

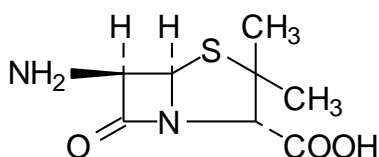


## The evolution of pharmacy Theme C, Level 2

### The development of medicines

#### Antibiotics

Antibiotics are a group of drugs which inhibit the growth (bacteriostatic) or kill (bactericidal) bacteria, fungi (antifungal), neoplasms (cytotoxic) and malaria parasites (antimalarial). This sheet deals with antibacterial drugs. Many are now available to treat infections, stemming from the discovery of penicillin by Alexander Fleming in the 1920s from his observation that a contaminating mould inhibited the growth of bacteria on culture plates. The drug remained undeveloped until 1940 when Florey and Chain isolated penicillin from cultures of the mould and demonstrated its powerful antibacterial properties when injected into animals and man. The production of large quantities of penicillin occurred in the US in the early 1940s since in the war years the UK did not have the resources available for development and production. The leading pharmaceutical houses in the US such as Lederle, Merck, Pfizer and Squibb developed the technology and were able to exploit their expertise and become research-oriented manufacturers of drugs and medicines on a global scale. It is said that penicillin was the Allies' secret weapon in the Second World War, enabling many wounded and infected combatants to return to their duties within days, such was its power in fighting infections.



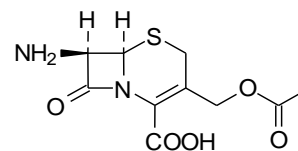
6-aminopenicillanic acid

Penicillin is a generic name now describing a number of different drugs, based upon the 6-aminopenicillanic acid (6APA) nucleus. This has a 4-membered beta lactam ring fused to a 5-membered thiazolidine ring and a number of small substituents essential for its activity.

Different chemical groups are attached through the 6-amino group, such as benzyl (penicillin G) and phenoxymethyl (penicillin V). Other groups confer important properties such as resistance to breakdown in the body and by bacteria, and

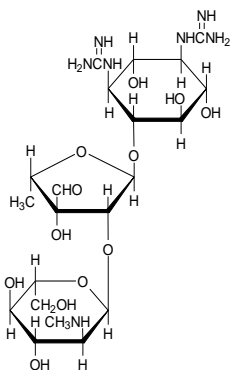
there is now a wide range of synthetic and semi-synthetic penicillins available for clinical use, including ampicillin, amoxicillin and flucloxacillin.

Related to the penicillins are the cephalosporins, such as Cephalosporin C. Again, these were developed from a mould, but did not become used until the isolation and synthesis of the nucleus 7-aminocephalosporanic acid enabled a range of antibiotics to be produced, including cefalexin, cephaloridine, and cefoxitin.



7-aminocephalosporanic acid

The discovery of penicillin stimulated a world-wide search for other moulds that produce antibiotics. Many were isolated but, for reasons of toxicity or undesirable side effects, only a few became used as drugs. One of the earliest discovered was chloramphenicol, first isolated from the mould *Streptomyces venezuelae* by the Parke, Davis Company. It is a broad spectrum antibiotic which was first used in typhus and, by mistake, in typhoid. It is now used mainly in treating typhoid and topically for ear and eye infections.



Streptomycin

The aminoglycosides are another group obtained from moulds. They were first discovered by Waksman, working in New Jersey, who isolated streptomycin from *Streptomyces griseus* which was found to be active against *Mycobacterium tuberculosis*. It became the first line drug for treating tuberculosis but was found to cause deafness in large doses, and is now used in smaller doses in combination with other anti-TB drugs. Other aminoglycoside antibiotics include neomycin, clindamycin and gentamicin, all used today in some infections.

In a search for a safer antibiotic than streptomycin, hundreds of soil samples were screened for antitubercular activity by Duggan at Wisconsin who isolated a golden actinomycete which had antibiotic activity. Isolation and elucidation of the chemical structure showed it to be a tetracyclic compound, named chlortetracycline, which was in full production by 1948 by the American Cyanamid Company. Around the same time a similar compound, oxytetracycline, was isolated by researchers at the Pfizer Company and marketed by that company, unusually by direct advertising to the public, a move which invoked much criticism at the time. A few years later the parent compound, tetracycline, was obtained which was as active as the others. The tetracyclines are broad-spectrum antibiotics, but are poorly absorbed from the intestine resulting in disturbances to the normal flora in the gut.

### FIND OUT MORE

#### Further reading:

Sneider, Walter, 'Antibiotics' in *Drug Discovery: a History*, (John Wiley, Chichester, 2005)  
 'Infections' in *British National Formulary*, (BMA & RPSGB, London, current edition)