# Antibiotics

An antibiotic was a substance, produced by one microorganism, which inhibited the growth of other microorganisms. The advent of synthetic methods has, however, resulted in a modification of this definition and an antibiotic now refers to a substance produced by a microorganism, or to a similar substance (produced wholly or partly by chemical synthesis), which in low concentrations inhibits the growth of other microorganisms. Chloramphenicol was an early example. Antimicrobial agents such as sulphonamides and the 4-quinolones, produced solely by synthetic means, are often referred to as antibiotics.

## History of Antibiotics

### Discovery of Penicillin

Fleming's contaminating mold was identified as belonging to the genus *Penicillium* ,which led to the name **penicillin** for the substance responsible for the antibacterial activity observed on the agar plate. Fleming published his work on penicillin in 1929, reporting that extracts of the mold were able to kill a number of gram positive pathogens in addition to the staphylococci and even the gram negative pathogen responsible for gonorrhea. Over the next 10 years, Fleming tried to progress penicillin further but was hampered by an inability to isolate and purify it. Early attempts to use crude penicillin topically in patients were not very successful, and Fleming did little further work on its clinical potential, focusing instead on its utility as bacteriological reagent. He never tested it in a model infection in mice! Meanwhile, Ernst Chain had taken on the task of isolating penicillin and solving its structure. The first results of this effort were published in 1940 , and by 1945, penicillin had

demonstrated its amazing curative properties in the clinic and was being produced and distributed on a large scale.

For their seminal work Florey, Chain, and Fleming were awarded the Nobel Prize in 1945. Over the ensuing years many generations of novel penicillins have been developed with improved spectrum, pharmaco-kinetics, and resistance to beta lactamase.

## The Actinomycetes Take Center Stage

Fleming's discovery of penicillin in 1928 coupled with Rene Dubos' discovery of **tyrothricin** in 1939, led Selman Waksman to start investigating microbes found in the soil as a source of novel agents active against bacteria. Dubos' work that led to tyrothricin was very different from Fleming's fortuitous discovery of penicillin, as it resulted from the first deliberate search for compounds produced by soil microbes that were capable of killing pathogenic bacteria. He actually fed gram positive bacteria at intervals to a large sample of mixed soils, hoping initially to find microbes that were capable of destroying the bacteria. In reality, he discovered a bacterium that produced **an alcohol soluble compound capable of inhibiting the growth of gram-positive bacteria that he called tyrothricin.** The alcohol extract was actually a mixture of two compounds: **tyrocidin** and **gramicidin**. Although neither antibiotic proved to be of clinical utility, their discovery was a seminal event demonstrating the utility of screening soil microbes. Tyrocidin proved very toxic, and, although gramicidin was able to cure experimental infections in mice, it also was too toxic for systemic use in humans. Gramicidin is a complex of six related compounds and still has utility today as a topical treatment for superficial infections; it is one of three

constituents in **Neosporin ointment**. Natural products synthesized by soil microbes are frequently produced as a complex of related molecules.

Waksman's group started testing all three of the known types of microbe found in the soil (bacteria, fungi, and actinomycetes) for their ability to produce antibiotic activity. It quickly became apparent that the actinomycetes were the most fruitful source of this activity. The subsequent systematic screening of soil actinomycetes led to **actinomycin** and **streptothricin**, which, like tyrocidin and gramicidin, were too toxic for clinical use as antibacterials. Nonetheless a clear direction had been set in the quest for novel antibiotics.

## The Discovery of Streptomycin

In 1943, Albert Schatz, a graduate in Waksman's lab found **Streptomycin**, which was active against gram negative bacteria and most importantly against *Mycobacterium tuberculosis* , the pathogen responsible for **TB (tuberculosis)**. It was quickly shown to be active in animal models of TB and then to be capable of curing the disease in actual patients by 1946.

Waksman was awarded the Nobel Prize in 1952 for his pioneering work with actinomycetes and for the discovery of streptomycin. His work led to the golden era of antibiotic discovery.

## Definitions

The following terms are commonly employed in connection with antimicrobial agents and their uses:

**A- Biocide:** a chemical or physical agent, usually broad spectrum, which inactivates microorganisms. Chemical biocides include hydrogen peroxide and phenols while physical biocides include

heat and radiation. Biocides are generally broad spectrum, in contrast to anti-infectives, which have narrower range of antimicrobial activity.

**B- Bacteriostatic:** a specific term referring to the property by which a biocide is able to inhibit bacterial multiplication ; multiplication resumes upon removal of the agent. ( The term "fungistatic" and "sporostatic" refer to biocides that inhibit the growth of fungi and spores, respectively).

**C- Bactericidal:** a specific term referring to the property by which a biocide is able to kill bacteria. Bactericidal action differs from bacteriostasis only in being irreversible ; i.e. the "killed" organism cannot longer reproduce, even after being removed from contact with the agent. In some cases, the agent causes lysis (dissolution) of the cells ; in other cases, the cells remain intact and may even continue to be metabolically active. (The terms "fungicidal", "sporicidal", and "virucidal" refer to the property whereby biocides are able to kill fungi, spores, and viruses, respectively).

**D- Sterilization:** a defined process used to render a surface of product free from viable organisms including bacterial spores.

**E- Disinfectants:** products or biocides used to reduce the number of viable microorganisms, or bio burden, on or in a product or surface to a level previously specified as appropriate for its intended further handling or use. Disinfectants are not necessarily sporicidal, but are sporostatic, inhibiting germination or outgrowth.

**F- Septic:** characterized by the presence of pathogenic microbes in living tissue.

**G- Antiseptic:** a biocide or product that destroys or inhibits the growth of microorganisms in or on living tissue (eg, skin).

**H- Aseptic:** free of, or using methods to keep free of, microorganisms.

**I- Preservation:** the prevention of multiplication of microorganisms in formulated products, including pharmaceuticals and foods.

**J- Antibiotics:** naturally occurring or synthetic organic compounds which inhibit or destroy selective bacteria, generally at low concentrations.