The Search for the Magic Bullet

Contents: Reading and questions about the development of chemotherapy.

Time: 1 to 2 periods. Homework time could be used.

Intended use: GCSE Biology, Chemistry and Science syllabuses. Links with work on health, bacterial diseases, dyes, and the role of chemicals in the prevention and treatment of illness.

Aims:

- To explain what is meant by chemotherapy and show how the idea of using chemicals to cure disease arose from the work of those investigating the use of stains to distinguish bacteria
- To put some of the main events in the development of chemotherapy into their historical context
- To show that much hard work and persistence may be required prior to important scientific discoveries
- To provide opportunities to practise skills in reading and comprehension.

Requirements: Students' worksheets No.805. For practical requirements, see below.

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This unit focuses on one aspect of an important tradition in Western medicine. The idea that particular diseases have particular causes was very powerful in the years following the discoveries by Pasteur, Koch and the other microbe hunters. Chemotherapy was therefore an important tool for curing diseases by attacking their cause. Koch, Ehrlich and Domagk all received Nobel Prizes for their work.

We are now in an era where the theory of specific causes seems to have severe limitations when applied to conditions such as heart disease, cancer and mental illness. The unit does not raise these issues directly but teachers might like to discuss them with students, and focus on some of the limitations of Western medicine.

Suggested use

This unit will probably have more appeal to students after they have done some related practical work. In Biology/Science courses they might first have some experience of staining cells. It would be particularly appropriate to use 'Ehrlich's haematoxylin' if available. Alternatively the notes below suggest an experiment to show how plant tissues can be stained selectively.

In Chemistry/Science courses this unit might be used following practical work to investigate selective dyeing of fabrics. A possible experiment is described in section 4 of the Science at Work booklet, *Dyes and dyeing.*

The time chart exercise at the end of the unit provides an opportunity to put some of the main events in the development of chemotherapy into the context of the history of medicine. It is a text-related activity which will help consolidate the reading that students have done.

Suggested experimental work on selective staining of plant tissue

Each group of students will need:

razor blade
microscope slide
dropping pipette
blotting paper
hand lens or low-power microscope
eye protection

access to:
stem of dead nettle
safranin solution
distilled water
ethanol
light green in clove oil

Procedure

1 Use a razor blade to cut a thin, transverse section of the stem of a dead nettle.
2 Place the section on a microscope slide. Cover with a few drops of safranin solution.
3 After a minute or two, remove the excess stain with blotting paper. Add a few drops of water and then remove it with blotting paper.
4 Cover the sample with a few drops of ethanol and then leave for 2 to 3 minutes.
5 Remove the excess ethanol with blotting paper.
6 Stain with a drop or two of light green in clove oil.
7 Draw off the excess stain with blotting paper. Add a few drops of pure clove oil, then blot dry.
8 Examine the stained specimen with a hand lens or low-power microscope.

The suggested procedure is intended to show in a simple way that dyes can stain parts of living things selectively. Safranin stains lignin red.

Acknowledgements Figure 1 supplied by the Wellcome Institute Library, London; Figure 3 supplied by The Mansell Collection.

THE SEARCH FOR THE MAGIC BULLET

Paul Ehrlich (1854-1915) is often regarded as the father of modern chemotherapy. Chemotherapy involves the use of chemicals to cure disease.

Ehrlich's idea was that it might be possible to make chemicals to kill the microbes which cause disease without harming other living cells.

Disinfectants destroy microbes outside the body but they cannot be used inside the body because they are so toxic. The problem is to find chemicals which will destroy an internal infection without harming the patient too much. The trick is to find a chemical 'bullet' which will destroy the cause of disease but leave healthy tissue unharmed.

