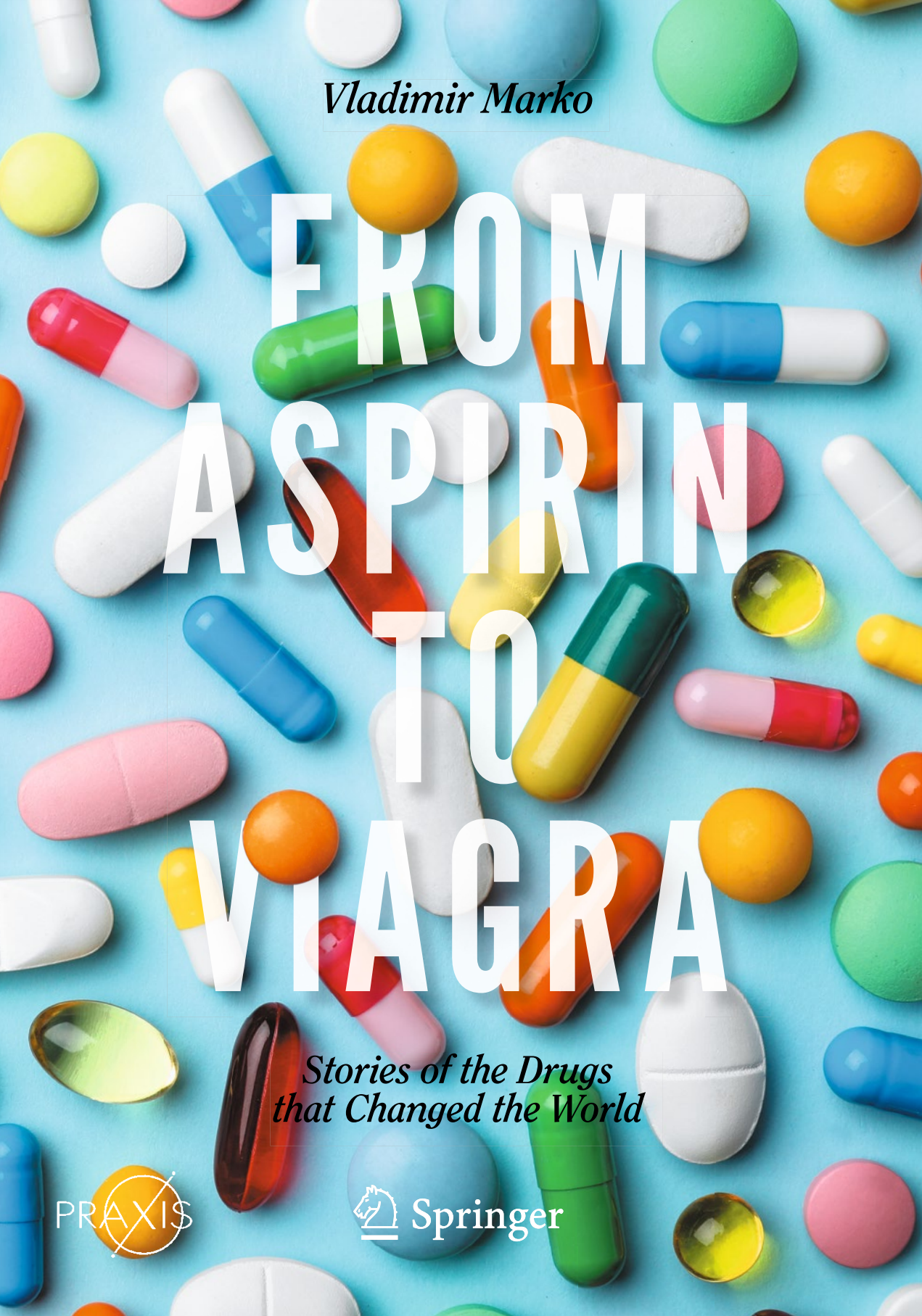
Vladimir Marko
FROM ASPIRIN TO VIAGRA
Stories of the Drugs that Changed the World
PRAXIS
Springer

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To my wife for 44 years of our lives

About the Author

Dr. Vladimir Marko PhD comes from Slovakia. He was born in 1952. He studied at the Slovak Technical University, finishing his studies in organic chemistry in 1975 and his PhD studies in biochemistry in 1980. He then spent ten years working as a researcher at the Institute of Experimental Pharmacology of the Slovak Academy of Sciences before changing his professional life completely by moving into business as a country representative of the Dutch company Chrompack, dealing with analytical instruments. From 1994, he worked for 20 years for the Danish-based pharmaceutical company Lundbeck, first as a representative and later as the Managing Director for Slovakia.

He is the author of numerous scientific papers concerning the synthesis and analysis of drugs and was the editor for a book dealing with drug determinations (Marko V., Ed.: *Determination of Beta-Blockers in Biological Material*, Elsevier Science Publishers, Amsterdam, New York, 1989, ISBN 0-444-87305-8). Dr. Marko has also authored several tens of popular articles that have been published in various Slovak weeklies, dealing with drugs, medicine and history.

He likes running (he has run 20 marathons) and mountaineering, and regards himself as a connoisseur of food and drink.

He has been married for 44 years, with no children.

Preface

Recently, I opened our medicine cabinet at home and found an assortment of 36 different drugs. And honestly, my wife and I consider ourselves to be healthy people. If we look back 100 years, we would have had, at best, bottles of aspirin and quinine. It is very difficult to imagine the world at the dawn of the 20th century, when we were unaware of the existence of very common things used today, like penicillin, insulin or vitamin C, let alone innovations like contraceptives or drugs that fight mental disorders. We did not know a large majority of the drugs that we see as a natural part of our lives today, to the point that often we are not even aware of how we depend on them. Had these drugs not existed, the majority of us would not even be alive today and would not be able to read this book. Our parents or our grandparents would likely have died due to one of the vast number of deadly diseases that have plagued humankind since the beginning of time.

