

## EDITORIAL

## TRAVELLING THROUGH TIME WITH ASPIRIN, A HEALING COMPANION

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**Four thousand years ago the willow tree was known for its palliative effects. Ancient Greeks used the extract from the cortex and leaves to treat pain, fever, calluses and to enhance semen quality. Bayer Company and Felix Hoffmann claimed discovery of aspirin, and chemists all over Europe dealt with the synthesis of the drug. During 1988 the use of Aspirin was extended from an analgesic, antipyretic to a life-saving drug as it was suggested that it reduced the danger of cardiovascular accidents. Aspirin is still a drug that can offer much to medicine.**

From the willow tree extracts to the synthetic acetylsalicylic acid, Aspirin traced a long journey in pharmaceutical history. Considered as the first discovered member of an evolutionary class of drugs known as nonsteroidal anti-inflammatory and one of the most widely used medications in the world, aspirin continues to surprise us with its applications and therapeutical properties.

*Willow tree: the precursor of aspirin*

Sumerians were the first civilization to provide medical advice for pain treatment 4,000 years ago. The Babylonians used willow tree bark and leaf extract to treat fever, pain and inflammation. Willow tree bark and leaves are also mentioned in ancient Egyptians scriptures (Ebers papyrus 1500 B.C.) (1-2). In Chinese medicine, leaves of *Populus alba* L. and *Salix babylonica* L. were used to palliate rheumatic pain and treat cold, haemorrhage and goiter. Willow tree bark was also used as a general antiseptic for the treatment of wounds and abscesses.

The father of medicine Hippocrates (3) (460-370 B.C.) recommended a brew from the bark (*Cortex salicis*) to treat ophthalmic pain and palliate the

pain during labor. In Ancient Greece the willow tree was well known for its medical applications. Aristotle (4), Theophrastus (5), and Dioscorides (6) used it for the treatment of nail diseases and callosities. Aetios (7) mentions the analgesic, antiseptic and dermatological qualities of the willow tree and suggests its application for the induction of menstruation. Improvement of the semen is also pointed out (3). Roman physicians knew all about the tea from the willow tree's bole and Roman legions always carried vast stocks of it as it was used mainly as a pain killer.

*The birth of aspirin*

In 1763, Edmund Stone made an extract from the cortex of a willow tree, dispensed it to 50 patients and he discovered its property on fever reduction. In 1828, Johann Buchner professor of pharmacology at Munich University, isolated a yellow bitter acicula crystal from willow bark and named it *salicin* from the willow tree's Latin name. In 1829, Henri Leroux improved the extraction process and managed to obtain 30 gr of salicin out of 1.5 kg of cortex. He is mentioned as the first to produce it in crystal form.

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In 1831, Johann Pagenstecher, a Swiss pharmacist, dispensed salicylaldehyde with the infusion of the “meadowsweet” bloom and sent it to the German chemist Karl Löwig, who, with oxidation, finally produced salicylic acid.

In 1853, the French chemist Charles Frederich Gerhardt compounded sodium salicylate with acetyl-chloride and synthesized a totally new substance, “acetylsalicylic acid”. The procedure was so complicated that he was forced to abandon it and never worked on this research again. He died at 40 years of age, not knowing what he had given up (8).

In 1863, Bayer was founded in Germany as a dye manufacturing company under the name Friedrich Bayer & Co., but the founders soon tried to advance the research on acetylsalicylic acid. For this purpose Felix Hoffmann (9), a young chemist, was hired to work in Bayer’s medical labs. In 1897, Hoffmann synthesized the first sample of ASA (acetosalicylic anhydride) and tested it on his own father for the relief of rheumatic pain. The company’s switch from dyes to pharmaceuticals was so rapid that the first lots of the drug were alkylated in empty beer bottles wrapped in towels before the company decided to invest in suitable equipment and proper facilities for its production (10). But Heinrich Dresser, chief of the pharmacological division for testing drugs, was not positive about the new substance as he thought it was just a bitter-tasting salicylic acid unworthy of production. Carl Duisberg, head of Bayer research, gave the drug to external pharmacologists and physicians to be tested. The test was a success and Bayer’s chemist, Arthur Eichengrün, even tested it on himself. After this success Dresser published a paper for the ASA, without mentioning Eichengrün and Hoffmann (11).

In fact, it is very difficult to determine who invented Aspirin; even though Charles Frédéric Gerhardt had already synthesized ASA, and named it “acetosalicylic anhydride”, which was not necessarily the same as “acetylsalicylic acid”, two Italians, Brugnatelli and Fontana, produced ASA in an impure form. Italian chemist, Raffaele Piria, synthesized ASA in a purer form in 1838. ASA in its purest form was produced by Johann Kraut in 1869. Acetylsalicylic acid was already under production in the factory of chemist Fabrik von Heyden in 1897, though without a brand name. Consequently, it is

doubtful that Hoffmann in 1897 truly synthesized a new chemical product and even less likely that he developed a new method for the production of a new substance that could be patented in Germany (9).

On March the 6<sup>th</sup> 1899, the product was named with its commercial appellation “ASPIRIN” (A– acetylation, SPIR– from the plant *Spiraea ulmaria* (meadowsweet), from which the salicylic acid was first isolated, IN– a common ending for drugs in that era). In 1899, the Bayer Company released ASA in its powder form and honored Hoffman for his discovery. The drug was advertised to more than 30,000 physicians. This was the first example of mass production and promotion of a drug; it soon spread in Europe and the United States (11).

