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Antibiotics: from prehistory to the present day

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Antimicrobials have been in use for many thousands of years in a variety of formats. In this article, I trace how we have moved from ingenious use of agents available in the environment to chemically engineered agents.

Introduction

In a generation brought up in the era of widely available antibiotics, it is easy to assume that, in the days before they were introduced, anyone with an infection eventually succumbed to its effects.

This is clearly not the case, as there were always survivors of even the most deadly infections, such as bubonic plague, diphtheria and TB, thanks to the efficiency of the innate immune response. However, it is fair to say that mortality rates were once much higher than they are today.

Ancient history

There is also good historical evidence that ancient civilizations used a variety of naturally available treatments for infection, for example herbs, honey and even animal faeces.[1] One of the more successful treatments was the topical application of mouldy bread, with many references to its beneficial effects from ancient Egypt, China, Serbia, Greece and Rome. This theme of the benefit of moulds continued over the years, with references by John Parkinson (1567–1640) (Figure 1) in his book *Theatrum Botanicum*, published in 1640.

Even some more-modern antibiotics may have been available in ancient times. Traces of tetracyclines have been detected in human skeletons excavated in Nubia and during the Roman occupation of Egypt.[2] The origin of the tetracycline remains a mystery.

Renaissance and enlightenment

The discovery of small living creatures or 'animalcules' by Antonie van Leeuwenhoek[3] (1632–1723) in 1676—using a microscope he designed—started the study of bacteriology after he had communicated his findings in 1665 to Robert Hooke (1635–1703), a founding member of the Royal Society. In the late 1800s, Robert Koch (1843–1910) and Louis Pasteur (1822–1895) were able to establish the association between individual species of bacteria and disease through propagation on artificial media and in animals.

The spread of gonorrhoea and syphilis[4] prompted more experimentation with possible treatments, particularly amongst the upper classes. Heavy metals such as arsenic, bismuth and mercury were all tried; they were administered either systemically or locally, by means of specially designed syringes. Although symptoms were improved, the administration and side effects often proved worse than the disease.

Dawn of the modern era

Pyocyanase was probably the first antibiotic to be used to treat human infections. Rudolf Emmerich (1856–1914) and Oscar Löw (1844–1941) discovered that the green bacteria isolated from injured patients' bandages inhibited the growth of other microbes.[5] They grew the organism (*Pseudomonas aeruginosa*) in batches and used the supernatant as a medicine, with mixed success.

It was not until Paul Ehrlich (1854–1915) (Figure 2) started working on the antibacterial effects of dyes that the modern era of antimicrobial chemotherapy really began. Ehrlich's early interest was in developing stains for the histological examination of tissues, in particular the basis of the Ziehl–Neelson stain for TB and the Gram's stain. He noted that some stains were toxic for bacteria and started searching for the 'magic bullet' of German folklore (originally devised to kill werewolves).[6] Salvarsan, an arsenic-based chemical discovered by Ehrlich and his team in 1909, proved an effective treatment for syphilis and was probably the first truly modern antimicrobial agent, though it was not an antibiotic in the strict sense of the word.

Ehrlich did not confine himself to chemicals. He was also very interested in immunology, and he worked with Robert Koch (1843–1910) and Emil von Behring (1854–1917) to improve a diphtheria antitoxin. Antitoxins then became the basis of antibacterial therapy. William Osler (1849–1919) described the use of 'anti-streptococcal serum' as a treatment for endocarditis whereby the bacteria isolated from blood cultures was injected into horses and the horse serum was then administered to the patients.[7]

Penicillin

Everyone is familiar with the story of how Alexander Fleming (1881–1955) discovered penicillin in 1928,[8] but others probably

Figure 1. John Parkinson (1567–1650). The first person to document the use of moulds to treat infections.

