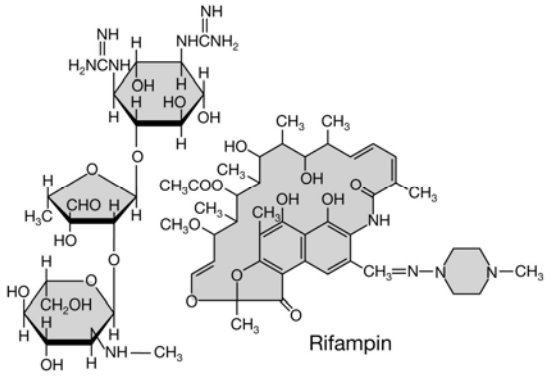
Classification of Antibiotics:

1. Inhibit growth – "stat"
   Kill bacterium – "cide"

2. Broad and Narrow spectrum

3. Production Types:
   - Natural
   - Synthetic
   - Semi-synthetic

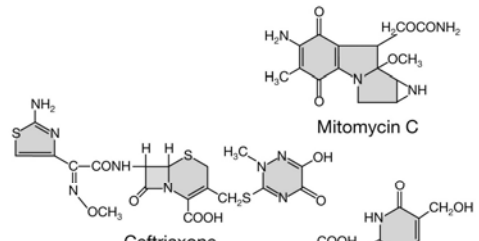
Representative structure



Streptomycin

Rifampin

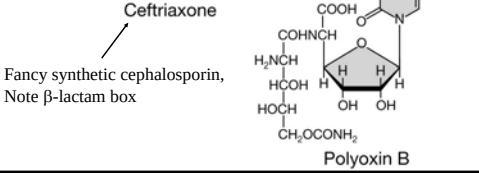
Representative structure



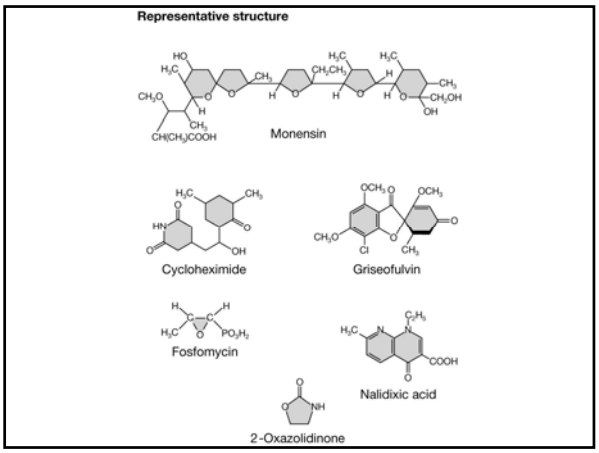
Mitomycin C

Ceftriaxone

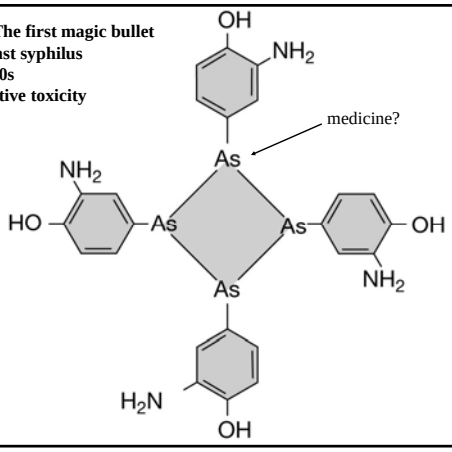
Fancy synthetic cephalosporin,
Note β-lactam box

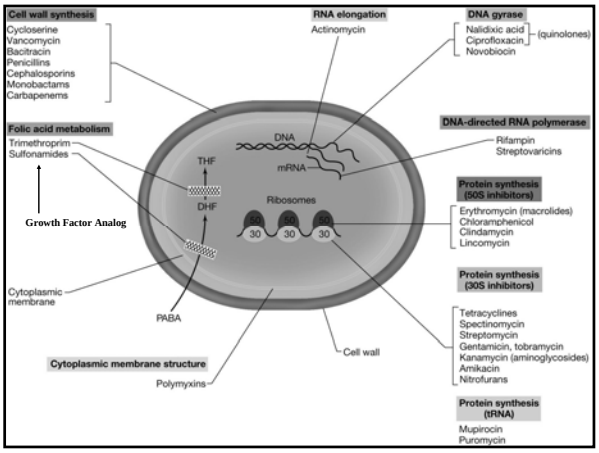


Polyoxin B



Salvarsan: The first magic bullet
Works against syphilus
Ehrlich, 1900s
Idea of selective toxicity





