Never say dye

A brief, colorful history of sulfa drugs, leading to Gerhard Domagk's discovery of prontosil, the first commercially available antibiotic.

Domagk (pictured above) and his colleagues synthesized thousands of compounds over 5 years before they were successful.

J.C.A. Morrant, MBBS, DObst, RCOG, DPM, FRCPC

Gerhard Domagk (1895–1964) was awarded the Nobel Prize in 1939 for his research into the antibacterial actions of a ruby-red dye, prontosil (sulfonamidocrysoidine). Germans were forbidden to accept the prize and the Nazis imprisoned Domagk until he refused it, a brutal act that left him with lifelong spells of palpitations and depression. He accepted his prize in 1947, after the Third Reich had collapsed, "born of lies and suffocated under its cruelty and blood," he wrote.

Domagk wore his old tails and a borrowed waistcoat to the ceremony. He was exhausted, celery-thin, and acquainted with grief; his mother had died from starvation during the war and the Nazis sent his son Wolfgang, aged 15, and his classmates to attack 6 million Soviet troops. As humble as the Curies, Domagk described his wife, Gertrude, and himself as "meagre."

Three decades earlier Domagk had volunteered to serve as a soldier in the First World War. After being wounded, he served as a medical orderly in the Ukraine, where he met many of the captains of death: cholera, which killed thousands; typhoid fever, which caused a true decimation of Napoleon's army in 1812; gas gangrene, in which the exotoxin of *Clostridium perfringens* rotted flesh and produced a nitrogenous gas with a sickening smell that made tyros faint; and tuberculosis, the greatest killer of all time. Even a small wound could cause death from septicemia.

Bacterial infections were believed incurable; "obviously" a drug that could kill bacteria would also kill healthy blood and body cells. Voltaire's joke, "the art of medicine consists of amusing the patient until nature cures the disease," seemed cruelly apt. Domagk's war experiences haunted him. He kept a skull on his desk as a memento mori and wrote, "I swore before God and myself to counter this destructive madness."

Others had sought a cure for infections. Antoine Béchamp synthesized arsanilic acid in 1859 and found it feebly effective against African sleeping sickness and yaws, but too toxic for use. In 1882 Paul Ehrlich and an audience of eminent physicians listened in stunned silence as Robert Koch, a country doctor, explained how he had stained pus from a tuberculous abscess with methylene blue (developed by Ehrlich) then counterstained it with vesuvin. He proved that the brilliant blue rods he discovered, "Koch's Bacillus" or *Mycobacterium tuberculosis*, caused tuberculosis. Freidrich Loeffler called the lecture "pure unadulterated gold." Ehrlich agreed: "[it was] the most important experience of my professional life." He had been fascinated by dye since his student days; friends joked about his colored fingers. Ehrlich believed a dye could be made that would act like a "magic bullet," fix to a bacterium, kill it, and leave other cells unharmed.

Ehrlich experimented with thousands of dyes. He also studied Béchamp's work, but mistakenly thought that *Trypanosoma brucei*, the protozoan causing African sleeping sickness, was related to *Treponema pallidum*, the spirochete causing syphilis. Ehrlich believed that an arsenic compound might kill the spirochete. He tested hundreds of arsenicals before giving the work to Dr Sahachiro Hata, who synthesized arsphenamine (which they called Salvarsan 606 because it was the 606th drug they tried) in 1910. Arsphenamine, the first chemotherapeutic drug (a word coined by Ehrlich), cured syphilis. Many patients could

This article has been peer reviewed.

Dr Morrant is a psychotherapist in Richmond, with an interest in literature, history, and gardening.

not tolerate the side effects of arsphenamine and Ehrlich counted himself a failure despite being awarded the Nobel Prize in 1908 for his work on immunology.

Streptococcal infections can also be captains of death. In 1924 President Calvin Coolidge's son blistered his heel playing tennis and died a week later from streptococcal septicemia. Streptococci caused four of the most lethal hospital diseases: cellulitis, erysipelas, wound infections, and puerperal fever, all mainly spread by the hospital staff. From the days of the powdered wig and gold-topped cane women were safer from puerperal fever if delivered at home, as doctors were often a grubby lot.

During the 1920s and 1930s Domagk shared Workroom Four at the Bayer factory with two chemists, Josef Klarer and Fritz Mietzsch. They synthesized thousands of compounds for him to test against a battery of bacteria, including a virulent strain of streptococcus. Five years passed without success. Then in 1932 Klarer inserted a sulfur atom into a dye molecule. The results were surprising, even shocking. First it worked, killing streptococci responsible for wound infections, pneumonia, puerperal fever, meningitis, gonorrhea, and so on. Second, French workers soon showed that the dye was unnecessary; it was the sulfa part of the molecule that cured. The finding refuted Ehrlich's belief that a bactericidal drug would be a dye. Third, the curative agent was sulfanilamide, a common industrial chemical, made by the ton, first synthesized by Paul Gelmo in 1909, so the patent had long expired. The sulfonamides are bacteriostatic drugs. Prontosil is a prodrug, metabolized to sulfanilamide. Body cells take in folic acid but the streptococci must synthesize it. Sulfonamides compete with streptococci for the enzyme dihydropteroate synthase, which converts para-aminobenzoic acid to folic acid. Without folic acid streptococci cannot reproduce and are destroyed by the immune system.

Box of five ampoules of pronotsil, circa 1936–1940. This free sample, produced by Bayer Germany, was probably intended for the Middle Eastern market. (Photo by Science & Society Picture Library/SSPL/Getty Images).

In 1935 the Domagks' 6-year-old daughter Hildegard pricked her hand with a needle. As she lay dying from septicemia her surgeon planned to amputate her arm. Domagk, aghast, stuffed the little one with prontosil. She recovered.

In England, Leonard Colebrook, a preternaturally cautious researcher, reduced the death toll from puerperal fever dramatically with sulfanilamide in 1936. That same year, President F.D. Roosevelt's son developed a streptococcal sore throat and sinus infection. He was near death when Eleanor Roosevelt agreed for prontosil to be given him and he slowly recovered. Prontosil became instantly famous. It was successful against an outbreak of meningitis in the US Army. Eleanor Roosevelt said, in her breezy way, "The Marines I have seen around the world have the cleanest bodies, the filthiest minds, the highest morale and the lowest morals of any group of animals I have ever seen." The sulfonamides prevented a huge number of working hours being lost to invalidism due to gonorrhea in the armed forces. Some officers gave them to their men before and after a date. There was an "orgy of overprescribing" and patent drug firms began to manufacture their own concoctions. Massengill, a rich manufacturer, produced Massengill's Sulfanilamide Elixir. The sulfanilamide was dissolved in diethylene glycol, an industrial solvent. One hundred fifty patients developed uremic encephalopathy and died from renal failure. The chemist, Harold Watkins, shot himself in the heart. The tragedy gave teeth to the FDA and many patent drugs disappeared.

The sulfonamides saved hundreds of lives after the attack on Pearl Harbor. In 1943, Winston Churchill developed pneumonia with atrial fibrillation and congestive cardiac failure. He was given "M and B, 693," i.e., sulfapyridine manufactured by May and Baker at their 693rd try. After this the sulfonamides were slowly eclipsed by penicillin and a phalynx of antibiotics with fewer side effects and broader antibacterial spectra. However, a few sulfonamides live on: for example, in the mixture trimethoprim-sulfamethoxazole. Domagk once said, "it is easy to kill but very difficult to save lives." He helped save the lives of millions.

And whatever happened to Domagk's young son Wolfgang? He couldn't beat the Russians, but trudged home and spent Christmas with his family. BCMJ