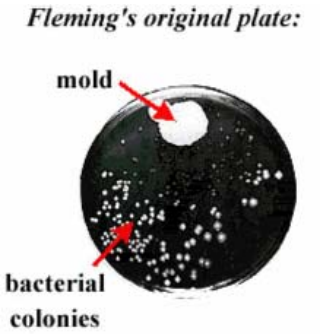
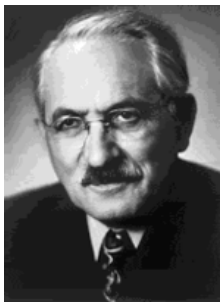
ANTIBIOTICS



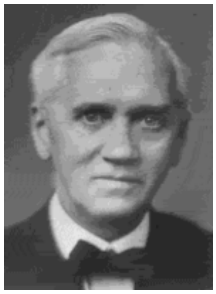
Antibiotic: Substance produced by a microorganism [or a similar product produced wholly (synthetic) or partially (semi-synthetic) by chemical synthesis] that is capable, in low concentrations, of inhibiting the growth of or killing other microoganisms.

I. NOBELISTS INVOLVED IN ANTIBIOTIC RESEARCH:

Gerhard Domagk
Nobel Prize: 1939
Prontocil



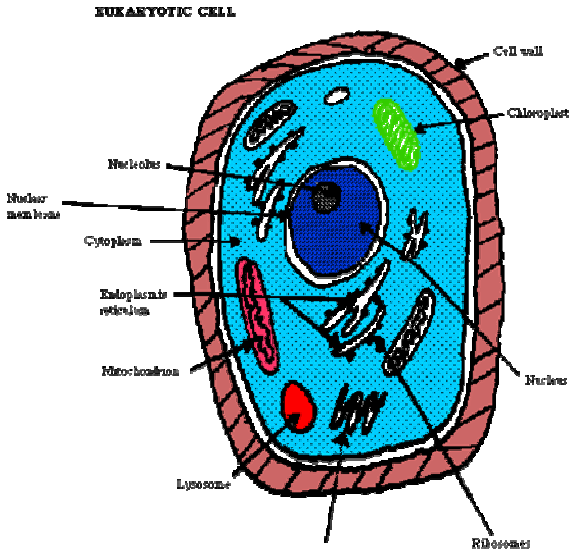
Selman Waksman
Nobel Prize: 1952
Streptomycin

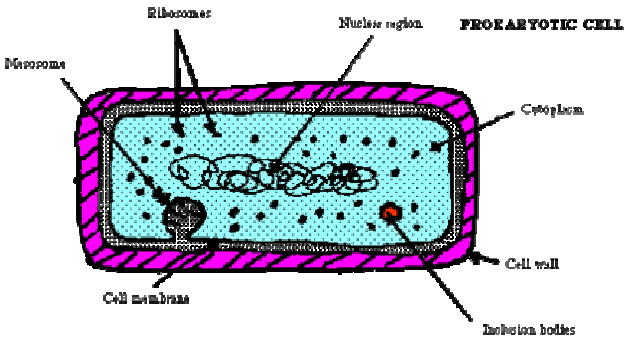


Alexander Fleming
Nobel Prize: 1945
Penicillin

II. Comparison of Eukaryotes and Prokayotes:

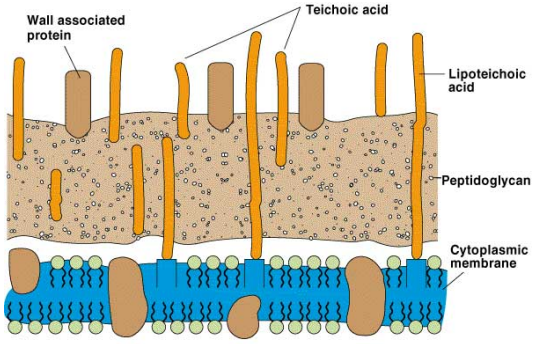
	EUKARYOTE	PROKARYOTE
Size	5 - 10 µm	1-3 µm
Cell Wall	Only in fungi/algae	Present
Cytoplasmic membrane	Present	Present
Nuclear membrane	Present	Absent
Genetic information	DNA (>1 chromosome)	DNA (1 chromosome)