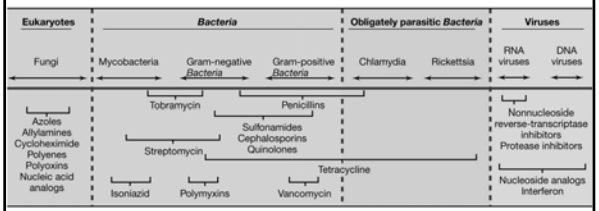
Antibiotics Affecting Replication, Transcription, & Translation

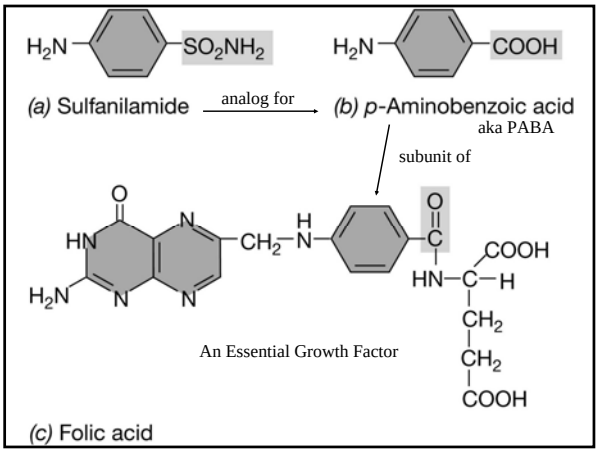
DNA replication:
Nalidixic Acid & Novobiocin – Inhibits DNA gyrase

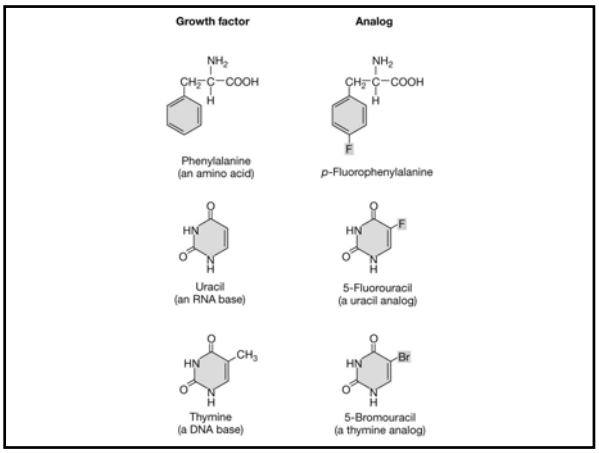
Transcription:
Rifampin – Beta subunit of RNA polymerase
Actinomycin – DNA binding, blocks elongation

Translation:
Streptomycin – Blocks initiation on SSU of ribosome
Chloramphenicol – Blocks elongation on LSU via peptide bond
Tetracycline – Blocks elongation SSU
Cycloheximide – Eucarya ribosome specific
Diptheria Toxin – EF blocker; both Archaea and Eucarya

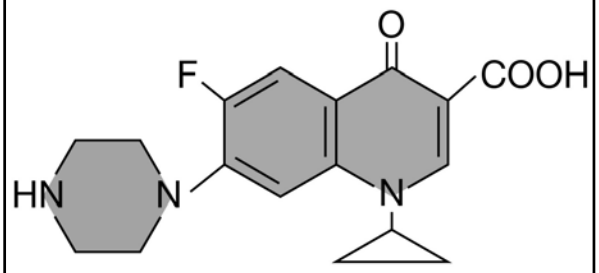
Antimicrobial spectrum of action for selected chemotherapeutics



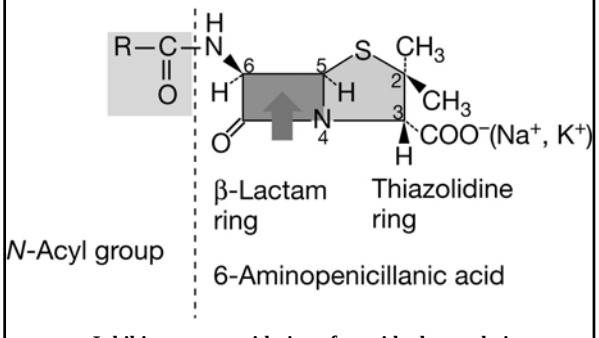




Cipro or ciprofloxacin, a quinoline
Not a growth factor!
Prevents DNA gyrase from supercoiling
Used for anthrax, etc.



