Pioneers in Antimicrobial Chemotherapy

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If we are not careful, we soon will be in the post-antibiotic era, and for some patients and some microbes we are already there” - Tom Friedan

Antibiotics revolutionized medicine in the 20th century. The era of antibacterial chemotherapy began in 1907 with the discovery of arsphenamine, first synthesized by Alferd Bertheim and Paul Ehrlich in 1907, used to treat syphilis. The first systemically active antibiotic, Prontosil was discovered in 1933 by Gerhard Domagk, for which he was awarded the 1939 Nobel Prize.

Fleming’s accidental discovery and isolation of penicillin in September 1928 marked the start of modern antibiotics. It was a discovery that changed the course of history and saved millions of lives.

Sir Alexander Fleming (1881-1955)

Sir Alexander Fleming was a Scottish bacteriologist and Nobel Prize winner, best known for his discovery of penicillin along with Ernst Chain and Howard Florey. He wrote many articles on bacteriology, immunology, and chemotherapy. He also discovered the enzyme lysozyme in 1923.

Following World War I, Fleming actively searched for anti-bacterial agents, having witnessed the death of many soldiers from sepsis resulting from infected wounds. By 1927, Fleming had been investigating the properties of staphylococci.

“When I woke up just after dawn on September 28, 1928, I certainly didn’t plan to revolutionise all medicine by discovering the world’s first antibiotic, or bacteria killer.” “But I suppose that was exactly what I did.” – Alexander Fleming.

He was already well-known from his earlier work, and had developed a reputation as a brilliant researcher, but his laboratory was often untidy. On 3 September 1928, Fleming returned to his laboratory having spent August on holiday with his family. Before leaving, he had stacked all his cultures of staphylococci on a bench in a corner of his laboratory. On returning, Fleming noticed that one culture was contaminated with a fungus, and that the colonies of staphylococci immediately surrounding the fungus had been destroyed, whereas other staphylococci colonies farther away were normal, famously remarking “That’s funny”. Fleming showed the contaminated culture to his former assistant Merlin Price, who reminded him, “That’s how you discovered lysozyme.” Fleming grew the mould in a pure culture and found that it produced a substance that killed a number of disease-causing bacteria. He identified the mould as being from the Penicillium genus, and, after some months of calling it “mould juice”, named the substance it released penicillin on 7 March 1929.

He investigated its positive antibacterial effect on many organisms, and noticed that it affected bacteria such as staphylococci and many other Gram-positive pathogens that cause scarlet fever, pneumonia, meningitis and diphtheria, but not typhoid fever or paratyphoid fever, which are caused by Gram-negative bacteria, for which he was seeking a cure at the time. It also affected Neisseria gonorrhoeae, which causes gonorrhoea although this bacterium is Gram-negative.

Fleming also discovered very early that bacteria developed antibiotic resistance whenever too little penicillin was used or when it was used for too short a period. Fleming cautioned about the use of penicillin in his many speeches around the world. He cautioned not to use penicillin unless there was a properly diagnosed reason for it to be used, and that if it were used, never to use too little, or for too short a period, since these are the circumstances under which bacterial resistance to antibiotics develops.

Selman Abraham Waksman (1888 –1973)

Selman Abraham Waksman was a Jewish-Ukrainian-American inventor, biochemist and microbiologist whose research into organic substances—largely into organisms that live in soil—
and their decomposition promoted the discovery of Streptomyces, and several other antibiotics. Waksman coined the term antibiotics which is widely used today.

Waksman’s team discovered more than 15 antibiotics. Two of these, streptomycin and neomycin, have found extensive application in the treatment of numerous infectious diseases. Streptomycin was the first antibiotic that could be used to cure the disease tuberculosis.

Waksman had been studying the Streptomyces family of organism since his college student days and had, for a time, been studying the organism Streptomyces griseus. Streptomycin was isolated from S. griseus and found effective against tuberculosis by one of Waksman’s graduate students, Albert Schatz.

The bacteria which produced the antibiotic streptomycin was discovered by Schatz in the farmland outside his lab, and tested by him. Waksman, however, eventually came to claim sole credit for the discovery leading to litigation and out of court settlement.

Gerhard Johannes Paul Domagk (1895–1964)

Gerhard Johannes Paul Domagk was a German pathologist and bacteriologist. He is credited with the discovery of first sulfonamide and first commercially available antibacterial, Prontosil, for which he received the 1939 Nobel Prize for Medicine.

He was forced by the Nazi regime to refuse the prize and was arrested by the Gestapo for a week. (This was because the Nazi-critical Carl von Ossietzky had won the Nobel Peace Prize in 1935, which had angered the German government and resulted in German nationals not being permitted by law to accept the Nobel Prize.)

Prontosil had a relatively broad effect against Gram-positive cocci, but not against enterobacteria. The discovery and development of this sulfonamide drug opened the era of antibacterials and more research.

Domagk’s work on sulfonamides eventually led to the development of the antituberculosis drugs thiosemicarbazone and isoniazid, which helped to curb the epidemic of tuberculosis which swept Europe after World War II.

References

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