The drugs we know of today have a short history. Until the 19th century, official medicine had no actual need for these drugs. For many centuries, starting from ancient times, diseases were thought to be caused by an imbalance of four basic bodily fluids: blood, phlegm, yellow bile and black bile. Doctors were meant to rebalance these fluids through methods like bloodletting, the use of leeches, serving laxatives, enemas, or substances inducing vomiting. Over the course of one year, the French King Louis XIII received 212 enemas, was induced to vomit 215 times and underwent bloodletting 47 times. His son and heir, Louis XIV, was rumored to have undergone more than 200,000 enemas, sometimes as many as four a day. The French playwright J.B. Molière illustrated the situation with official medicine very well in one of his plays: "(*Doctors) can talk fine Latin, can give a Greek name to every disease, can define and distinguish them; but as to curing these diseases, that's out of the question.*" Those who were reliant on the help of this kind of medicine were more or less out of luck. When George Washington became ill in 1799 and began to complain of neck pain, the medical help that was

called upon did everything within their capacity to assist. They induced blisters and let his blood. He ended up losing about two and a half liters of blood, but despite—or more likely because—of this treatment, George Washington died ten hours later.

It was much easier for the common people. They would often seek help from the unofficial medicine practiced mostly by village women. These healers were not interested in the official teachings of bodily fluids. Instead, they would focus more on the objects that they found around themselves. They knew of the properties of many different flowers and herbs and would use them to cure diseases, although this came at the risk of being accused of witchcraft and burned at the stake. Some of these methods are still used today. An example of the difference between official and unofficial medicine was the approach to treating scurvy in the 18th century. Scurvy, as we now know, is a disease caused by the deficiency of vitamin C. Official medicine said that it was caused by a disease of the black bile, which they considered to be dry and cold. For this reason, they considered it necessary to treat it with something warm and moist, such as a broth brewed of barley. They did not use citrus fruits because these were also cold. A Miss Mitchell from Hasfield, located in the province of the Duchy of Gloucestershire, knew nothing of black bile and instead used a mixture of medicinal herbs, wine and orange juice to treat scurvy.

This book contains stories from the history of ten different drugs that have greatly influenced humanity. They are, in alphabetic order: aspirin, chlorpromazine, contraceptive pills, insulin, penicillin, Prozac, quinine, vaccines, Viagra, and vitamin C. The selection of these drugs is often subjective. The author's intent was not to describe the drugs as such, but instead to map the road that was taken to their discovery or invention. The road was often rough, but also adventurous. At the same time, the author looked to record the circumstances associated with their subsequent life. This book is also about the people who chose this path. The majority of them, with the exception of a few charlatans, were inspired by their deep need to help others and by their belief that what they were doing was the right thing, even if by today's standards their methods were harsh.

Vladimir Marko
January 2020

1

Aspirin

No other medicine has such a long and rich history as aspirin. The story of aspirin dates back to ancient times, when people were just beginning to learn of the medicinal properties of willow bark – a kind of predecessor of aspirin. Willow bark was a part of ancient Egyptian, classical, and medieval medicine, though the first scientific mention of its effects comes from the mid-18th century.

It has been over 120 years since aspirin was first introduced as a pharmaceutical preparation, yet even today you would be hard pressed to find a household that does not have those little, white, acetylsalicylic acid-containing tablets in the medicine cabinet. It is hard to imagine that this small wonder can relieve pain, reduce fever and stop a migraine, prevent heart attacks, strokes and thrombosis, and even potentially be used to treat certain types of cancer.

In the stories about the history of aspirin, you will meet a curious vicar, an unrecognized Jewish inventor, and one of the first great captains of industry. You will also meet a spy, uncommonly resourceful marketers, and, of course, plenty of dedicated chemists and physicians. The history of aspirin plays out against the backdrop of the history of the pharmaceutical industry as a whole, allowing us to see how the industry developed from modest beginnings in the late 19th century, when it was something of a pendant on the dye industry chain, all the way through to today, when it is one of the largest and most powerful economic sectors with an annual turnover of nearly a trillion dollars.

The name *aspirin* itself can be contentious. While in some countries, such as Germany, the name Aspirin is a registered trademark with strict rules for capitalizing the first letter, in most countries the word aspirin is used as a genericized name without the initial capital.

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Story 1.1: The curious reverend and the bark of the willow

Chipping Norton is a smallish, idyllic town in the county of Oxfordshire, England, situated about 30 km northwest of Oxford. According to the most recent census taken in 2011, it has an exact population of 6,337 residents. It is home to the Church of the Virgin Mary which dates back to the 15th century and it also boasts the oldest golf course in the county. The church was recently used as a location for a recording studio, frequented by such legends as Duran Duran, Status Quo and Alison Moyet. We should note that as a village, Chipping Norton is not only idyllic, but also very healthy. Nine out of ten residents claimed to be satisfied with their own health, according to a recent study.

Let us go back 260 years. If a similar study had been carried out in the mid-18th century, the era where our first story takes place, we would have found the results to be the exact opposite. By all accounts, almost everyone would have been afflicted with some of the many common illnesses at the time. High humidity, poor hygiene and malnutrition were, by and large, the main reasons for the majority of diseases. The causes of illness were unknown and treatment methods were from medieval times at best. Essentially, only two medical interventions existed at the time – laxatives and bloodletting – and a visit to the doctor was much more expensive than self-treatment, which only made matters worse. At the time of our story, the Reverend Edward Stone himself was not particularly healthy. When we meet him in 1758, he is 56 years old, quite an advanced age for a man in the 18th century. He lived alone on the outskirts of the town and his position as chaplain in nearby Chipping Norton secured him a comfortable living. Like many older people, Edward suffered with rheumatism.

The rheumatic pain, however, did not prevent him from taking regular strolls beside a small stream that flowed through Chipping Norton, and the town council had planted an alley of willows which made his walks more pleasant. On one such occasion, he unwittingly peeled off a piece of willow bark and put it in his mouth. He was immediately hit with a strong, bitter taste. It reminded him of the taste of cinchona bark, which he was very familiar with as it was the only effective way to treat a fever at that time. That fever was malaria, something the people of the 18th century were not aware of. The good Reverend Stone got the idea to use willow bark in place of the much more expensive cinchona as a way of treating fevers. There was also a scientific reason behind his decision. In the latter half of the 18th century, the prevailing theory was that things which were alike belonged to the same group. Therefore, they believed that each disease should be treated with a substance that in one way or another resembled the disease itself. They used deep blue iris flowers to treat bruises; jaundice was treated with yellow goldenrod flowers; lung illnesses were treated with lungwort leaves, which are lung-shaped. The same principle can be seen in the centuries-long use of crushed rhinoceros horn to increase male potency (the similarity requires no

explanation). Sadly, even though many of the medicinal methods that follow this principal have long fallen out of use, rhinoceroses are still being slaughtered in the "Viagra Era."