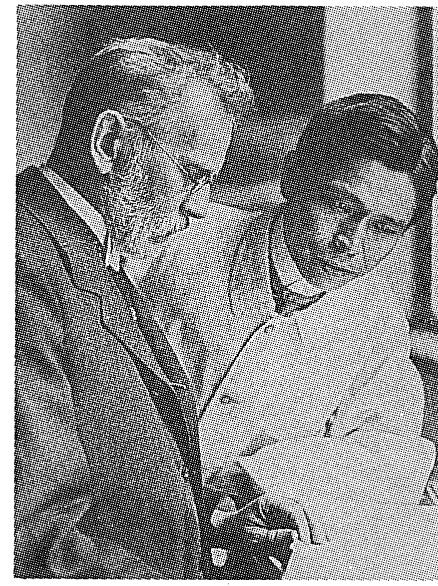

Figure 1 Paul Ehrlich and his colleague Sahachiro Hata.

How did Ehrlich get his idea?

It seems that Ehrlich's thinking was influenced by his interest in dyestuffs. He preferred to experiment with dyes in the chemistry laboratory when he should have been studying medicine at the University of Breslau. This meant that he took a long time to pass his medical exams.

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.

Robert Koch (1843-1910)

Among the new dyes were magenta and methylene blue. In the 1870s, Robert Koch developed the methods used to study bacteria. He used magenta and methylene blue to stain bacteria on glass slides 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).

Answer questions 1 and 2.

Questions

1. *Why is it so difficult to find a chemical which will kill the microbes which cause disease without harming the healthy parts of the body?*
2. *How did the discovery of synthetic dyes help Koch in his research to identify the bacteria which cause disease?*

Figure 2 Bacteria magnified 5000 times. These particular bacteria are found in soil.

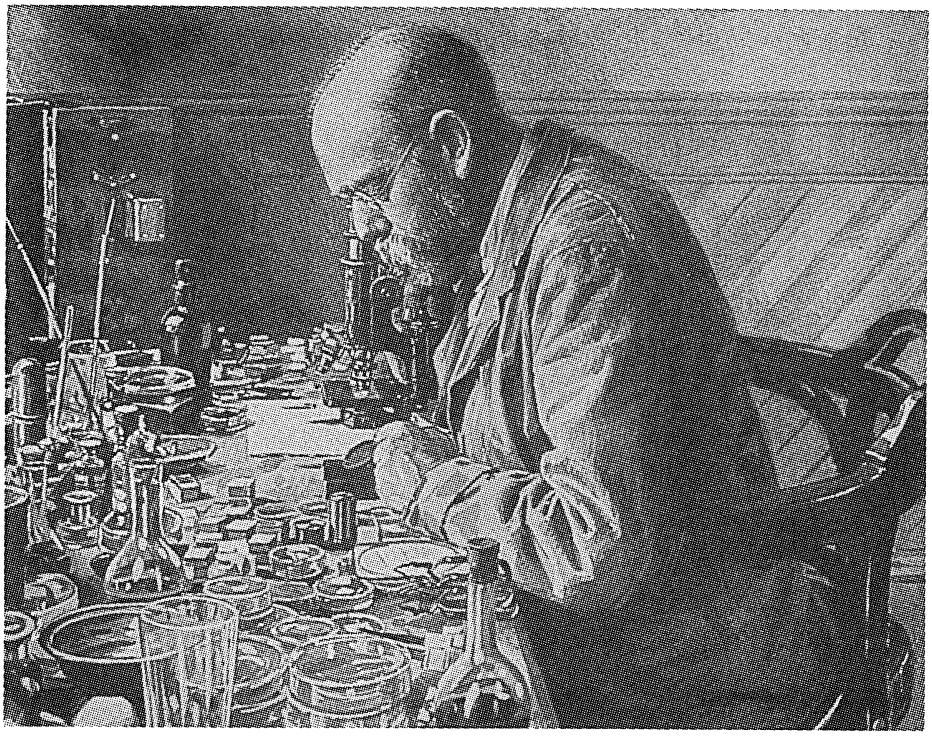

Figure 3 Robert Koch in his laboratory.

Paul Ehrlich was one of Koch's best assistants. He was particularly interested in the idea that dyes can be used *selectively.* Some dyes will take well on wool but not on cotton. Certain dyes will stain some animal cells but not others.

