Medicine for Managers

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Antibiotics – history and development

There can't be anyone who doesn't think that, in the history of medicine and social care, that antibiotics should be high on the list of great developments along with clean water and vaccination. Perhaps the discovery is synonymous with Alexander Fleming but the power of some drugs to cure or prevent infections was known much earlier than the twentieth century.

Antibiotics must have saved millions of lives over the years and it is easy to forget now how relatively minor infections, which used to kill patients even in my clinical practising lifetime, can now be eliminated with a course of tablets or injections.

There is evidence that knowledge of treatments for infections were known before Christ. Traces of tetracycline have been found in skeletons from Sudanese Nubia dating back as far as 500 BC and in skeletons from Roman Egypt from around 350 AD. The inclusion of tetracycline containing agents in the diet of such races and tribes suggests deliberate administration in the diet. Documentary evidence suggests that infection rates were low in these populations.

Chinese herbalists too have been using agents with antibacterial properties for millennia. The drug *artemisinin*, an anti-malarial agent which was extracted from the *Artemesia* plant in the 1970s, has been used for thousands of years in the treatment of many illnesses.

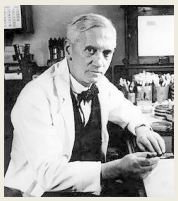
Today some Jordanese use red soils for the treatment of skin infections and these soils have been found to contain bacteria which produce antibiotics. This has also been passed down from generation to generation for thousands of years.

Perhaps the two people most associated with the modern development of antibiotics are Paul Ehrlich and Alexander Fleming.

Paul Ehrlich (1984-1915) was a German

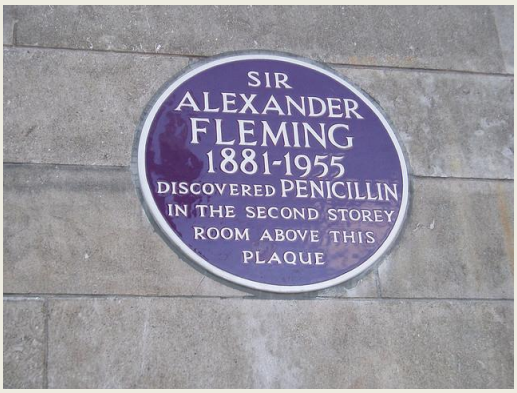
physician and scientist who worked in the field of antimicrobial chemotherapy. He developed an early technique for staining bacteria in order to be able to identify and distinguish them. He stated his belief that

chemicals could be synthesised that would destroy the organisms. He alighted on the infection syphilis which was endemic and incurable at the time. At that time the only treatment was a mercuric compound which was largely ineffective and with severe side effects.



Ehrlich studied the organic arsenical componds and reviewed hundreds of formulations. Compound number 606 was found to cure rabbits and later humans of the disease.

It was marketed by Hoechst under the name *Salvarsan*. A less toxic formulation *Neosalvarsan* was later introduced. It became the most commonly prescribed drug for more than thirty years. Its mode of action is still unknown nearly 100 years later.



Ehrlich's foundations led other chemists to study chemical formulations and their effects on bacteria. Pharmacists at Bayer identified sulphonamideochrysoidine (*Prontosil*). Subsequently the active part of the molecule, sulphanilamide, was identified and manufactured in bulk. The drug and similar formulations are still in use today.

Serendipity resulted in perhaps the most important of all pharmacological discoveries when, on September 3rd 1928, Alexander Fleming discovered penicillin at St Mary'sHospital. He noticed the antibacterial effect of the bacterium *Penicillium* which would destroy other bacteria near it on a Petri dish containing agar medium. He persisted with his belief of the efficacy of the drug until 1940 when he abandoned the idea for lack of interest. Fortunately, in the same year, Florey and Chain published a paper describing the process for purifying penicillin which was then tested clinically. The spectacular results led to its mass production in the year 1945.

Salvarsan, *Prontosil* and *Penicillin*, the first three antimicrobial drugs, set the standard and led to a golden era between 1950 and the late 1970s resulting in the discovery of a number of classes of antibacterial drugs.

During that period many believed that infections would be eliminated. However some voices expressed caution and Fleming himself pointed out that resistance to penicillin developed if it was used in too small doses or for too short a period.

Over time there came the recognition of ***antibiotic resistance***. Even in the 1940s it

had been discovered that some bacteria could manufacture enzymes in response to exposure to antibiotics which would result in the degradation of the drug and it being rendered ineffective.

It became clear that some bacteria were sufficiently versatile that they could develop resistance to a number of antibiotics and, over the last fifty years, resistant strains have increased dramatically such that it is estimated that, in the EU, more than 25,000 people die each year from infections for which no effective antibiotic can be found and, in the United States, it is likely that over 70,000 die annually from hospital acquired infections.

Resistance to antibiotics can develop in a number of ways.

Bacterial mutations can make the organisms insensitive to the antibiotic, enzymes which destroy the antibiotic may be produced or protective secretions may be produced through which the antibiotic cannot penetrate.

It is now possible that anyone could acquire an infection which will be resistant to any antibiotic.

Following the explosion in antibiotics in the 1970s, it soon became clear that resistance was already developing and researchers round the world worked to modify the structures of antibiotics o make them less susceptible to bacterial defence mechanisms.

Many modified formulations were produced. Unfortunately, however, despite all the research carried out, there have not really been any novel classes of antibiotic in the last twenty years.

The main problem with existing and with any new antibiotic is that, over time, resistance will develop.

There is almost a competition to see how quickly new antibiotics can be produced and how long they will remain effective.

Unfortunately, the decline in efficacy of antibiotics is due in significant part to their overuse in health- care and vetinary medicine.

They have been used for viral infactions against which they are completely ineffective. They have been used in many circumstances where the infection would have been self-limiting.

They have commonly been prescribed under pressure from patients believing that they are a magic panacea able to treat anything that caused symptoms for more than a few days.

Sadly doctors have frequently buckled under pressure fearing allegations of failure to treat if they failed to prescribe.

Another problem has been the failure of people to follow the regime of prescribing when the drug was prescribed. Tuberculosis offers a good example where a prolonged course of several antibiotics is necessary.

Failure to stop taking them too soon results, in simple terms, in organisms that are damaged but not destroyed and able to develop resistant forms. Compliance with course instructions is essential.

In some parts of the world, where medical care is less well established, less regulated, based on poor diagnostic facilities or lacks proper prescribing guidelines, compliance or monitoring, resistance to antibiotics develops more quickly.

Indeed in many countries antibiotics are freely purchasable over the counter of pharmacies and the activity has resulted in gross misuse in some cases.

In vetinary medicine, antibiotics are not used simply for infected animals. They are also used for prophylactic purposes and growth promotion and critics say that they are poorly targeted, again promoting resistance. In parts of Scandinavia more recent regimes have curbed the prophylactic and growth reasons for antibiotic use and the benefits have been encouraging.

The antibiotic era and usage is a very short period in human evolutionary and history scales. It has saved millions of people from otherwise fatal or severely debilitating infections.

However the classes of drug have suffered major ups and downs and the golden era of antibiotics may be over because bacteria during the same evolutionary period have developed huge diversity in terms of metabolic and protective mechanisms.

Perhaps there is another Fleming and penicillin just round the corner or perhaps bacterial destruction to maintain health will be based on completely different approaches in the future.

I shall review practical use of antibiotics, indications and complications next time.

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