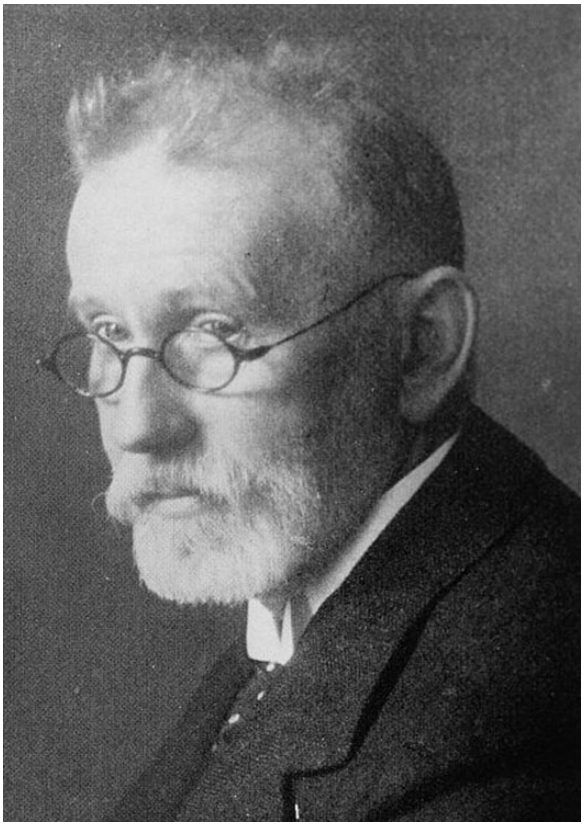

Figure 2. Paul Ehrlich (1854–1915). The father of antimicrobial chemotherapy.

got there before him. In 1870, Sir John Scott Burdon-Sanderson (1828–1905) described how culture fluid covered in mould inhibited the growth of bacteria. The year after, Joseph Lister (1827–1912) experimented with '*Penicillium glaucium*' (sic), demonstrating that it had an antibacterial effect on human tissues, and in 1875, Dr John Tyndall (1820–1893) presented his experiments with *Penicillium notatum* to the Royal Society. Finally, in 1897, Ernest Duchesne (1874–1912) observed Arab stable boys treating saddle sores with mould propagated on their saddles. He took this mould, confirmed as *Penicillium notatum*, and used it to successfully treat induced typhoid in guinea pigs.[3]

Fleming realized that there was great potential in penicillin, but there were significant challenges in translating what could be demonstrated in the laboratory into a medicine that could be made widely available. He tried to attract the interest of chemists over a number of years but finally gave up in 1940 to pursue other interests. Fortunately, Howard Florey (1898–1968), a pharmacologist and pathologist, and Ernst Chain (1906–1979), a biochemist working in Oxford, published a paper the same year describing a purification technique. This breakthrough ultimately led to penicillin becoming available for limited use in 1945.[9] Undoubtedly a lifesaver, penicillin still had problems. It had a very short $t_{1/2}$ and poor bioavailability, issues that persist when it is given today.

Whilst Fleming was trying to purify penicillin, in Germany scientists at Bayer were following Ehrlich's lead and exploring the antibacterial effects of dyes. Sulfanilamide had been synthesized in 1908 and, by combining it with a dye, in 1931 Prontosil was produced; this combination proved effective in treating streptococcal infections in mice. In 1933, a boy dying of staphylococcal septicaemia was given the drug with miraculous success. In 1935, researchers realized that the dye component was unnecessary, as Prontosil was metabolized to sulphanilamide, and so the sulphonamide[10] era had begun. Sulphonamides allegedly saved the lives of Winston Churchill and the son of Franklin D. Roosevelt.

The Golden Age

After this kick-start, the following 20 years became the 'Golden Age' of antibiotic discovery. Initially, the best source of new agents was from other naturally occurring microorganisms and after streptomycin[11] was isolated in 1944 from *Streptomyces griseus* (an organism found in soil), a worldwide search began. Every effort was made to reach all corners of the globe, but resources were limited. Eli Lilly had the bright idea of asking Christian missionaries to send back a soil sample from every exotic place that they visited. A sample from Borneo sent in 1952 grew *Streptomyces orientalis,* from which vancomycin was eventually extracted; vancomycin became available for patient use in 1958.[12]

By this time, resistance to antibiotics was becoming apparent, and scientists looked at new ways to improve on existing agents to combat this obstacle. Beecham developed methicillin in 1959 as the first penicillinase-resistant β-lactam antibiotic, and penicillin's spectrum of activity and pharmacokinetics were improved by the introduction of ampicillin in 1961.