But let us return to the Reverend Stone's willow bark theory. He reasoned that since fevers arose from the wet and cold, its treatment could be successful using something also found in wet and cold places. This is where the willow comes in and so this willow bark marks the beginning of the history of aspirin.

If you should ever dare to taste a piece of willow bark like Edward Stone, you would instantly be hit with a very intense, bitter taste. Together with this taste, a very small amount of salicin would enter your body. The name salicin comes from the Latin word for willow, *salix*. The salicin that enters the body later decomposes into salicylic acid. This is the exact same salicylic acid created in your body when you swallow that small white pill called aspirin. Aspirin and willow bark have the same active substance that reduces fever, reduces pain and has a whole host of other healing effects. Our distant ancestors similarly experimented with willow bark because their survival depended on their knowledge and use of everything they found around them. They were very likely familiar not only with the distinct taste of willow bark, but also its medicinal properties. Willow bark is most likely one of the oldest natural healing substances in the world.

The first written mention of willow bark, from which we can at least assume the writer was aware of its medicinal effects, dates back 3,600 years. It is on an ancient Egyptian papyrus manuscript called the *Ebers Papyrus* that originates from around 1550 BCE, but some parts of it also contain knowledge recorded from a significantly older period. Measuring 20 m long and 30 cm high, the papyrus contains writing on both sides. It is the most valuable piece of information found about ancient Egyptian medicine and health sciences. It also contains about 700 different magical formulae and medicinal products, 160 of which are plants such as dates, figs, grapes and pomegranates, as well as many different spices and seasonings such as coriander, caraway, fennel, mint and thyme. We can find willow among them, with its effects described in three different places.

Willow bark and willow bark preparations can be found later in history as well. Hippocrates, the most famous doctor of antiquity, also known as the "Father of Medicine," suggested the use of willow bark as a remedy against the pain of childbirth and to reduce fevers as far back as 500 BCE. Around 500 years later, the therapeutic possibilities of willow bark were introduced by Pliny the Elder in his 37-volume work. Another 130 years later, Galen of Pergamon also suggested willow bark to be an effective pain killing method. Given that he was a doctor for gladiators, he had plenty of experience with treating pain.

Willow bark is not the only natural source of salicin. Numerous different plants also contain it, including a plant with a pleasant name, meadowsweet (Latin *Filipendula ulmaria* or, in the older nomenclature, *Spiraea ulmaria*; remember this name, because we will come back to it).

The medicinal use of willow bark and other natural sources containing salicin did not end with the invention of aspirin. Dry willow bark and meadowsweet can be found in today's pharmacies as well, often promoted as a natural alternative to aspirin. The Yupiks are a curious example of how healing practitioners were able to use natural sources as medicine. They are an Eskimo tribe that live in Western Alaska and in Eastern Siberia. They knew of and used the healing properties of *castoreum*, a sticky secretion that beavers (*Castor* in Latin) use to mark their territory. The Yupiks dried the *castoreum* and used it as a pain killer. Modern analytical methods later discovered that *castoreum* has a very high salicin content, as a result of beavers gnawing willow bark to build their dams. *Castoreum* is a valuable resource today, and due to its animal scent it is a sought-after ingredient for perfumes, even by the most popular brands.

Now let us return to the latter half of the 18th century and to Edward Stone, because the story of this English cleric from Chipping Norton is a real milestone in the history of aspirin. His work is one of the first clinical tests of medicinal products in history. It is also an example of how sometimes an incorrect assumption can lead to a positive result.

Given that he scientifically verified his method – that which originates from the moist and cold is treated with that which grows in the moist and cold – he started to collect willow bark. It had to be dried, so Reverend Stone asked the local blacksmith if he could dry it in his workshop. When he dried around half a kilogram of it, he decided to test its effects. He knew nothing of what an effective dose might be, so he started with small amounts. In today's measurement standards, his initial dose was one and a quarter grams of willow bark powder and he served the powder once every four hours. The symptoms started to subside a little bit, so he increased the dose to two and a half grams, causing the fever to disappear completely. We do not know who his first patients were or how he convinced them to take part in his "clinical test." After the first success, word apparently spread around and over the course of five years Reverend Stone treated – and cured – 50 patients of their fevers.

He recorded his entire procedure in a report he sent on April 25, 1763 to the highest scientific authority in England at the time, Lord Macclesfield, President of the Royal Society of London. This report contained a very meticulous description of his procedure, his scientific reasoning and results, which are preserved to this day. His ancient style of writing resembles an extract from a very beautiful work of literature. Considering later developments, the first sentence of his letter is practically a prophecy: "*Among many of the useful discoveries, which this age hath made, there are very few which deserve the attention of the public more than what I am going to lay before your Lordship*."

He was correct in this statement. In most others, however, he had been mistaken. His first mistake was the belief that he had found a way of curing fevers. He had not. He had merely found a way to reduce body temperatures, and it was not

due to the fact that willows and fevers originate in moist environments. Today, we know that willow bark contains salicin, from which salicylic acid is created in the organism. We also know that salicylic acid reduces temperatures and relieves pain.

Only a church, an alms-house, three inns and a few other buildings remain from the time of Edward Stone in Chipping Norton, although the alley of willows where the local stream used to flow is still said to exist. Today's willows, however, are just a reminder of the trees that grew there long ago when Edward Stone took his piece of bark to experiment with, his efforts becoming part of the history of aspirin.

Story 1.2: The three fathers and the two miracle drugs

On Monday, August 26, 1856, 18-year-old William Henry Perkin patented his method for producing a purple dye he named *mauveine*. Purple, the color of the powerful, rich and famous, made Perkin rich and famous as well. But the impact of the discovery was far more wide-ranging than just the fame and fortune of one person – Perkin's mauveine ignited the chemical dye industry which would shape the chemical industry for the next 50 years. The dyeing industry would become not only the chief field of the chemical industry but also a very lucrative business and dye factories sprang up like mushrooms in the latter half of the 19th century. Many have long since closed their doors, but some remain in business to this day, one of which is Friedrich Bayer & Comp., incorporated in August 1863.

