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# History of Antibiotics

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## Abstract

Introduction: Antibiotics are medicines used to treat or prevent bacterial infections. They can either kill or inhibit the growth of bacteria. Aim: The aim of this historical review is to provide information on the discovery and use of antibiotic formulations over time. Review Methods: The study material consisted of scientific publications related to the subject, such as those recorded in the literature of this study, and relevant writings. Results: The first known use of antibiotics was by the ancient Chinese over 2,500 years ago. Chinese have discovered the therapeutic properties of moldy soybeans and used this substance to cure furuncles (pimples), carbuncles and similar infections. Sir Alexander Fleming was a Scottish biologist and pharmacologist and he was involved in research of Bacteriology, Immunology and Chemotherapy. He is well known for the discovery of the first antibiotic, penicillin, in 1928, for which he received the Nobel Prize in Physiology and Medicine in 1945, along with Florey and Chain. Conclusions: The antibiotic, slowly established itself as the drug-salvation. Modern treatment has the privilege of having potent and safe antibiotic formulations.

**Keywords:** Antibiotics; History of antibiotic; Penicillin.

## 1. Introduction

The term "antibiotics" refers to naturally produced substances of various microorganisms such as bacteria or fungi, which are able to inhibit the growth of other microorganisms and destroy their cells [1]. With the production of semi synthetic derivatives in modern era, the term “antibiotics” has been replaced by the term "antimicrobials" which refers to natural, semi synthetic and synthetic substances capable of inhibiting the proliferation of microbes and thus leading them to apoptosis [2]. Before the emergence of antibiotics, the man was almost completely exposed to infections. Diseases such as pneumonia, meningitis, or tuberculosis were treated very difficult or not at all. Humanity lived under the fear of major epidemics. Specialties such as surgery, pediatrics and hematology had high mortality rates as a consequence of infections [3]. Since then and for many years, medicine has changed form. Without the stress of infection, physicians were able to broaden and advance their research. Specialties such as surgery and hematology flourished. Moreover, for several decades, mankind has been relieved of the fear of major pandemics (eg, plague, syphilis) and diseases - spots such as tuberculosis have been effectively treated. Antibiotic was slowly established in the consciousness of the average human as medicine-salvation [4]. Over time, dozens of new antimicrobial agents have been discovered, with various mechanisms of action, and it is well documented that the current arsenal provides complete protection against almost all pathogens [5].

Nowadays, antimicrobials are widely used drugs not only in medical practice, but also in agriculture, livestock farming, fish farming, as growth enhancers or as growth-protective agents [6, 7].

It is important to specify at this point that chemotherapeutic drugs acting against bacteria and have been produced from living organisms are called antibiotics, while those produced artificially in the laboratory are called antimicrobials [8].

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### 1.1. Aim

The present historical review provides information on the discovery and use of antibiotics over time and their contribution to the treatment of microbial diseases and the progress of medical science in general.

## 2. Review Methods

The study material consisted of scientific publications related to the subject, such as those recorded in the literature of this study, and relevant writings. The method used was based on literature search of review and research studies, drawn from Medline, Pub Med, Iatrotek, a Greek database and the Hellenic Academic Libraries Association (HEAL - Link), using the following key words: antibiotics, history of antibiotics, penicillin. The exclusion criterion for the articles was the language other than Greek and English.

### 2.1. Antibiotics over the Years

The first known use of antibiotics was by the ancient Chinese over 2,500 years ago. Chinese have discovered the therapeutic properties of moldy soybeans and used this substance to cure furuncles (pimples), carbuncles and similar infections. Alexander [9] Many other ancient civilizations, including ancient Egyptians and ancient Greeks already used molds and plants to treat infections due to the production of antibiotic substances from these organisms. But at that time, compounds that develop antibiotic action was unknown [1, 10].

The first steps in microbial observation took place in 1665 by Robert Hooke, who was the first scientist who observed using a simple microscope, apart from the structure of small organisms and plants, microbes and fungi [11]. Hooke, observing a thin cork cut, said that the smallest building blocks of life were small "kits", called cells. Using an improved version of a composite microscope with two lenses, he managed to see individual cells. The discovery of Hooke marked the beginning of cell theory, the theory that all living beings are made up of cells [8]. A few years later, in 1674, Anton van Leeuwenhoek, after constructing microscopes with zoom lenses from X300 to X500, began to observe protozoa and large bacteria. He was the first who managed to observe live microorganisms with some of the 400 microscopes he had constructed [2]. In 1676 he argued, based on his observations, at the Royal Society of London that the micro-organisms he observed with the large lenses were alive[12]. Van Leeuwenhoek made detailed plans of these tiny animals that they were living in the water, the faces, and in the stuff he took from the mouth. In these designs the first bacteria and protozoa were depicted [13].

However, the use of microscopes was forbidden to the researchers of that time, and thus the effective beginning of microbiology became two hundred years later when Luis Pasteur and Robert Koch managed to associate microbes with infections. In 1859, Pasteur formulated the first principles of microbiology, and in 1876 Koch proved that carbon disease is associated with carbon bacillia and eventually in 1882 tuberculosis was linked to tuberculosis mycobacteria [14].

The history of antimicrobial drugs began in the late 1890s when two German researchers, Rudolph Emmerich and Oscar Löw, discovered the first antibiotic, pyocyanase, derived from the cultivation of the microbe Pseudomonas aeruginosa, with dubious effectiveness and safety in the patient population used against cholera and typhus [15].