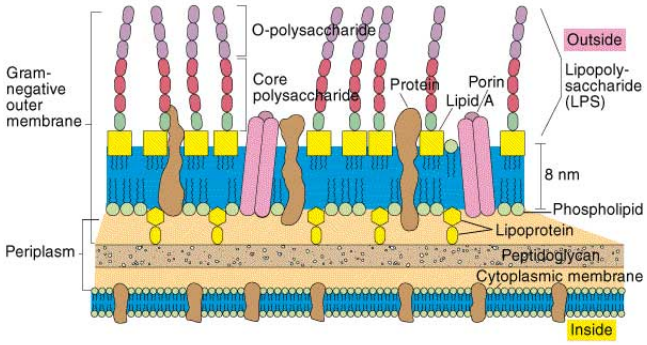




III. GRAM-POSITIVE and GRAM-NEGATIVE ORGANISMS

Gram staining is based on the ability of bacteria cell wall to retain crystal violet dye during solvent treatment. The cell walls for Gram-positive microorganisms have a higher peptidoglycan and lower lipid content than Gram-negative bacteria.



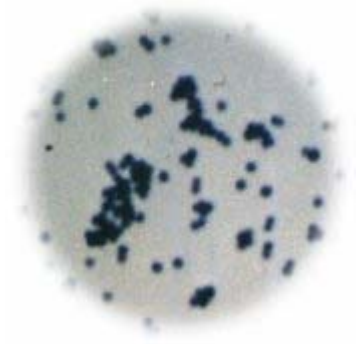


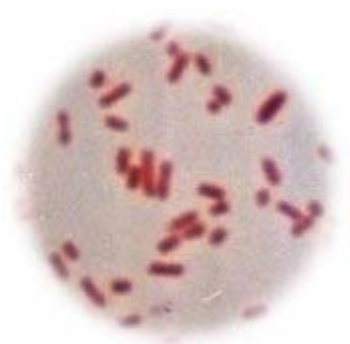
Common Gram-positive organisms:

Streptococcus
S. aureus
Bacillus anthracis
Clostridium botulinum

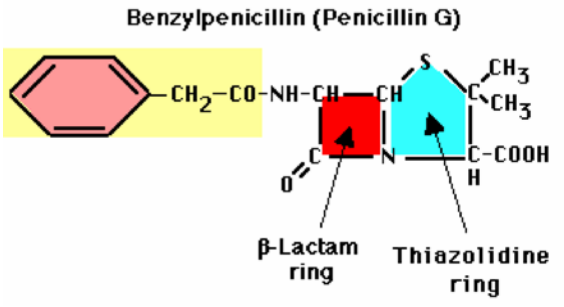
Common Gram-negative organisms:

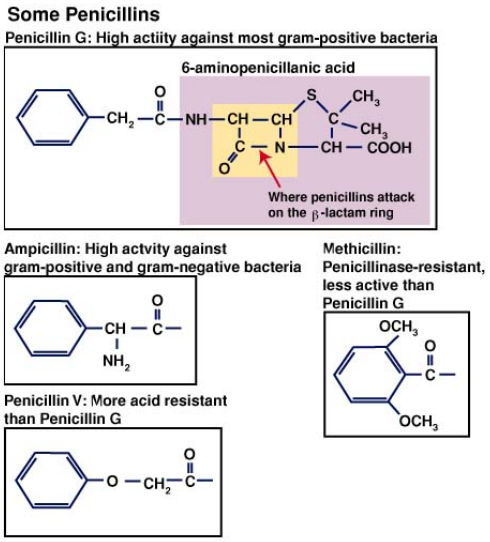
Klebsiella pneumonia
Shigella
Yersinia pestis
Salmonella typhimurium
Salmonella enteriditis