But let us return to willow bark. A pure form of salicin was isolated in 1829 and it was assumed that this is what gave the bark its healing properties. Surprisingly, salicin is not the substance that reduces fevers and relieves pain, as it is unstable and breaks down in the human body. It is metabolized in part into salicylic acid, which is the substance that actually causes salicin to have antipyretic and analgesic properties – the same effects as willow bark. At the time, it was relatively simple to mass-produce salicylic acid chemically and it was therefore expected to gain prominence rapidly. It did not. There was one major disadvantage to using salicylic acid, in that it caused severe gastrointestinal discomfort. The fact that it is still used today to remove warts is proof of how aggressive the substance can be. Patients who took it complained of severe irritation when swallowing the drug and extreme burning sensations in the stomach. They had to work on finding a compound with two properties – it had to be gentler on the digestive tract and metabolize into effective salicylic acid.

That is where the famous history of Farbenfabriken vormals Friedrich Bayer & Comp. begins (for simplicity, we will refer to it by the company's more familiar name – Bayer). The primary focus of the company was the production of dyes, and they even included that in the name. Bayer was one of the first dye

manufacturers to realize that their new-found knowledge could be put to another use, in the development and manufacture of medicines. In 1890, the company established a small pharmaceutical department, staffed by three young scientists who would later become the "fathers" of aspirin: Heinrich Dreser, Arthur Eichengrün and Felix Hoffmann. Each of them had a different personality and each contributed to the development of aspirin in his own way.

Born in 1860, Heinrich Dreser was the oldest of the three and by the time he took up employment at Bayer, he was already a full professor at the University of Bonn. His father was a physics professor, and Heinrich was brought up to be painstaking and methodical. He was a perfectionist and not very popular among his colleagues, but he was highly respected in his field of pharmacological drug testing. His methodological approach is evidenced by the fact that he was one of the first scientists to test drugs on laboratory animals.

Little information remains about his private life, apart from the fact he was a wealthy man. His contract with the parent company contained a clause that entitled him to royalties on the drugs he tested in his laboratory. After he left the company in 1914, he established a pharmacological institute in Dusseldorf. He played the violin, viola, and cello and was married twice; his first wife died and he married his second wife just prior to his own death. He died, childless, of a stroke at the age of 64. There was one more thing he was known for, but we will return to that at the end of this story.

Arthur Eichengrün, the second of the "fathers of aspirin" was extroverted and charismatic, the exact opposite of his older colleague. He was born in 1867 as the son of a Jewish cloth merchant and began his employment in the pharmaceutical department at Bayer on October 1, 1896, where he took over responsibility for the development of new drugs. Unlike the lives of his colleagues, his own life is well-documented and may be worth making into a movie. He was successful, likeable, and rich. He was married three times and had six children. He had what you might call a turbulent life. After leaving Bayer, he went on to establish a successful company that manufactured compounds based on cellulose. The success of the company was built on his inventions (he held 47 patents) and with the start of World War I, military contracts added to that success. When the war ended, he was quickly able to turn his focus from military applications of his products to civil applications.

His company continued to prosper, and it would probably have continued to do so for many years had Arthur Eichengrün not been Jewish. His success came to a halt in the 1930s. With the rise of Nazism in Germany, his company was slowly "Aryanized" and in 1938, ownership was transferred to the Germans. Eichengrün effectively lost all his assets, but his problems were only just beginning. In 1943, he was arrested and transported to the concentration camp in Terezín (Theresienstadt in German). Not only did he survive the concentration camp, but when the war ended he regrouped and continued his scientific work. In spite of the tragedies that struck his life, he lived to a relatively old age, dying in 1949 at the age of 82.

The youngest of the trio, Felix Hoffmann, was born in 1868 as the son of an industrialist. Like his two older colleagues, he received a first-rate education in chemistry. He went to work for Bayer in 1894, shortly after earning his doctorate. He worked in the department that was later taken over by Arthur Eichengrün. Unlike his boss, though, Felix Hoffmann was an introvert and there is even less information remaining about his life than there is about the life of Heinrich Dreser. Once the development of aspirin was finished, he did not continue in his scientific career and instead worked in marketing, where he remained until his retirement in 1928. He died unmarried and without children on February 8, 1946.

In official documents, August 10, 1897 is considered the vital date in the history of aspirin. That was the day Felix Hoffmann prepared acetylsalicylic acid using a process that yielded a quality good enough to make it ready for mass-production and for use as a medicine. Allegedly, one of the reasons for Hoffman's interest in acetylsalicylic acid was purely personal. His father used it to treat his rheumatism but, like all patients, he complained of the terrible taste. A son's love played a role in the history of aspirin.

Felix Hoffmann was not the first to be interested in acetylsalicylic acid. That would be a Frenchman named Charles Frédéric Gerhardt, a professor at the University of Montpellier. He had prepared it nearly 50 years earlier, but while Gerhardt's goal was to study the properties of substances (in his case acids), Felix Hoffmann turned his attention to preparing the compound as the basis for manufacturing a new drug. When you look at how each of these chemists approached the subject, it is easy to see the difference between academic research and corporate research.

When Felix Hoffmann prepared acetylsalicylic acid, his boss, Arthur Eichengrün, immediately sent it to Heinrich Dreser's pharmacology group for research – and he surprisingly refused. He was convinced the new substance would have "enfeebling" effects on the heart. He even said something to the effect of it not having much practical use. He was far more hopeful about another compound he was working on at the time, and like acetylsalicylic acid, it too went down in history. But we will come to that later.

Fortunately, Eichengrün did not give up. He went around Dreser and, after testing the new compound on himself, he secretly sent it for clinical trials to Berlin. The results were good, and when two independent studies subsequently confirmed the benefits of the new substance, Dreser was forced to give his approval, which he did in September 1898.