#### *Publicity and application of aspirin in 20<sup>th</sup> century*

In 1900, Bayer introduced aspirin in water-soluble tablets (the first medication to be sold in this form), reduced the cost and put the inscription “Does not affect the heart” on the package. The inscription, as many researchers believed later on, was a scientific irony and an inaccurate statement, as earlier observations had shown enfeebling action on the heart in large dosages (12-13). This inscription was prohibited in 1930 and nowadays aspirin is considered an excellent drug for the heart. Failing to continue the “Heart” campaign Bayer, began the “Cold” campaign “throw off that cold”. Approximately two decades later that was also prohibited. Also in progress were the “Demand” campaign (Demand Bayer Aspirin) and the “2 seconds” campaign (shortest time to feel the Aspirin’s palliative effect).

As mentioned in the Text-book of Pharmacology and Therapeutics of 1901, Aspirin was considered to be more an analgesic (even for cancer pain) than an antipyretic. It is still being used as a pain killer for cancer patients during the terminal stage of their illness.

In 1915, Aspirin manufactured in tablet form became available without a prescription. As soon as the First World War ended and Germany surrendered, Bayer had to give away its registered trademark of Aspirin. Thus “Aspirin” became a generic name in the countries that emerged as winners of the war but remained a registered trademark of Bayer in countries like Germany, Mexico, Canada and over

80 other countries. After the patents ended many pharmaceutical companies in America began the mass production of Aspirin. Their campaigns were destined to be doomed. The First World War had ended but Bayer's war against the world had just begun.

The 1918, the Spanish flu pandemic which is thought to be a precursor of H1N1 virus could also be called Aspirin "virus". Pathologists of that period mention that among the flu pandemic survivors were patients in whose medication Aspirin was not included. Great numbers of patients affected by the Spanish flu died from pneumonia (secondary bacterial infection); today we know that Aspirin causes lung fluid concentration, angioedema, stupor, it suspends inflammatory factors and provokes lung and gastric haemorrhage. Aspirin causes great difficulty for the human organism to shed exogenous fungi (14). We also must consider Reyes Syndrome in childhood caused by the vast amount of Aspirin used. Ironically, in early October of 1918, just before the flu's deadliest peak, the US Navy and The Journal of the American Medical Association proposed the use of Aspirin against the virus. Physicians prescribed Aspirin in large dosages.

During the 1920's Aspirin was used for the treatment of pain associated with rheumatism, lumbago and neuralgia. In the 1930's Bayer began a big commercial campaign throughout Europe (especially in France) and Asia (especially China) (8). The end of the Second World War left Germany in ruins; but Bayer, with its pride and ego wounded, launched an offensive commercial policy to establish an economic victory against rivals; a policy that changed drug promotion forever. They hired chemists to contact and advise physicians 'help doctors to help their patients' (11). In 1948, Dr. Lawrence Craven, a doctor from California, observed that not one of his 400 patients treated with Aspirin suffered a heart attack. He recommended to his colleagues that 'an Aspirin per day dramatically reduces the danger of heart attack'. Aspirin made the 1950 Guinness Book of Records as the world's most popular pain-killing drug.

Aspirin's antiplatelet action was first observed in 1967 by Harvey Weiss and Louis Aledort who divided their patients into two groups: Aspirin takers and non-takers. With the use of a fine needle they

examined the degree of bleeding and the clotting time; they observed that the group of Aspirin's takers had a longer coagulation time (15). In 1969, Aspirin was included in the astronauts' medical kits in the Apollo project.

At the beginning of the 1970's the world of medicine began to understand how Aspirin works and they discovered that it inhibits the production of prostaglandins (16). These chemical substances are involved in the process of inflammation. In 1971, the English pharmacologist, Sir John Vane, who considered Aspirin to be a mysterious drug, experimented on himself and found out that it suspends inflammation factors.

In 1984, Toleraid® microcoating (clear coat) was added to the authentic Aspirin and made it easier to swallow.

In 1988, the use of Aspirin was extended from a palliative to a life-saving drug. The FDA suggested that it reduces the risk of myocardial infarction, protects from unstable angina pectoris and is suitable for patients who have already suffered from an infarct. The FDA also approved its use to prevent or to improve damage of ischemic cerebral attack. An intensive research on its involvement in the prevention of oesophageal cancer started at the same time. A 1996 study under the Massachusetts Institute of Technology shows that double the number of people chose Aspirin, instead of the personal computer, as the invention that they could not live without.

In 1998, the results of the Thrombosis Prevention Trial (TPT; Lancet) confirmed ASA's efficacy in the prevention of myocardial infarction in patients with cardiovascular risk factors. At the same time (1998) The Hypertension Optimal Treatment study (17), demonstrates that in combination with anti-hypertensive drugs it reduces the infarct incidents in patients with high blood pressure.

Americans consume 50 million tablets of Aspirin per year. Every man over 40 years of age and women over 50 consume the miracle 100-year-old drug. Every year 70 million pounds of Aspirin are produced which makes it the most proliferous drug all over the world.

For 60 years Aspirin won every battle against its generics and was the king of analgesic drugs. The first defeat in battle came in 1956 with the

introduction of paracetamol on the market, and eventually the war was lost by the introduction of ibuprofen in 1969. In an attempt to force its way back onto the market even chocolate Aspirins were introduced. Half a century after dropping the cold campaign (failure of supporting evidence), Bayer introduced Aspirin combined with vitamin C and started a new commercial promotion under the “cold protective’s” flag (18).

### CONCLUSION

The unique story of aspirin to a great extent epitomizes the stories of many pharmaceutical products developed both for therapeutic efficacy and for profit. Franz Kafka once explained to his fiancée Felice Bauer, in the course of their tormented relationship, that aspirin was one of the few things that eased the unbearable pain of being (11). It is quite possible Aspirin will make news again. Its history is always a motivation for continuous research and we, as historians, shall wait to record the next chapter of the “Aspirin” adventure.

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