How to build a better mouse trap: Penicillin
A β-lactam antibiotic



Inhibits transpeptidation of peptidoglycan chains
Forms the old 1-2-punch with autolysins

Semi's are made to be acid-stable and more broad spectrum

Difference b/t ampicillin and penicillin is only one amino group.

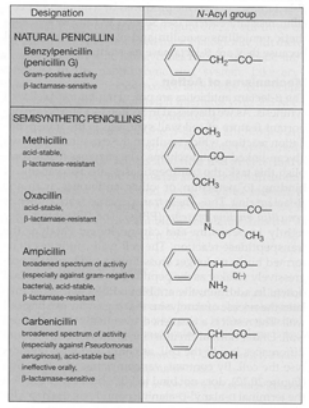
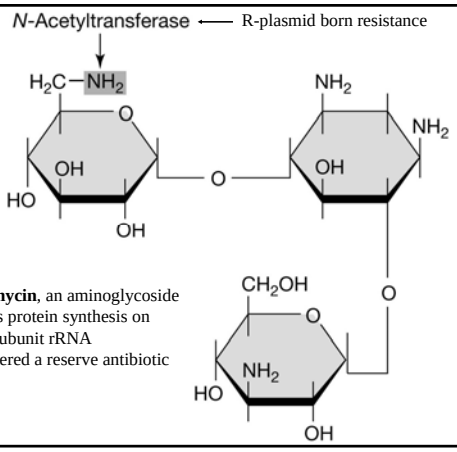
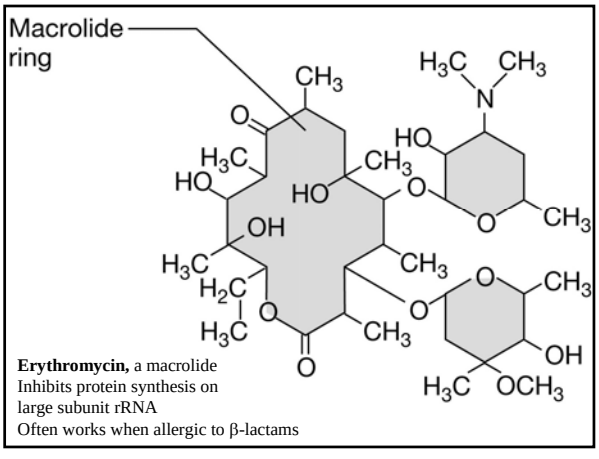


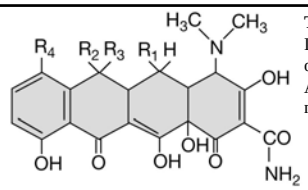
Figure 20.19 The structures of some important penicillins.



Kanamycin, an aminoglycoside
Inhibits protein synthesis on small subunit rRNA
Considered a reserve antibiotic



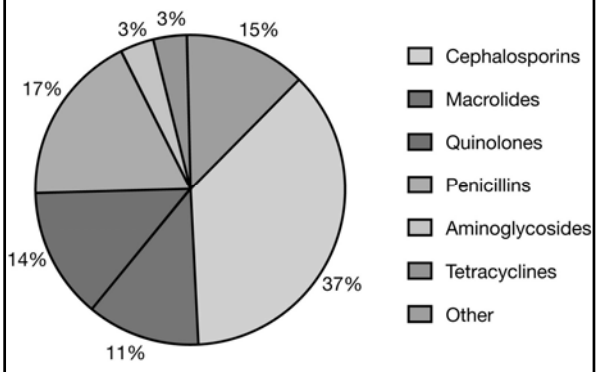
Erythromycin, a macrolide
Inhibits protein synthesis on large subunit rRNA
Often works when allergic to β-lactams



Tetracyclines
Inhibits protein synthesis on small subunit rRNA
Along with β-lactams make up the majority used

Tetracycline analog	R_1	R_2	R_3	R_4
Tetracycline	H	OH	CH_3	H
7-Chlortetracycline (aureomycin)	H	OH	CH_3	Cl
5-Oxytetracycline (terramycin)	OH	OH	CH_3	H

Annual Worldwide Production of Antibiotics



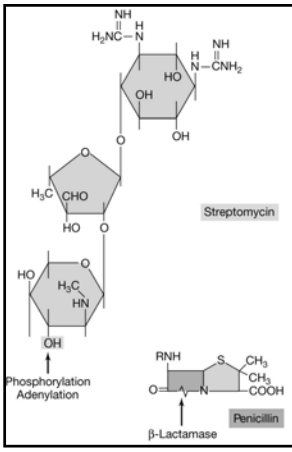
Overall more than 500 metric tons!