Thus, Bayer introduced a new drug to the pharmaceutical market. It was registered by the Imperial Patent Office on March 8, 1899 under the name Aspirin. There are three parts to the name: *A* for acetylation, *spir* for the spirea plant, and *in* as the typical suffix for drug names that make them easy to pronounce.

So, who is the real father of aspirin? Right after Aspirin was approved, Heinrich Dreser was tasked with writing about the properties of the new drug for a science

magazine. The first scientific information about the new drug was made public in 1899, but there was a catch. He named only himself as the author of the article – maybe out of spite for being forced to approve the drug. His text did not mention Hoffman or Eichengrün, nor give any information about how Aspirin was developed, so the contribution of the other two chemists remained unknown for many years. It was not until 1933 that the first mention of Felix Hoffmann's participation in the development of aspirin was mentioned; Hoffmann is now officially credited as having invented it.

Fifty years later, Arthur Eichengrün wrote a detailed report about the process by which aspirin was invented and, at the same time, claimed to have invented it. He claimed that acetylation of salicylic acid had been his idea and that Hoffmann had only brought his idea to fruition. His arguments were convincing, as was his reason for why his name had never been associated with aspirin. It was inconceivable in the time of Nazism that a Jew would be the inventor of such an important drug. However, Felix Hoffmann is still officially credited for the invention of aspirin, and on its website even Bayer confirms this. We will probably never know the exact role and contribution of each of the three "fathers" in the development of aspirin, but the fact remains that Arthur Eichengrün was the first to have the idea to acetylate salicylic acid, Felix Hoffmann was the first to hold the finished product in his hand, and Heinrich Dreser was the first to describe aspirin.

But more important than who invented it is the fact that aspirin is one of the first drugs that definitely resulted from teamwork.

That could easily be the end of the story about how aspirin was discovered, but there is just one more thing. The acetylation of salicylic acid was not the only reaction of this type pursued by Felix Hoffmann. At the same time, he was trying to acetylate morphine, a substance isolated from opium, which has remarkable pharmacological properties. It effectively relieves pain and acts as a cough suppressant, but it is also addictive, which greatly reduces its possibilities for use. While the acetylation of salicylic acid was meant to prepare a non-irritating alternative, the acetylation of morphine was meant to prepare its non-addictive alternative to morphine. Hoffmann was also successful with this acetylation and although he was not the first in this case either, he was able to prepare a pharmaceutically usable product. The resulting substance, diacetylmorphine, was tested with positive results. It effectively suppressed coughs and was useful for other respiratory problems. The effects were so powerful that some users called it "heroic." This was the substance that Heinrich Dreser had more faith in than aspirin. Bayer released two "miracle" drugs around the same time – one was a drug called Aspirin that reduced temperatures and relieved pain, while the other was a drug that suppressed coughs and provided relief for lung diseases. It was called Heroin. Today, we know that both aspirin and heroin have had a significant influence on humanity, but that is a different history that we will not be covering here. But we do owe

you an answer about what was said about Heinrich Dreser. Rumor had it that he was addicted to heroin.

Felix Hoffmann died without any direct heirs, but his two 'children' live on: the immensely useful aspirin and the immensely harmful heroin.

Story 1.3: The industrialist and his business

Carl Duisberg did not go down in history as a famous inventor, but he did go down as a great organizer and leader. Today his name is long forgotten, but during his lifetime it was a name as respected as Rockefeller or Rothschild.

Duisberg was instrumental in the invention of aspirin and in making aspirin the most successful drug in history. He was also instrumental in transforming a small dye manufacturer into one of the giants of the pharmaceutical industry. When he took a job at Bayer as a chemist at the age of 23, it was a small factory that manufactured dyes. When he died at the age of 74, he left behind one of the largest companies in the world.

Duisberg was born on September 29, 1861. His father had hopes that his son would take over the small weaving business founded by Carl's grandfather, but Carl Duisberg wanted to be a chemist. He graduated from high school at the age of 15, from university at 18, and received his doctorate at the age of 20. There was a glut of chemists at the time and it took Duisberg a while to find employment. He signed his first permanent employment contract on September 29, 1884 – his 23rd birthday – with a small dyeworks in Eberfeld, not far from his home town. The dyeworks was called Farbenfabriken vormals Friedrich Bayer & Comp.

His personal development continued along the same trajectory, and six years later he took over the reins of the company. It was at that moment that the company began its transformation from a medium-sized dye manufacturer into a very successful company in an up-and-coming industry – pharmaceuticals. The first step was to set up a small pharmaceutical department with top-notch equipment and hire young, ambitious chemists Heinrich Dreser, Arthur Eichengrün and Felix Hoffmann. We know how the rest of the story goes.

But the invention of aspirin was only just the beginning of its history; it continues today, more than 120 years after Felix Hoffmann first synthesized the white crystals of acetylsalicylic acid.

Carl Duisberg knew from the beginning that aspirin was a potential goldmine for Bayer, but since it was not difficult to produce, there was a risk that other manufacturers would cut into their business. He had to protect his product from the very beginning. Bayer's battle with the competition is a part of the history of aspirin.

Attempts to protect the product proved difficult from the start. The first step was to secure exclusivity by way of a patent, but they had no chance of obtaining

a patent in Germany as many chemists before Hoffmann had already synthesized acetylsalicylic acid in various qualities. They focused instead on two large countries – Great Britain and the U.S. – and succeeded. The U.S. patent issued on February 27, 1900 was particularly important for the further development of aspirin and the growth of Bayer. These were only victories in individual battles, however, as the war continued. Competitors in both countries challenged the patents, leading to a period of massive litigation.

Farbenfabriken vormals Friedrich Bayer & Comp. *vs*. Chemische Fabrik von Heyden, one of the largest patent disputes in Great Britain, began on May 2, 1905 and ended 70 days later. At play was the aspirin patent, and the victor's spoils would include not only the entirety of the huge British market, but the markets of the British colonies, including India, Canada, and Australia. Bayer was handed a humiliating defeat.

Duisberg's dreams of a monopoly in the British Isles came to a definitive end on July 8, 1905, but the U.S. market was still up in the air. At the same time the legal proceedings were taking place in Great Britain, similar proceedings were under way in the U.S., against an American company located in Chicago. As in Great Britain, Carl Duisberg and his Bayer were fighting to retain their monopoly on aspirin.