IV. PENCILLIN:



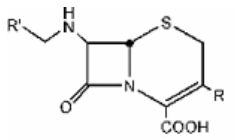


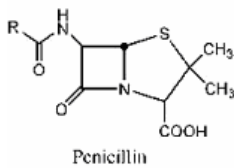
An expanded role for the penicillins came from the discovery that natural penicillins can be modified chemically by removing the acyl group to leave 6-aminopenicillanic acid and then adding acyl groups that confer new properties. These modern semi-synthetic penicillins such as Ampicillin, Carbenicillin, and Oxacillin have various specific properties such as: resistance to stomach acids so that they can be taken orally, a degree of resistance to penicillinase (a penicillin-destroying enzyme produced by some bacteria) extended range of activity against some Gram-negative bacteria. Although the penicillins are still used clinically, their value has been diminished by the widespread development of resistance among target microorganisms and also by some people's allergic reaction to penicillin.

V. OTHER COMMON ANTIBIOTICS

A. Cephalosporins

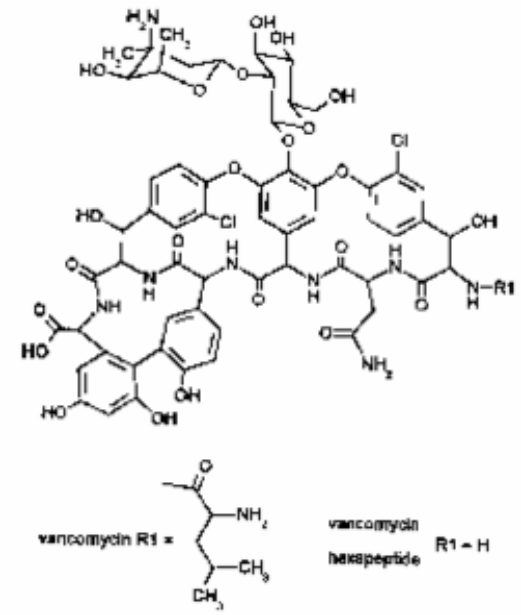
Beta-lactams with a similar mode of action to penicillin but with less allergenicity.

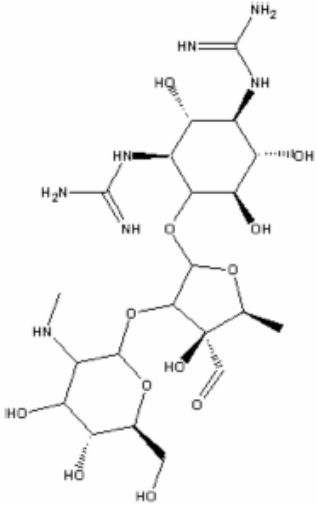




B. *Streptomyces*-derived Antibiotics

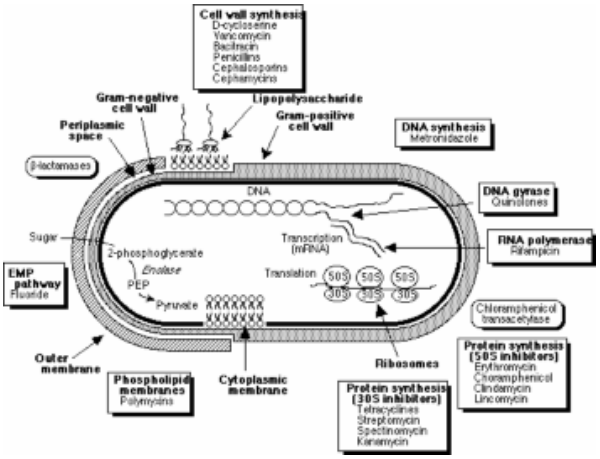
Actinomycetes, especially the *Streptomyces* species, have yielded most of the antibiotics used today in clinical medicine. Examples: amphotericin B, erythromycin, streptomycin, tetracycline, neomycin, and vancomycin.