Mechanisms of Antibiotic Resistance

1. Lacks structure antibiotic inhibits:
   Mycoplasms lack a typical cell wall
2. Impermeable to the antibiotic:
   Gram - bacteria impermeable to penicillin G
3. Alteration of antibiotic:
   β-lactamase degrades antibiotic e.g., springs open the mouse trap
4. Modifies the target of the antibiotic
5. Genetically modifies the pathway that the antibiotic affects
6. Efflux of the antibiotic:
   Tetracycline gets pumped back out of the cell

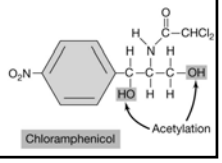
TABLE 20.7 Mechanisms of bacterial resistance to antibiotics

Resistance mechanism	Antibiotic example	Genetic basis of resistance	Mechanism present in:
Reduced permeability	Penicillins	Chromosomal	*Pseudomonas aeruginosa* Enteric *Bacteria*
Inactivation of antibiotic (for example, penicillinase; modifying enzymes methylases, acetylases, and phosphorylases; and others)	Penicillins	Plasmid and chromosomal	*Staphylococcus aureus* Enteric *Bacteria* *Neisseria gonorrhoeae*
	Chloramphenicol	Plasmid and chromosomal	*Staphylococcus aureus* Enteric *Bacteria*
	Aminoglycosides	Plasmid	*Staphylococcus aureus*
Alteration of target (for example, RNA polymerase, rifamycin; ribosome, erythromycin, and streptomycin; DNA gyrase, quinolones)	Erythromycin Rifamycin Streptomycin Norfloxacin	Chromosomal	*Staphylococcus aureus* Enteric *Bacteria* Enteric *Bacteria* *Staphylococcus aureus*
Development of resistant biochemical pathway	Sulfonamides	Chromosomal	Enteric *Bacteria* *Staphylococcus aureus*
Efflux (pumping out of cell)	Tetracyclines Chloramphenicol	Plasmid Chromosomal	Enteric *Bacteria* *Staphylococcus aureus* *Bacillus subtilis*

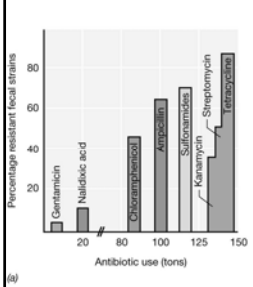


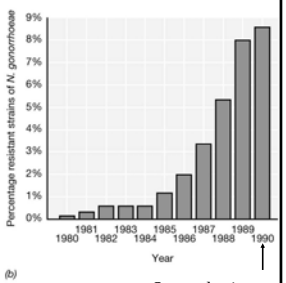
R plasmid encoded enzymes attack these various sites.

Rem: N-acetylation in Aminoglycosides too!

