

A story of drug discovery

Article A – Putting the story together

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Chemotherapy involves the use of chemicals to cure disease. The problem is finding chemicals that will destroy an internal infection without harming the patient. In other words, the trick is to find a chemical 'bullet', which destroys the cause of disease but leaves healthy tissue unharmed.

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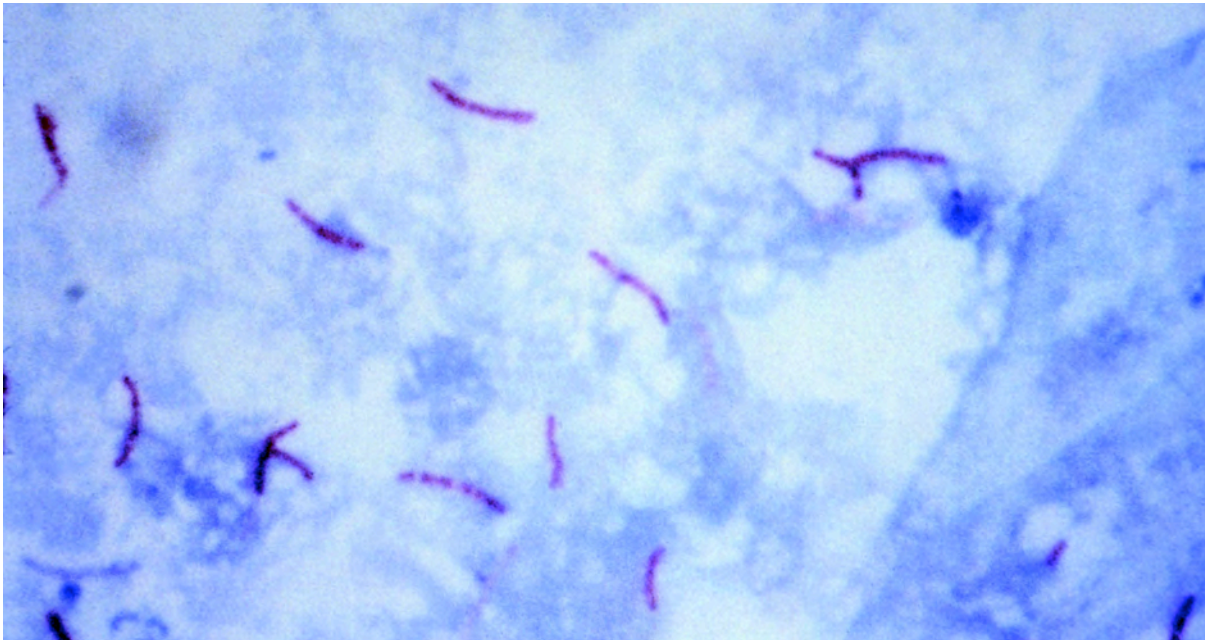
Paul Ehrlich (1854–1915) is often thought of as the father of modern chemotherapy. This is because he was the first person to imagine it might be possible to make chemicals to kill disease-causing micro-organisms without harming healthy cells in the body.

It seems that Ehrlich got his ideas from his interest in dyes. He preferred to experiment with dyes in the laboratory when he should have been studying medicine at the University of Breslau in Germany. This meant that he took a long time to pass his medical exams.

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The first synthetic dye was made by William Perkin in England in 1856. German chemists visited London and Manchester to learn about dye manufacture. Soon the industry began to develop rapidly in Germany. Methods were discovered of making new dyes based on chemicals from coal. Among the new coal-tar dyes were magenta and methylene blue.

In the 1870s, Robert Koch (1834–1910) developed the methods that are still used today. He used magenta and methylene blue to stain bacteria so that they could be seen under the microscope. With these methods, Koch and his fellow workers discovered the causes of eleven diseases including anthrax (1863), tuberculosis (1882) and cholera (1883).



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Paul Ehrlich was one of Koch's assistants. He was very interested in the fact that dyes can be used selectively. Some dyes take well on wool but not on cotton. Some dyes stain some animal cells but not others. He showed that if methylene blue is injected into an animal, it dyes nerve cells but not other parts of the body.

Seeing what dyes could do, Ehrlich began a hunt for 'magic bullets'. He thought it might be possible to inject a dye into a patient that would kill microbes but leave healthy parts unharmed. He had a theory that dyes form chemical bonds with cells. His ideal drug would attach itself to the cells of disease-causing micro-organisms and destroy them. The drug would be harmless to the cells of the infected person because it would not bond to them.

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During a long period of research, Ehrlich investigated the effect of coal-tar dyes on trypanosomes – the blood parasites that cause sleeping sickness. He showed that the dyes were effective in killing the parasites in infected mice. Unfortunately, he had not found a ‘magic bullet’ because the dyes also poisoned the mice.