Cephalosporins started to emerge in the 1960s and their evolution divided them into three generations according to their spectrum of activity, with the antipseudomonal third-generation agent ceftazidime appearing in the late 1970s. Serendipitously, in 1975, the first edition of this Journal included a paper describing the antimicrobial activity of cefamandole.[13]

Bacterial β-lactamase inhibitors[14] were first identified as a by-product of *Streptomyces clavuligerus* cultures in 1976. From these were derived clavulanic acid, which was combined with amoxicillin to become co-amoxiclav, and thienamycin, which became the precursor for the carbapenems.

Thienamycin evolved into imipenem, which was very effective *in vitro* and in animal models but unfortunately had a very short $t_{1/2}$ in human trials. Further investigation identified a novel enzyme in the human kidney, dihydropepidase I, that rapidly metabolized imipenem. By adding cilastatin to imipenem, the $t_{1/2}$ was increased, and this combination was made available for use in the UK in the late 1980s. Meropenem was licensed in 1995 and had a similar spectrum of activity but was associated with fewer adverse effects.[15]

Two β-lactamase inhibitors, tazobactam and sulbactam, have been combined with other agents to extend their range of activity.[14] Piperacillin/tazobactam was first licensed in the USA in 1993 and was the subject of a supplement in this Journal the same year. The combination is now used extensively in the UK as a *Clostridium difficile*-sparing replacement for the cephalosporins that had previously been the popular choice for empirical therapy.

As a number of available broad-spectrum antibiotics became available, the incidence of infections caused by resistant bacteria increased with selection pressure. Until the early 1980s, the treatment of pseudomonal infections required the use of intravenous antibiotics and admission to hospital.

Nalidixic acid was available for clinical use in 1967,[16] though its use was limited to the treatment of uncomplicated urinary tract infections. The development of the fluoroquinolones moved this group of antibiotics back into the premier league, particularly since they were all orally available. Ciprofloxacin was introduced in in the mid-1980s, when I was a trainee microbiologist, and I have followed the oscillations in fortune of this agent over the years. Many other new quinolones either failed to become clinically available or were withdrawn owing to adverse effects following their launch. It is of interest to reflect on this: many of the earlier antibiotics, such as macrolides and tetracyclines, cause similar (or even worse) adverse effects, but are still widely used.

As time moved along, resistant Gram-positive infections such as MRSA and enterococci were proving increasingly more challenging to clinicians, so antibiotic development shifted attention towards these bacteria.

Vancomycin was still being used as the first-line agent for these infections, but it was not easy to administer, it was weakly bactericidal and resistance was emerging for enterococci. Teicoplanin, which was isolated from *Actinoplanes teichomyceticus*, was the first of the new glycopeptides, and it became available in Europe in the 1990s.[17] Although it was easier to administer, its activity against staphylococci was disappointing and its use for glycopeptide-resistant enterococci (GRE) limited. Nevertheless it is still used widely today.

The use of glycopeptides in the outpatient setting has led to the search for longer-acting agents. Dalbavancin first underwent clinical trials in 2007, but it did not become available until 2014, about the same time as oritavancin, which was licensed in the USA as a single-shot treatment for skin and soft tissue infections.

Oxazolidinones were originally investigated for plant diseases. The first antibiotic in this class was cycloserine, which was used first in 1956 to treat TB. Linezolid was approved for use in 2000 and has proved a useful alternative to glycopeptides because of its good oral availability and activity against GRE. This use is despite its association with a range of adverse effects and drug interactions.[18] Echoing its beginnings, linezolid is also proving to be a useful agent in the treatment of drug-resistant mycobacteria. Newer antibiotics in the same class, such as tedizolid, have recently become available, and so far the data from clinical trials are encouraging in respect to adverse events.