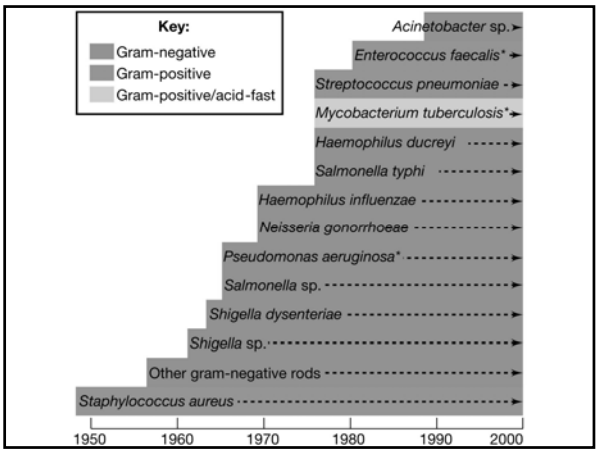


The emergence of antimicrobial drug-resistant bacteria

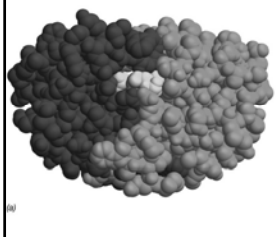




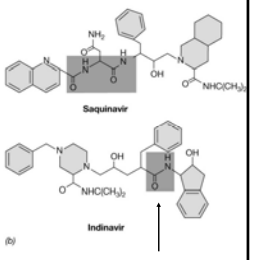
Stopped using penicillin



Computerized Drug Design



HIV protease homodimer
required for HIV maturation



Peptide bond analogs &
non-nucleoside RT inhibitors

Microbial Sources of Antibiotics

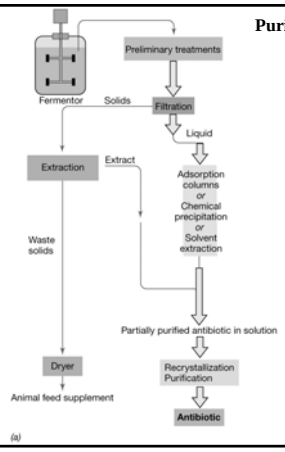
Microorganism	**Antibiotic**
Bacteria:	
***Streptomyces* spp.**	**chloramphenicol** **erythromycin** **kanamycin** **rifampin** **streptomycin** **tetracyclines**
***Bacillus* spp.**	**bacitracin** **polymyxin**
Fungi:	
***Penicillium* spp.**	**penicillin**
***Cephalosporium* spp.**	**cephalosporins**

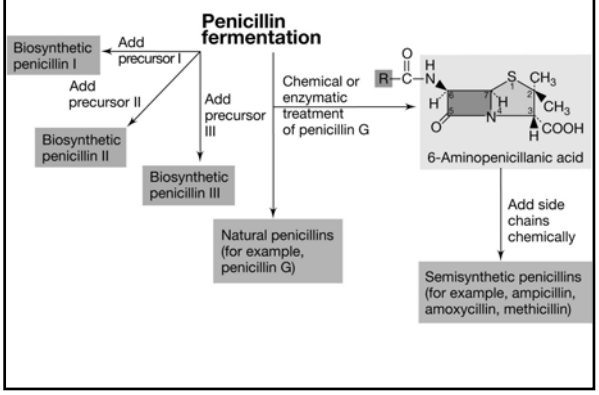
Production of Antibiotics:

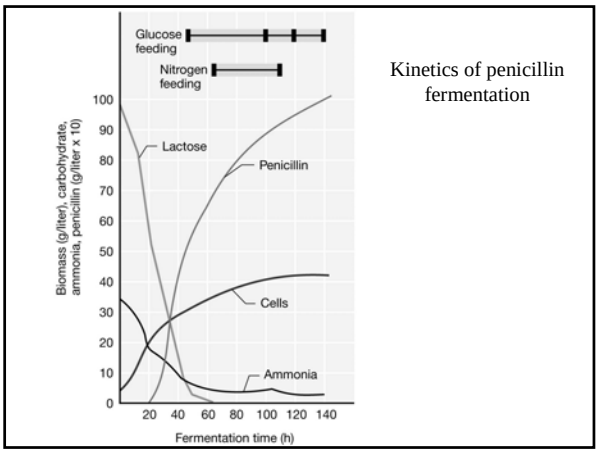
Secondary Metabolites produced near the end of a bacterium or fungus life cycle:

1. Formed @ end of stationary phase of growth
2. Not essential for growth or viability
3. Formation depends upon the media, possible over production

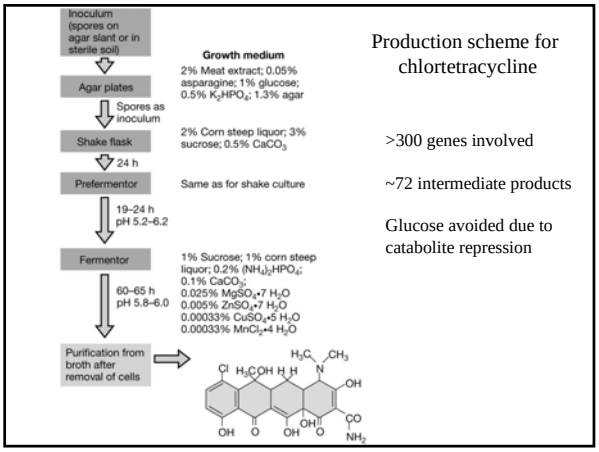
Purification of an antibiotic







Kinetics of penicillin fermentation



Production scheme for chlortetracycline

>300 genes involved

~72 intermediate products

Glucose avoided due to catabolite repression