Ehrlich showed that selective dyes could be used to classify blood cells. He also showed that if methylene blue is injected into an animal it will dye nerve cells but not other parts of the body.

The first search

Ehrlich began a hunt for 'magic bullets'. He thought it might be possible to inject dyes into a patient which would kill microbes but leave healthy parts unharmed.

During a long period of research he investigated the effect of azo dyes on blood parasites called trypanosomes. Sleeping sickness is one of the diseases caused by these parasites.

Ehrlich showed that the dyes were effective in killing the parasites in infected mice. Unfortunately he had not found a 'magic bullet' because they also poisoned the animals.

After his lack of success with azo dyes Ehrlich decided to study arsenic compounds. Azo dyes are nitrogen compounds. Arsenic is in the same group of the Periodic Table as nitrogen so Ehrlich thought that arsenic compounds might be worth investigating.

If at first you don't succeed ...

Over six hundred arsenic compounds were made and tested 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 be effective against trypanosomes in mice. Unfortunately it had no effect on the parasites which cause sleeping sickness in human beings.

Ehrlich now decided to try it on other microbes. He used it with the treponeme which causes syphilis.

Ehrlich found his arsenic compound cured syphilis in rabbits. He later found it cured the disease in humans too. He had discovered the first synthetic chemical to control a parasitic disease. He called the new drug 'Ehrlich 606' after the long struggle for success. It was patented in Germany and sold as 'Salvarsan'.

Answer questions 3 to 5.

Questions

3 *How did Ehrlich's work with dyes help him to think of the idea of 'magic bullets' to treat illnesses?*

4 *For what chemical reason did Ehrlich decide to investigate arsenic compounds after his lack of success with azo dyes?*

5 *Why was the first 'magic bullet' called 'Ehrlich 606'?*

Prontosil

Another drug was discovered as a result of research into dyes in the 1930s. A new red azo dye had been made and a sample was passed to Gerhard Domagk. 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, Hildegarde. 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'. It became famous when it was used to fight an outbreak of child-bed fever at Queen Charlotte's Hospital in London.

Answer questions 6 to 8.

Questions

6 *Why did Domagk decide that a dye which was fast on wool might also be attracted to the proteins of bacteria?*

7 *The 'magic bullets' such as Prontosil became less important in the treatment of bacterial disease after the 1940s. Suggest a reason for this.*

8 *All chemotherapy is likely to have some unpleasant side-effects. Suggest a reason why.*

TIME CHART

On the left-hand side of this chart are some of the important events in the history of the discovery of medicines.

- On the right-hand side, fill in the important events in this unit. Put each event in the right position for its date.

Important events in the history of the discovery of medicines		Important events in this unit
• Edward Stone reported the use of extracts of willow bark to treat fevers in 1763.	1760	
	1770	
• Digitalis from foxgloves used to treat heart disease for the first time in 1785.	1780	
	1790	
	1800	
	1810	
• Quinine isolated from cinchona bark used to treat malaria, 1820.	1820	
• Agostino Bassi showed that a fatal disease of silkworms was spread by the spores produced by the fungus which causes the disease (1835).	1830	
	1840	
• Salicylic acid made synthetically in 1852.	1850	
	1860	
• Compounds of salicylic acid used to treat rheumatism from 1876.	1870	
• Louis Pasteur showed the use of a vaccine to prevent anthrax in 1881.	1880	
• Acetyl salicylic acid made by Felix Hofmann in 1893 and sold as aspirin from 1899.	1890	
	1900	
• Frederick Banting and Charles Best discovered the connection between diabetes and the hormone insulin (1921).	1910	
	1920	
• Penicillin discovered by Alexander Fleming in 1928.	1930	
• Professor Florey and Dr Chain developed the use of penicillin as an antibiotic from 1939—1940.	1940	
	1950	
	1960	
• Milstein announced the production of monoclonal antibodies in 1975.	1970	
	1980	