Inhibition of *Staphylococcus aureus* bacteria by a *Penicillium* mold colony.

Discover a New Antibiotic

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"There are other possibilities, notably those connected with naturally occurring substances. Little, however, has been done to purify or to determine the properties of any of these substances."
-Ernst Chain

Antibiotics

Treatment of disease by using chemical substances is called **chemotherapy.** Here, we are interested in antimicrobics although the term also refers to chemical treatment of noninfectious diseases. Chemotherapeutic agents prepared from chemicals in the laboratory are called **synthetic drugs.** Chemicals produced naturally by bacteria and fungi to act against other microorganisms are called **antibiotics.** The success of antimicrobics is based on the fact that some chemicals are more poisonous to microorganisms than to the hosts infected by the microbes.

The birth of modern chemotherapy is credited to the efforts of Paul Ehrlich in Germany during the early part of the twentieth century. While attempting to stain bacteria without staining the surrounding tissue, he speculated about some "magic bullet" that would selectively find and destroy pathogens but not harm the host. This idea provided the basis for chemotherapy, a term he coined.

In 1928, Alexander Fleming observed that the growth of the bacterium *Staphylococcus aureus* was inhibited in the area surrounding the colony of a mold that had contaminated a Petri plate. The mold was identified as *Penicillium notatum,* and its active compound, which was isolated a short time later, was named penicillin. Similar inhibitory reactions between colonies on solid media are commonly observed in microbiology, and the mechanism of inhibition is called antibiosis.

In 1940, a group of scientists at Oxford University headed by Howard Florey and Ernst Chain succeeded in the first clinical trials of penicillin. Intensive research in the United States then led to the isolation of especially productive *Penicillium* strains for use in the mass production of the antibiotic. A large number of semisynthetic penicillins have been developed in attempts to overcome the disadvantages of natural penicillins. Scientists develop these penicillins in either of two ways. First, they can stop synthesis of the molecule by *Penicillium* and obtain only the common penicillin nucleus for use. Second, they can remove side chains from the completed natural molecules and then chemically add other side chains that, among other things, make them more resistant to penicillinase. Thus the term semisynthetic: part of the penicillin is produced by the mold, and part is added synthetically.

Antibiotics are rather easy to discover, but few are of medical or commercial value. Some are used commercially other than for treating human disease-for example, in veterinary medicine.

More than half of our antibiotics are produced by species of *Streptomyces*, filamentous bacteria that commonly inhabit soil A few antibiotics are produced by bacteria of the genus *Bacillus,* and others are produced by molds, mostly of the genera *Penicillium* and *Cephalosporium*. The table shows the sources of many antibiotics in use today.

Bacteriocins

Table of selected bacteriocins

Lactic acid bacteria have been used in food production for many years. The bacterial fermentations contribute to flavor and preservation. The preserving action of the lactic acid bacteria was assumed to be due to their production of organic acids and hydrogen peroxide until 1944 when a powerful antimicrobial agent called nisin was isolated from *Lactococcus lactis.* The agent was identified as a bacteriocin. **Bacteriocins** are peptides secreted by cells to inhibit or kill closely related species. Bacteriocins often contain unusual amino acids that are made by modifying the amino acids prescribed by the genetic code. Nisin belongs to one class of bacteriocin called lantibiotics. **Lantibiotics** are antimicrobial peptides that contain the amino acid lanthionine. Lantibiotics are produced from peptides after these peptides have left the ribosome. (This is called post-translational synthesis.)

Nisin works by attaching to the plasma membrane of target cells. This alters the membrane's permeability and decreases the proton motive force (required to make ATP). The operon that codes for lantibiotic production also carries a gene for resistance to the lantibiotic so the cell producing the lantibiotic does not kill itself.

In the 1990s, the attention of microbiologists turned to lantibiotics and other peptides for food preservatives and antibiotics. The advantages of these peptides is that are readily digested in the human intestines, they are nontoxic and do not induce allergies, and resistance mechanisms haven't developed yet. Moreover, they are already consumed in foods such as fermented dairy and meat products.

The only lantibiotic currently approved for use a a food preservative is nisin, which is produced by *Lactococcus lactis*. Nisin is bactericidal against gram-positive bacteria such as *Clostridium,* it inhibits endospore germination, and it has recently been shown to kill the gram-negative bacteria *Salmonella*. Nisin is used in processed cheese to prevent growth and gas production by *C. sporogenes*.

Microbiologists are screening natural populations of eukaryotes and prokaryotes looking for lantibiotics and other peptides that will kill pathogens. Additionally, genetic engineering might be useful to increase the spectrum of activity, solubility, and stability of antimicrobial peptides. Antimicrobial peptides that show promise against some important pathogens are listed below.

The plate assay is most often used to screen for the presence of antimicrobial agents.

Antibiotic resistance

Resistant Staphylococcus aureus

Through natural selection, organisms best adapted to fit their environment will survive and reproduce. In an antibiotic-laden environment, the "fittest" bacterium is one that is resistant to antibiotics. Bacteria become resistant to chemotherapeutic agents by three major mechanisms: (1) destruction or inactivation of the drug (e.g., ß-lactamase); (2) prevention of penetration to the target site within the microbe (e.g., multidrug resistance pumps); and (3) alternation of the drug's target site (e.g., a change in one amino acid in a ribosome may make a microbe resistant to certain macrolife antibiotics.)

Hereditary drug resistance is often carried by plasmids or by transposons. Some plasmids, including those called **resistance (R) factors,** can be transferred between bacterial cells in a population and between different but closely related bacterial populations. R factors often contain genes for resistance to several antibiotics.

Asked to list the reasons for emergence of drug-resistant bacterial strains, a spokesman for the National Institutes of Health blamed the unnecessary use of prophylaxis, use of antibiotics in animal feeds, the availability of over-the-counter antibiotics in many countries, and misuse by health professionals. It has been pointed out that the indiscriminate use of antibiotics may result in a vast majority of

colonies are growing in the zone of inhibition about the penicillin disk.

infections being causing by antibiotic-resistant bacteria.

The figure shows penicillin-resistant *Staphylococcus aureus* colonies growing in the zone of inhibition around the penicillin-containing disk.

Read more about vancomycin-resistant *S. aureus.*

References

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