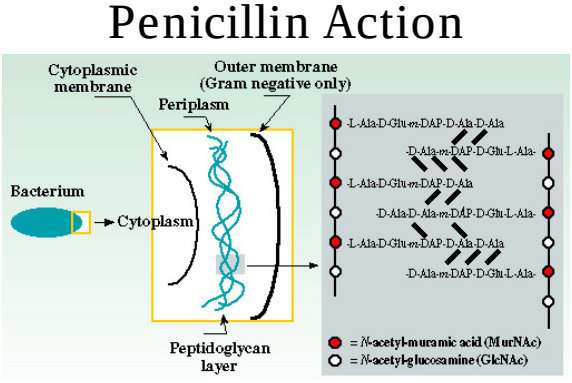


V. Mechanism of Action of Common Antibiotics

Mechanism of action	Antibiotic	Bacterial Target
Inhibition of cell wall synthesis	β Lactams: Penicillin Cephalosporin Bacitracin Vancomycin	Transpeptidase Peptidoglycan Transporter Ala-ala dipeptide
Inhibition of protein synthesis	Aminoglycosides Streptomycin Gentamycin Neomycin Tetracyclines Erythromycin	30S ribosome 50S ribosome Free ribosomes
Inhibition of nucleic acid synthesis	Quinolones Rifampin	DNA gyrase DNA-dependent RNA polymerase
Inhibition of cytoplasmic membrane function	Polymyxin	Membrane lipids
Antimetabolites	Sulfonamides	Folate synthesis



VI. PENCILLIN MECHANISM OF ACTION



Penicillin inhibits an enzyme called transpeptidase from making the membrane component peptidoglycan

Penicillin prevents completion of synthesis of peptidoglycan, a key component of the bacterial cell wall. Peptidoglycan is unique to prokaryotes, and this explains the selectivity of penicillin. The enzyme called transpeptidase cross links the strands of peptidoglycan and produces a strong, rigid structure. Transpeptidase recognizes the D-alanine component of the cell wall. D-alanine, in turn, bears a structural similarity to part of the four-membered -lactam ring of penicillin. Transpeptidase binds irreversibly to -lactam antibiotics. After this occurs, it cannot participate in cell wall biosynthesis. The growing bacterium will lyse because the thinning cell wall can no longer protect it from the hypotonic environment.

VIII. MECHANISMS OF ANTIBIOTIC RESISTANCE:

Antibiotic degrading enzymes

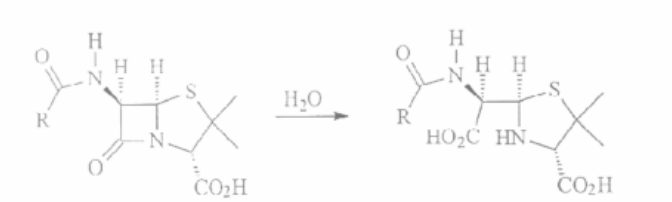
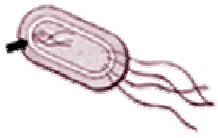


Figure 6: Cleavage of penicilling by β-lactamase
from Armitage, 1999, Bioorganic Chemistry: Lecture 36

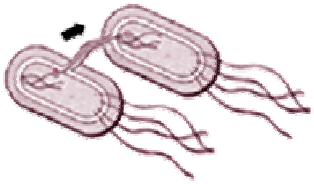
Current penicillin prescriptions such as augmentin contain beta-lactamase inhibitors to block cleavage of the penicillin.

Antibiotic resistant genes
Pumping mechanisms to remove antibiotic from bacterial cell
Enzymes that modify antibiotics

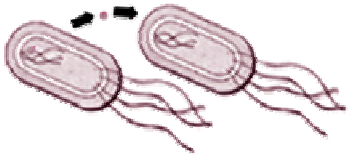
Bacteria acquire genes conferring resistance in any of three ways.



In **spontaneous DNA mutation**, bacterial DNA (genetic material) may mutate (change) spontaneously (indicated by starburst). Drug-resistant tuberculosis arises this way.



In a form of microbial sex called **transformation**, one bacterium may take up DNA from another bacterium. Pencillin-resistant gonorrhea results from transformation.



Most frightening, however, is resistance acquired from a small circle of DNA called a **plasmid** that can flit from one type of bacterium to another. A single plasmid can provide a slew of different resistances. In 1968, 12,500 people in Guatemala died in an epidemic of Shigella diarrhea. The microbe harbored a plasmid carrying resistances to four antibiotics!