After his lack of success with coal-tar dyes, Ehrlich decided, in 1904, to study arsenic compounds. He had been experimenting with dyes that were nitrogen compounds. Arsenic is in the same group of the periodic table as nitrogen so Ehrlich thought that arsenic compounds might be worth investigating.

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Ehrlich and his helpers made and tested over six hundred arsenic compounds, with no positive results. Ehrlich decided to try every one again. In 1909, he was working with a Japanese colleague, Sahachiro Hata. Together they found that the six hundred and sixth compound hit the target. Its effectiveness had been missed by a technician during the first series of trials.

The ‘magic bullet’ was found to work against trypanosomes in mice. Unfortunately, it had no effect on the parasites that cause sleeping sickness in human beings.

Ehrlich now decided to try this chemical on other microbes. He found it could be used to cure syphilis (a sexually transmitted disease) in rabbits. He later found it cured the disease in humans too. By 1911, he was able to announce the discovery of the first synthetic chemical to control a parasitic disease. He called the new drug ‘Ehrlich 606’ as a reminder of the long struggle for success. It was patented in Germany and sold as Salvarsan.

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In the 1930s, another drug was discovered as a result of research into dyes. A sample of a new red azo dye was passed to Gerhard Domagk. At the time, Domagk was director of a laboratory investigating the value of dyes as drugs.

Domagk was interested in the new dye because it stuck strongly to wool. Wool is a protein, and this suggested to him that the dye might stick strongly to the proteins of bacteria. When tested on mice the dye was found to be very effective against a variety of bacterial diseases.

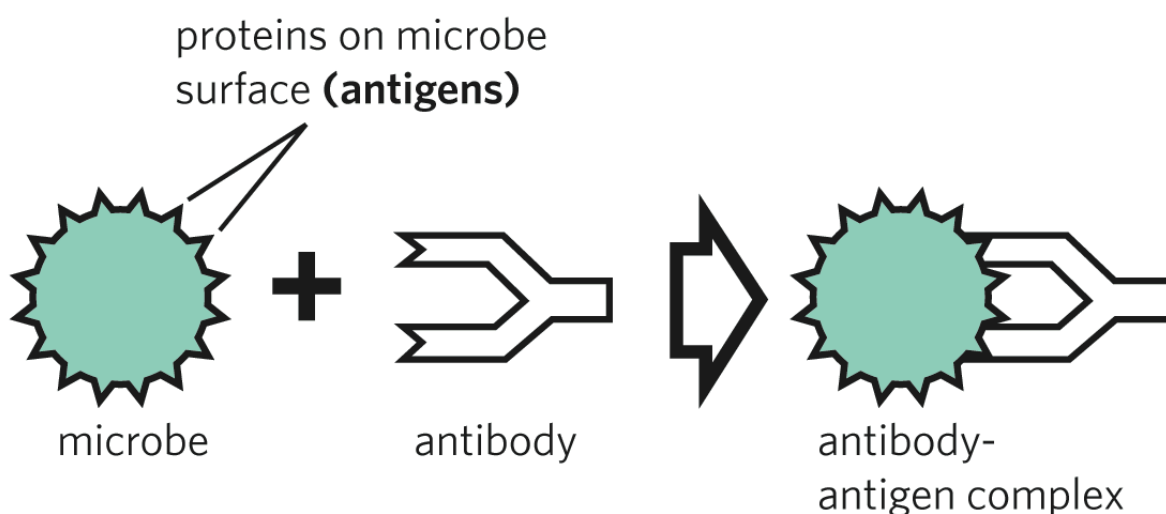
The first person to be treated with the new drug was Domagk's daughter, Hildegard. She picked up a serious infection by accident in his laboratory. Her life was in danger. As a last resort, Domagk suggested treatment with the red dye. It was successful and her life was saved. The red dye was the first of the sulphonamide drugs. It was called Prontosil.



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Antibodies are made by the body in response to attack by bacteria or viruses. Every micro-organism has uniquely shaped proteins on its surface. These proteins are called antigens. Antibodies have shapes that can lock onto a particular antigen and 'neutralise' it.

In 1975, César Milstein and Georges Köhler developed a technique for the large-scale production of monoclonal antibodies (antibodies of the same type). They used 'hybrids' of lymphocytes (white blood cells) and tumour cells to produce antibodies designed to lock onto specific proteins on the surface of bacteria and other cells.



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Today chemotherapy is important in the treatment of cancer. The underlying principle of chemotherapy is to treat the cancer with chemicals that interfere with the process of cell division. Chemotherapy drugs are effective against cancer cells because these cells divide rapidly, whereas most normal cells do not.

In 1998, Herceptin, a monoclonal antibody, was approved for the treatment of breast cancer. Herceptin works by interfering with the way in which breast cancer cells divide and grow.

The search continues for drugs that can kill cancer cells but not normal cells.