At the time, aspirin sales were gaining momentum in the American market, and in 1905 represented a quarter of all of Bayer's sales in the U.S. In 1909, that figure reached 30 percent. A large part of this success was due to the establishment of the company's own production facility in Rensselaer, New York, in 1903, meaning production did not have to rely on imports from Europe.

There was a darker side to Bayer's success with aspirin, however. Numerous other manufacturers capitalized on their success, and as a result only half of the aspirin sold in the U.S. was the original Bayer product; the remainder consisted of counterfeits. This made the outcome of the American patent lawsuit that much more important for Carl Duisberg. After numerous delays, a verdict finally came down in 1909 and Bayer won.

But the battle with competitors did not end there, as even after the patent was upheld there were still many manufacturers that continued to make aspirin, often of dubious quality. Aspirin was such a profitable commodity that smuggling it in from Europe was worth the risk. Bayer was forced to fight with everything it had, and to promote "their" product they launched a massive advertising campaign – something that was unheard of at the time for ethical drugs. To differentiate their product from the products of competitors, every "real" aspirin tablet manufactured by Bayer was embossed with the Bayer cross logo that intersects at the letter "Y." It was slow progress, but gradually the majority of profits from the aspirin sold in the U.S. filled the coffers of Bayer. Over time, the company that began as a smallish dye manufacturer became the largest chemical manufacturer in Germany.

Carl Duisberg continued to keep a close eye on his child and in 1912, he proudly and ostentatiously opened a new factory on the banks of the river Rhine in Leverkusen. The sprawling complex, taking up nearly 25 acres of land, was one of the largest and most modern manufacturing plants in the world. The complex consisted of dozens of production buildings, huge laboratories, a Japanese garden, and the largest chemical library in the world – all managed with Carl Duisberg's German precision. Leverkusen was the impressive headquarters of the largest chemical company in Germany and Duisberg took up residence in the palatial home situated on the premises. Everything was heading in the right direction, right up until the time Gavrilo Princip fired the shots that led to war, with Germany mobilizing on August 1, 1914.

At first, the situation did not seem all that bad for Bayer, having already lost the large market of one of Germany's foes, Great Britain, long before the war. Their primary market, the United States, was neutral at the start of the war and furthermore, there was a pro-German sentiment among Americans. But then, on April 6, 1917, two years and eight months after the war began, the U.S. declared war on Germany. Suddenly, everything changed.

The U.S. immediately seized control of property belonging to its enemies, including the American subsidiary of Bayer. At that moment, Carl Duisberg lost control over the company's property in the U.S., including the production plant in Rensselaer. But there were many losses still to come. The pro-German sentiment of American society that had been prevalent at the start of the war began to move in a decidedly anti-German direction. Six months after entering the war, the U.S. created the Office of Alien Property Custodian (APC), which was responsible not only for administering the property of the enemy but also for the fate of the property when the war ended. The fate of Bayer's property in the U.S. was definitively sealed in a very short time – just a month after the armistice was signed by the parties at war. On December 12, 1918, the APC announced it would auction off the assets of Bayer in the U.S. All the U.S. assets of the company were offered up in one package that included all tangible property – the production plant in Rensselaer and all the inventory – as well as all intellectual property, including patents and trademarks. One of the most valuable prizes included in the package was the trademark for Aspirin. The property was bought by Sterling Products Inc., for $5.3 million, which today is the equivalent of $123 million. Bayer not only lost all of its U.S. assets, it definitively lost its monopoly on aspirin as well. Carl Duisberg could only stand by and watch.

His activities at home in Germany during World War I are not directly related to the history of aspirin, but should be mentioned anyway. He personally participated in the development of a chemical weapon – the lethal poison gas phosgene – and as a true experimenter, he was one of the first to try out the effects of the gas on himself. He was also active in industrial diplomacy. Following the

example of American corporations and cartels, he convinced four of his biggest competitors – BASF, Hoechst, Agfa (or rather, its predecessor), and the now little-known Leopold Cassella & Comp. – to create the German coal tar dye industry syndicate (*Interessengemeinschaft der deutschen Teerfarbenfabriken*). From the beginning, this giant was known as IG Farben; our story will come back to this syndicate.

No matter how cruel December 12, 1918 may have been for Carl Duisberg and his aspirin, life went on and so did the history of aspirin. Aspirin was put to a first test soon after the end of World War I. From 1918 to 1919, a massive flu pandemic raced around the globe in several waves. It went down in history as the Spanish flu and remains one of the greatest pandemics in human history. Conservative estimates put the death toll at around 18 million people, the same as the number of casualties in the war that had just ended. Aspirin was the only effective drug at the time. Although it did not cure the flu, its ability to reduce fever gave many patients a chance to recover. The role of aspirin in the pandemic was later questioned, but the majority view remains – without aspirin, the number of casualties would have been significantly higher.

It was actually this pandemic that kicked off the golden age of aspirin. Nobody had a monopoly any longer on the production or the name, and over a short period of time there was a veritable explosion in the number of aspirin manufacturers around the world, but primarily in North America. The "real" Aspirin – the one bought at auction by Sterling – was suddenly faced with hundreds of competitors. Manufacturers offered aspirin under various names and in various combinations. Along with Aspirin, pharmacies stocked Aspro; Calaspirin (a combination of aspirin and calcium); Cafiaspirina and Anacin (aspirin and caffeine); Alka-Seltzer (aspirin with sodium bicarbonate); and many others. These versions of aspirin were practically indistinguishable from one another, and only the advertising campaigns of their manufacturers and the amount each manufacturer was willing to invest in marketing could make or break any of them. This created enormous pressure, which resulted in aspirin gradually becoming a mandatory component of every first-aid kit, and it could be found in practically every woman's handbag. The little white tablet for pain and fever became an icon of interwar America. The period from 1919 to 1941 is commonly referred to as the "aspirin age."

Carl Duisberg was still around to witness many of these events but, fortunately for him, he passed away before the fate of IG Farben became known. He was not there to see how "his" syndicate became one of the biggest supporters of the Hitler regime. The syndicate ceased to exist when World War II ended, and 23 of Duisberg's former colleagues stood trial before a military tribunal at Nuremberg. Ten of them were convicted of war crimes.

