back to c. 1550 B.C. The Egyptian medical Ebers Papyrus describes the use of the plant for treatment of rheumatism and swelling. Over the centuries the plant has been known under several names: *Colchicum* and *Ephemerum* by the Greeks, *Hermodactyl* in the 6th cent. A.D. and during the Byzantine Empire, *Surugen* by Arabic scholars (10th - 13th cent. A.D.) and *Herbstzeitlose* during the Renaissance. The plant grows in Colchis, a Greek and Roman area located on the eastern coast of the Black Sea, now part of Georgia: hence the name of *Colchicum*.

The works of the Roman physician Alexander of Tralles (c. A.D. 550) contain the first record of the use of the plant for gout. During the following centuries the plant's popularity in gout treatment waxed and waned, presumably due to its high toxicity.

Colchicum's use in gout treatment was reintroduced in the late 18th century, not by a physician but a military officer in the French Army: Nicolas Husson, who concocted a panacea called "Eau Médicinale". A number of imitations followed and over time the active ingredients were found to be from *Colchicum* corms. In 1848, the British physician Alfred Baring Garrod (1819 -1907) made a major contribution to our knowledge of gout. He demonstrated the increased levels of uric acid in the joints of gout patients. Later he also showed that *Colchicum* does not actually affect the levels of uric acid in the joints and is therefore not a suitable long term treatment for the condition.

Colchicum was isolated chemically in 1820 by French chemist Pierre-Joseph Pelletier and pharmacist Joseph Bienaimé Caventou. In 1833, Geiger and Hesse extracted an active ingredient, which they named colchicine. Several chemists over the years have further elucidated the compound's chemical structure, including Zeisel (1883) and Michael J. S. Dewar (1945). Although the synthesis of colchicine has been experimented on, the drug continues to be produced from the extraction of the autumn crocus. This process is taking place in Asia, particularly in China.

Colchicine has been used for centuries in gout treatment, obviously long before any drugs approval legislation came into being. Also, very few modern studies of the drug have been conducted, particularly in double-blind, placebo-controlled trials which are now the gold standard for the development of pharmaceutical products. In Britain, Colchicine has been approved by NICE, the NHS body which determines the approved use of drugs. NICE quotes an 1987 Australian study, which clearly demonstrated the usefulness of the drug for acute gout.

In the USA however, the approval of the drug by the Food and Drug Administration (FDA) has had a rocky path which has lead to a 50-fold increase in price. For Colchicine to be approved by the FDA, an American trial had to take place and this was done by only one pharmaceutical company, URL Pharma. In 2009 the company was granted approval to market Colchicine as the branded new product Colcrys. Although it had the same active pharmaceutical ingredient as Colchicine, Colcrys was sold for \$5.00 per pill as opposed to 10 cents. The “unapproved” Colchicine continued to be available until 2010, when the FDA ordered a halt to its sale. Although the patent for Colcrys has now expired, Colchicine remains an unapproved drug to-date and its USA production cannot be restarted legally. In 2015 a generic version of Colcrys was finally approved, which hopefully will lead to the costs coming down. Thus an age old drug extracted from a plant became a cash cow for a pharmaceutical company, with the help of the FDA.

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