Daptomycin,[19] like many of the other antibiotics described in this review, was derived from a soil organism, *Streptomyces*

Table 1. Examples of Supplements of the Journal that focus on particular antibacterial drugs

Antibacterial	Supplement
β-Lactams	
ceftazidime	1981; **8** Suppl B: 1–358
ceftazidime	1983; **12** Suppl A: 1–122
clavulanate/β-lactam antibiotics	1989; **24** Suppl B: 1–226
imipenem	1983; **12** Suppl D: 1–153
imipenem	1986; **18** Suppl E: 1–232
meropenem	1989; **24** Suppl A: 1–320
meropenem	1995; **36** Suppl A: 1–223
piperacillin/tazobactam	1993; **31** Suppl A: 1–124
Fluoroquinolones	
enoxacin	1984; **14** Suppl C: 1–344
norfloxacin	1984; **13** Suppl B: 1–142
ciprofloxacin	1986; **18** Suppl D: 1–260
pefloxacin	1986; **17** Suppl B: 1–118
enoxacin	1988; **21** Suppl B: 1–136
fleroxacin	1988; **22** Suppl D: 1–234
ofloxacin	1988; **22** Suppl C: 1–2
ciprofloxacin	1990; **26** Suppl E: 1–142
ofloxacin	1990; **26** Suppl D: 1–83
pefloxacin	1990; **26** Suppl B: 1–101
temafloxacin	1991; **28** Suppl C: 1–130
sparfloxacin	1996; **37** Suppl A: 1–161
grepafloxacin	1997; **40** Suppl 1: 1–101
trovafloxacin	1997; **39** Suppl 2: 1–97
ciprofloxacin	1999; **43** Suppl 1: 1–41
levofloxacin	1999; **43** Suppl 3: 1–90
moxifloxacin	1999; **43** Suppl 2: 1–100
gemifloxacin	2000; **46** Suppl 3: 1–37
gemifloxacin	2000; **45** Suppl 3: 1–107
Miscellaneous	
vancomycin	1984; **14**: 1–109
teicoplanin	1988; **21**: 1–172
teicoplanin	1991; **27**: 1–73
linezolid	2003; **51** Suppl 2: 1–53
dalbavancin	2005; **55** Suppl 2: 1–35
tigecycline	2013; **68** Suppl 2: 1–55

roseosporus, which was obtained from Mount Ararat in Turkey. Daptomycin was first evaluated in the late 1980s; however, trials were halted owing to adverse musculoskeletal effects, but the agent was resuscitated and launched in the USA in 2003.

The end of the Golden Age

Meanwhile, on the recognition that the introduction of infection control measures could reduce the incidence of MRSA and GRE, attention reverted to the problem of resistance in Gram-negative bacteria. Treatment of infections caused by pan-resistant *Acinetobacter*, Enterobacteriaceae and *Pseudomonas* was proving a challenge to clinicians, particularly in the intensive care scenario. Older drugs such as colistin, chloramphenicol, minocycline and fosfomycin were reconsidered, either alone or in combination with newer agents.

Tigecycline,[20] a derivative of tetracycline, was introduced in 2005 and was the first broad-spectrum agent to be licensed since moxifloxacin in 2000.

Following on from tigecycline, in the 2010s came ceftobiprole and ceftaroline, cephalosporins active against MRSA. More recently, cephalosporin/β-lactamase combinations such as ceftolozane/tazobactam, ceftazidime/avibactam and ceftazidime/sulbactam[21] have been developed, with activity against resistant strains of *Pseudomonas* and carbapenemase-producing Enterobacteriaceae.

Conclusions

The *Journal of Antimicrobial Chemotherapy* has played its part in the history of antibiotics, publishing research, leading articles and Supplements (Table 1).

Although science is trying to keep pace with the emergence of more and more resistant bacteria, extra efforts are needed to conserve our existing antibiotics and develop new ones. The wider use of antibiotic combinations could help to bridge the gap but, although *in vitro* data are available, more clinical outcome results are needed for validation.

One of the recurring themes in this review is that many of the great advances in the discovery of antibiotics were the result of the isolation of novel environmental bacteria. This work is time consuming. Many strains have to be tested for their products before even a potential agent can be identified. Research into novel bacterial targets linked to WGS may eventually make this work easier, but in the meantime, natural habitats where these microorganisms are found are being eroded by deforestation and global warming. There may not be much time left!

Transparency declarations

None to declare.

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