Carl Duisberg died on March 19, 1935, but two years before his death he personally illuminated the giant Bayer logo in Leverkusen. It was the typical Bayer

cross placed between two factory smokestacks. At 236 feet (72 m) tall and illuminated with 22,000 light bulbs, it was the world's largest illuminated advertisement at that time.

By the time Duisberg died, he had received many honors. Streets and squares in several German cities were named after him, and an education institution still bears his name. He was a visionary who brought the pharmaceutical industry full circle – from a mere appendage of the chemical industry to its own separate industry, and one of the most profitable. According to the obituaries, he was "*a man who may be regarded as the greatest industrialist the world has yet had*."

Story 1.4: The great German patriot and the Great Phenol Plot

As mentioned, the United States remained neutral at the beginning of World War I and there was a prevailing pro-German attitude. This is not surprising. Great Britain stood on the other side of the front and the memory of British rule – that had ended 130 years before – was still etched in the collective memory of the American people. The fact that Great Britain, with the most powerful navy in the world, blocked trade between the central powers (Germany, Austria-Hungary, and the Ottoman Empire) and the rest of the world, including the U.S., did nothing to ease the anti-British sentiment. The U.S. was beginning to feel the shortage of basic raw materials, one of which was phenol. This is a simple organic compound obtained primarily from coal tar, and is a precursor to many more complicated compounds, of which aspirin is one. It is also used to produce trinitrophenol, a substance similar to trinitrotoluene (TNT), which is also used to manufacture explosives. Since it was wartime, phenol was naturally an important strategic material and Great Britain was not only preventing the enemy from trading phenol, it was carefully guarding phenol for the needs of its own military.

The Bayer factory in Rensselaer only handled the final phase of aspirin preparation, the acetylation of salicylic acid, and the company purchased the input raw material from its American suppliers. However, if there was no phenol, there were no input raw materials, and if there were no input raw materials, there was no acetylsalicylic acid. The situation was so critical that the factory almost stopped production in 1915. Fortunately for Bayer, and for aspirin, there was another American who needed phenol. This was Thomas Alva Edison, the wizard of Menlo Park, considered the most prolific inventor in history and the holder of an incredible 1,093 patents. He needed phenol to produce condensite, which is a resin chemically similar to Bakelite. Edison used it to make discs for one of his most famous inventions, the phonograph. Like Bayer, he was also facing a phenol shortage, so he solved the problem by opening his own factory to produce phenol. By June 1915, he was producing 12 tons of phenol per day. Since he only needed

nine tons for himself, three were left over. This is where Dr. Hugo Schweitzer steps into the history of aspirin.

Dr. Hugo Schweitzer was German. He was born in 1861 in Upper Silesia, which at the time belonged to Prussia and is now a part of Poland's Warmia-Mazury Province. His contemporaries remembered him as a friendly, energetic, and goal-oriented young man. These traits would characterize him until his untimely death.

After completing his chemistry studies, he briefly worked in Ludwigshafen, Germany in the research laboratories of *Badische Anilin und Soda Fabrik* (later known as BASF). He did not remain long in research, or in his homeland, emigrating to the U.S. in 1889 and settling in New York. He obtained U.S. citizenship in 1894.

Schweitzer's remarkable and controversial career began in New York. After arriving there, he quickly became part of professional society and was soon a prominent member of New York's chemical community. He is no doubt the only American chemist who can boast of being both secretary of the American section of the British Society of Chemical Industry and the chairman of the American chapter of the German Chemical Society (*Verein Deutscher Chemiker*). In 1904, he became one of the first presidents of the prestigious Chemist's Club in New York. He was highly regarded as an excellent organizer and passionate orator. When William Henry Perkin – the very same Perkin who set chemical production in motion at the age of 18 – arrived in the U.S. in 1906, it was Schweitzer who delivered the welcome speech in his honor.

However, Dr. Hugo Schweitzer was first and foremost a German with a strong belief in the cause of his homeland. Soon after World War I erupted, he was deeply involved in pro-German propaganda. He was an experienced organizer, wrote regularly for a weekly periodical called *The Fatherland*, and founded a company in the U.S. that published translations of the great German authors. He himself translated a German songbook into English. He was a member of the German propaganda council in the U.S. and was even its chairman shortly before his death. Primarily, though, he knew how to use his standing and contacts and he published and lectured unflaggingly to promote the German Empire.

He crossed paths with Bayer in 1897 when he accepted employment as head of the company's pharmaceutical laboratory in New York. He was companion and chief adviser to managing director Carl Duisberg on his journey to the U.S. in 1903, earning his trust to such an extent that Duisberg named him president of the *Synthetic Patent Company* which managed Bayer's U.S. patents. Although he would later strike out on his own, Schweitzer remained in contact with Bayer – which is how he learned of the problems with phenol.

He knew that Bayer was suffering a shortage of this raw material, and he also knew that Edison's factory had begun producing three tons more every day than

Edison required. Schweitzer did three things. He signed a contract with Edison to buy all of his excess phenol from July 1, 1915 through March 1916, at a price that was substantially higher than the market price. He also made a deal with the manufacturer of the intermediate product needed to produce aspirin, whereby the manufacturer would immediately buy the phenol that would be used by Bayer to make salicylic acid. Schweitzer could use the remaining phenol that would not be used to manufacture aspirin any way he wanted. He then established a company called the *Chemical Exchange Association* through which the deal would be organized.

It all seemed legal and sound, and everyone was happy – Edison, Bayer, and Schweitzer – until the day of July 24, 1915, less than a month after the deal had been set up, when Heinrich Albert lost his briefcase on the El train heading toward Upper Manhattan; and who should discover it but none other than the American Secret Service agent who had been following Mr. Albert.

Heinrich F. Albert was not just anyone. He had official duties as the commercial attaché at the German embassy in the U.S., but he was responsible for "other" pro-German activities in America, from propaganda to espionage. More than $30 million passed through his hands, an exorbitant amount in today's money. His activities did not escape the notice of the Secret Service, which assigned agents to follow him – and ultimately the lost German briefcase ended up in the hands of the Americans.

