THE FOX GOT YOU

Art and science project by
photography artist Françoise Sergy

The drug ASPIRIN

The story of Aspirin reads like a novel. For those wanting to know more, I recommend the book "Aspirin" by Diarmuid Jeffreys. Here I shall just highlight the main players in this ongoing saga.

Historically, Aspirin is associated with two plants: the willow and meadowsweet. Both contain salicylic acid which is present in many other plants, where it functions as a plant hormone. The earliest known therapeutic use of willow dates from the Sumerian civilisation in Mesopotamia (now southern Iraq) around 5000 BC. The Egyptian Ebers Papyrus, dating approx. 1550 B.C., mentions myrtle, which also contains salicylic acid, for the treatment of rheumatism. The Greek physician Hippocrates ('the father of medicine') used willow as an analgesic and the Roman physician Celsus used it against the four classic signs of inflammation - redness, heat, pain and swelling. Throughout the centuries willow remained an important plant within folk medicine. Across the world, there is record of its past use in China, southern Africa and by Native Americans. As for meadowsweet, its therapeutic effect on the stomach is described by English herbalist Nicholas Culpeper in 1682 and over the centuries it has had many uses, including that of flavouring mead, the Middle Ages alcoholic drink.

In 1758 the English Reverend Edward Stone started a scientific experiment using white willow bark (Salix alba) to treat a condition called the agues, which caused fever and could be fatal. We now understand that the agues were malaria: The mosquitoes present then in Europe were capable of carrying the malaria parasite. Edward Stone believed that both cause and cure of a disease could be found in the same location. This was a popular theory at that time. The agues were prevalent in marshy areas, where the willow also grows. The bitter taste of the bark reminded him of "Peruvian bark", a known but expensive treatment which came from the south American Cinchona tree (this tree is the original source of the antimalarial drug quinine). After seeing positive results from his experiment, Stone continued to administer the bark powder to his newly found patients for five years. In 1763, he wrote a letter to the Royal Society, the famous learned society for science, detailing his experiment and its outcome. Despite Stone himself not being an established scientist, his work was published by the Royal Society and he has been known ever since as the discoverer of the active ingredient later to become Aspirin.

The precursor of the drug's active ingredient is called salicin. This was first isolated from willow bark by the German chemist Johann Andreas Buchner in 1828. In 1838 Italian chemist Raffaele Piria produced an acid from salicin, which he called salicylic acid. Earlier, in 1830, Swiss pharmacist Johann Pagenstecher had started work on isolating the active ingredient of meadowsweet, or Spiraea ulmaria as it was known at the time. He produced a tincture from the flowers and sent a report to a Swiss journal, which was read by German chemist Karl Jacob Löwig. Löwig used the tincture to isolate an acid, which turned out to be the same as that made by Piria. Salicylic acid started being used to treat fever and rheumatism but soon fell out of favour because of its side effects: The acid badly irritated the mouth and stomach, unlike herbal remedies made from willow bark and meadowsweet. In 1853, French Chemistry Professor Charles Gerhardt managed to synthesise acetylsalicylic acid, which has the advantage of being much milder on the stomach lining. Gerhardt had invented ASA, as it is now known but the chemical process involved had been so laborious that he abandoned the project. It would take another 46 years for the efficient synthesis of ASA to be achieved. Meanwhile, Scottish doctor Thomas John MacLagan began experimenting with salicin, both from willow bark and meadowsweet, to treat rheumatic fever. In 1876, the Lancet medical journal published MacLagan's findings which showed that salicin was very effective in reducing symptoms of fever, inflammation and pain. The price of salicin shot up and soon many other studies were published with similar results.

The next chapter in the Aspirin's story comes from the German dye industry. In the late 1880s, through a prescribing error at a pharmacy, it was discovered that a by-product of coal-tar distillation used in making dye had a fever reducing effect. The substance happened to be chemically related to salicylic acid, even though it had never been intended as a medical treatment. Luckily the patient who was administered it by mistake did not suffer any harm... The dye-making company Bayer began producing a similar compound and selling it as a new drug, with a brand name, something unheard of before. This was to change the purpose of the company over time, from that of making dye to making drugs. For the first time, medicines began to be developed on an industrial scale, as the result of a purely commercial decision rather than a medical one. The modern pharmaceutical industry was born.

Bayer's lab had two sections: the pharmaceutical group which developed new drugs, headed by Arthur Eichengrün and the pharmacology group which tested these new drugs, headed by Heinrich Dreser. In 1897, Eichengrün asked one of his chemists, Felix Hoffman, to work on a version of salicylic acid which wouldn't have its nasty side effects. Later that year, Hoffman succeeded in making ASA in a way that was much more efficient than previous attempts by Gerhardt. The substance was passed onto Dreser's lab for testing but he decided against it because his focus at the time was on another drug. Eichengrün took matters into his own hands, started testing ASA on himself and asked other colleagues to conduct discreet trials in Berlin. All reports came back positive: ASA did not cause unpleasant stomach irritation and was a potent analgesic. Bayer's bosses then ordered more trials and in the end, Dreser had to accept that ASA would go into production. The drug was named in 1899, by using meadowsweet's then Latin name Spiraea, with an "A" in front to acknowledge the acetylation process and an "in" at the end to make it roll off the tongue. Aspirin was born.

Within fifteen years of its launch, Aspirin was one of the most used drugs in the world and sales more than doubled during the 1918-1920 flu pandemic. This period of its history is dominated by patent wars. Bayer was transformed into one of the biggest chemical companies in Germany, in parts thanks to profits from the sales of Aspirin. In 1925, six German chemical manufacturers came together to form one large organisation, IG Farben. The cartel became associated with the Nazi Party and ended up bankrolling it to the tune of 80 million marks. It also funded and was directly involved in horrific concentration camps' so called "scientific experiments". Senior executives were tried for war crimes at Nuremberg in 1948. IG Farben was then broken up by the Allied Powers and Bayer returned to pharmaceutical production, much as it did before the war. Aspirin continued to be one of its most profitable drugs.

In the 1950s, Paracetamol started competing with Aspirin. It had been found that Aspirin still caused damage to the stomach, even though much less so than salicylic acid, and people were looking for alternatives. Soluble Aspirin was developed, which had less side effects. In 1962 Ibuprofen came on the market, developed by Boots, the first new analgesic and anti-inflammatory agent for many years. Both Aspirin and Ibuprofen belong to a class of drugs called Nonsteroidal anti-inflammatory drugs (NSAIDs). Aspirin's domination was on the wane.

In 1982, English pharmacologist John Vane won the Nobel Prize, together with Sune Bergström and Bengt Samuelsson, for discovering how Aspirin works. The molecule stops the production of prostaglandins, which are hormone-like compounds with many important functions. One of these functions is the regulation of inflammation. Prostaglandins play a wide ranging role in the body, which explains why Aspirin is now known to affect several, seemingly unconnected diseases.

Aspirin's three main modes of action are: Firstly, in very large doses, it acts on the swelling, heat and pain of inflammation, such as in rheumatism. Here it has largely been replaced by other drugs, because of its damaging side effects on the stomach lining. Secondly, in average doses, it inhibits pain, such as for headaches. This is still the most common use of the drug. Thirdly, in small doses, Aspirin helps to "thin the blood" and prevent heart attacks and strokes (more on this in the article on the William Harvey Research Institute). More recently it has also been found that Aspirin reduces the risk of some cancers and may have a role to play in dementia. The story of this wonder drug is set to continue well into the 21st century.

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