In 1909 Paul Ehrlich introduced the arsenic-based drug Salvarsan, which acted against Treponema pallidum, the bacterium, which is responsible for the disease of syphilis. This discovery laid the foundations for the further development of antimicrobial agents [16]. However, the milestone in the development of antimicrobial drugs was the discovery of penicillin by Alexander Flemming in 1928, which is used until today in clinical therapies [17].

The antibiotic properties of Penicilium sp. was originally described in France by Ernest Duchesne in 1897. However, his work did not affect the scientific community until the discovery of penicillin by Alexander Fleming. In 1932, the first sulphonamide, prothosyl, was discovered, by Bayer's research team and, Gerhard Domagk in the same year proved its efficacy against major bacterial infections [18].

The first antibiotic available to doctors in 1946 was penicillin, a product of the Penicilium fungus. It can be considered "a child of the war", as extensive research and observations were preceded, before its development, during the Second World War [2]. Its discovery was regarded a modern miracle, as penicillin could treat all types of infections caused by staphylococci and streptococci. Given the fact that these two pathogens cause the greatest number of known infections, it is easy to understand the relief following this discovery [19].

By the end of the 1940s and early 50s, the use of streptomycin and tetracycline was discovered and the era of antibiotic chemotherapy became well tolerated in clinical medicine. These antibiotics were effective against a range of pathogenic bacteria including bacillus tuberculosis [2].

In the 1970s there was, for the first time, scientific interest in terms of the presence of pharmaceuticals and especially the presence of hormones in the environment [1]. In the 1980s the interest in the topic of hormones passed into the background and there was intense research activity concerning the presence in the environment of substances such as heavy metals, polycyclic aromatic hydrocarbons, chlorinated dioxins, pesticides and detergents. Since the mid-1990s other substances, such as analgesics, anti-rheumatic drugs and antibiotics, have been added to the research lists [2, 19].

### 2.2. The Contribution of Fleming

Sir Alexander Fleming was a Scottish biologist and pharmacologist and he was involved in research of Bacteriology, Immunology and Chemotherapy. He is well known for the discovery of the first antibiotic, penicillin, in 1928, for which he received the Nobel Prize in Physiology and Medicine in 1945, along with Florey and Chain. Another important discovery is that of the lysozyme enzyme, in 1922 [20].

In 1928, Fleming was investigating the properties of staphylococci. He already had some reputation from his previous research, as an intelligent researcher but also as a careless laboratory technician: he often was forgetting the microbial crops he was working on and generally his lab was usually very messy [17]. After returning from a vacation, Flemming noticed that many of the microbial cultures tablets were infected with a fungus (commonly: molded) and threw them into a detergent container. But then he had to show to a visitor what he was looking for, so he took some of the tablets that were not submerged in the detergent. Then he noticed a zone around the mold that was free of bacteria. This should have happened if the mold produced some bactericidal substance [21].

Fleming managed to isolate a specimen of mold, he correctly identified it as a penicillin fungus, and for that reason the new substance took the name of penicillin. Fleming investigated the bactericidal action of penicillin on many microorganisms. He found that it affected bacteria such as staphylococci and generally all Gram positive pathogens but not the germs of typhoid or paratyphoid fever, for which he was seeking for a treatment at that time. It also affected gonorrhea, although this is caused by a Gram negative microorganism [12].

However, attempts to cure human infections with this material proved not encouraging, because the substance was unstable and powerless. Only after a few years, researchers at Oxford University have examined the possibility of producing stable penicillin in quantities sufficient to treat human diseases. In 1941 the drug was used to treat serious infections. The results were impressive as patients taking penicillin experienced rapid and complete recovery. World War II prevented the production of penicillin on a large scale in the United Kingdom. Methods for the mass production, determination and stabilization of the antibiotic have been developed in the United States. The production of penicillin was the beginning of an era called the golden age of chemotherapy [21].

After 1948, a large number of growth-inhibiting substances or bacteria and some fungi were discovered. Fleming published his discovery in 1929 in the British Journal of Experimental Pathology, but its significance did not become apparent until a decade later. Fleming continued his investigations, but he realized that the cultivation of penicillin was quite difficult and then it was even more difficult to isolate the antibiotic substance of the mold. Even Flemming himself stopped dealing with penicillin in 1932. His personal impression was that due to the problem of its production in a large quantity and its slow action, penicillin would not be important in the fight against infections [20].

Fleming was also convinced that penicillin would not remain sufficiently within the human body to kill germs effectively. However, Fleming has abandoned his research on penicillin shortly before Florey and Chain undertook its research and start its mass production with funds from the US and British governments. The mass production began after Pearl Harbor's bombardment. During the invasion of Normandy had enough penicillin prepare for the needs of all the wounded allied forces [17].

## 3. Conclusions

It is rare times in human history where some discovery radically changed the course of events. The fire, the wheel, the gunpowder and the nuclear energy are typical examples of such nodal discoveries. Undoubtedly, in this category of the most important moments in the evolution of human civilization is also the discovery of antibiotics [22].

Antibiotics slowly established themselves as medicines-salvation. Modern treatment has the privilege of having powerful and safe antibiotic formulations.

However, times and seasons have changed and now patients and physicians need to be retrained to the proper use of antibiotics, because there is a risk of over-consumption of them. Proper use of antibiotics by health scientists as well as by citizens is therefore necessary so that antibiotics continue to be the "guardian-angel" of all patients.

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