The documents found in Heinrich Albert's briefcase indicated that the money used to finance Dr. Hugo Schweitzer's phenol deal with Thomas Alva Edison had come from the covert sources of Heinrich Albert. An ordinary business transaction suddenly turned into an anti-American conspiracy. According to a calculation that was later made public, the contract he signed with Edison had allowed Schweitzer (and therefore, Germany) to swindle the U.S. out of 680,000 tons of phenol that could have been used to produce over two million tons of explosives, enough to fill four freight trains of 40 cars each. While that calculation is a slight overestimation, it truly was a massive amount.

There were ultimately no legal repercussions, as the documents did not prove to be incriminating enough to bring charges against any of the co-conspirators. In addition, the U.S. was still a neutral country at the time so it was really just "business as usual," although very advantageous business if you were the German embassy. The entire conspiracy ended with some articles in the anti-German newspaper, the *New York World*, and a few columns in *The New York Times*. While Heinrich Albert hid out at the embassy, Hugo Schweitzer defended himself by claiming that his actions had saved the lives of many soldiers on the front, Bayer had obtained sufficient salicylic acid, and Thomas Alva Edison had sold the rest of his phenol to the U.S. military. When Dr. Hugo Schweitzer died of pneumonia just before Christmas in 1917, the obituary in *The New York Times* only noted his pro-German position and his propaganda activities.

The great phenol conspiracy made a comeback in mid-1918, when the activities of the Office of Alien Property Custodian went into full swing under the leadership of A. Mitchell Palmer, an attorney, unsuccessful candidate for senate, and ambitious public official. The office became one of the largest businesses in the U.S., unsurprisingly, as it gradually seized and administered all the property of German companies situated in the United States. That property was worth nearly $1.5 billion (U.S.), which would be $30 billion in today's money. Palmer worked closely with the special Bureau of Investigation, an earlier name for the FBI. In mid-1918, the chief of the Bureau of Investigation raised the issue of a German conspiracy against the interests of the U.S. The details were no different from those that were known in 1915, but the actors had changed. In 1915, the Great Phenol Plot was the anti-American conspiracy of the German embassy in the United States. Money poured through the embassy's commercial attaché and the entire deal was conducted by a German propagandist. In 1918, Bayer was added to the scheme. In its revelations, the Bureau of Investigation named Dr. Hugo Schweitzer as the director of the American subsidiary of Bayer and with this false claim, Bayer officially became a co-conspirator, despite the fact that the company had used only a small portion of all the phenol the conspirators bought from Thomas Edison. Along with being tagged the director of Bayer, Hugo Schweitzer was also named as German spy number 963192637. The number was allegedly assigned to him by the Imperial Ministry of War, a ministry that never actually existed.

But no one spoke up. Dr. Hugo Schweitzer was dead, Dr. Heinrich F. Albert was pursuing a political career in Germany, and the American subsidiary of Bayer was fully focused on trying to save its assets – which we know they failed to do. Six months after the company was implicated in the great phenol conspiracy, A. Mitchell Palmer sold all the American assets of Bayer in the course of one afternoon.

Story 1.5: The man from New Zealand and marketing magic

World War I ended in 1918, and with it the aspirin monopoly of Bayer. The company had long before lost the patent in Great Britain and across the Commonwealth. The U.S. patent expired in 1917, and when its assets were sold at auction in December 1918, Bayer also lost its trademark in the United States. Practically every producer could now use the name *aspirin*. When World War I ended, a new war could begin – the aspirin wars. In just a few years, dozens of manufacturers cropped up in the U.S. alone, each of them offering the same thing – acetylsalicylic acid pressed into small white pills. Every now and then, one of them would add a miniscule amount of something else, like caffeine or calcium, but they made no difference to the effectiveness of the drug. Marketing was what was needed.

Success depended on each manufacturer's cleverness, and on how much money they were willing to part with. Just as soon as a new medium came on the scene, aspirin manufacturers added it to their marketing mix. Newspapers and magazines were a given, and when radio was invented and became more widespread, aspirin commercials were aired during prime broadcasting hours, much to the delight of radio station owners. With the rise of automobiles, billboards began appearing on roadsides and many of them hosted aspirin advertisements. Even automobiles themselves were an advertising medium.

There were many marketing magicians in the history of aspirin. One was Max Wojahn, a German emigrant and chief of the export department at Sterling for Latin America, the same Sterling that bought Bayer's assets at auction. When the company entered the Latin American pharmaceutical market in the 1920s, the market was completely unregulated. Pharmacies were brimming with aspirin (and other drugs) of various provenance and quality. Apart from the aspirin manufactured by Sterling in the U.S. (with the Bayer logo stamped on the tablet), there was locally-produced aspirin and aspirin smuggled in from various parts of the world, including the "original" aspirin manufactured in Germany also bearing the Bayer logo on every tablet.

Max Wojahn concentrated on the most difficult product to replicate – Cafiaspirina, aspirin with a bit of caffeine added – and he began to promote it. In short order, Cafiaspirina advertising was everywhere; in newspapers, on posters and billboards, on cars, newsreels, and later radio. He created a traveling sales team that was the largest and most effective on the entire continent at the time, with massive advertising costs to match. In the late 1920s, promotional costs represented 15 percent of sales; by 1934, it was 55 percent Sales grew at the same pace, however, and in 1929 the net profit from aspirin sales in Latin America was $1.25 million (the equivalent of $17 million today). But even that was not enough for Max Wojahn. To spread the news about Cafiaspirina to the most remote areas, he came up with an entirely new form of promotion. He turned his sales force into roving movie theaters, equipping their vehicles with gramophones, movie projectors and an electric generator, and sent them off to sell the product. If they were unable to reach a remote area by car, he put the mobile movie theaters on boats. The procedure was always the same: The sales rep would show up, wait for it to get dark, set up the generator, then turn on the projector and start the show. They showed various programs, such as old American newsreels, Mickey Mouse cartoons, short silent movies, and the like. The content was not really the point, as most members of the audience were seeing a movie for the very first time. Courtesy of Max Wojahn and his Cafiaspirina, the indigenous peoples living high in the mountains were inducted into the age of mass media.

Of course, that was just a side effect of the entire activity, as the most important part of the show was the aspirin commercials inserted between movie clips.