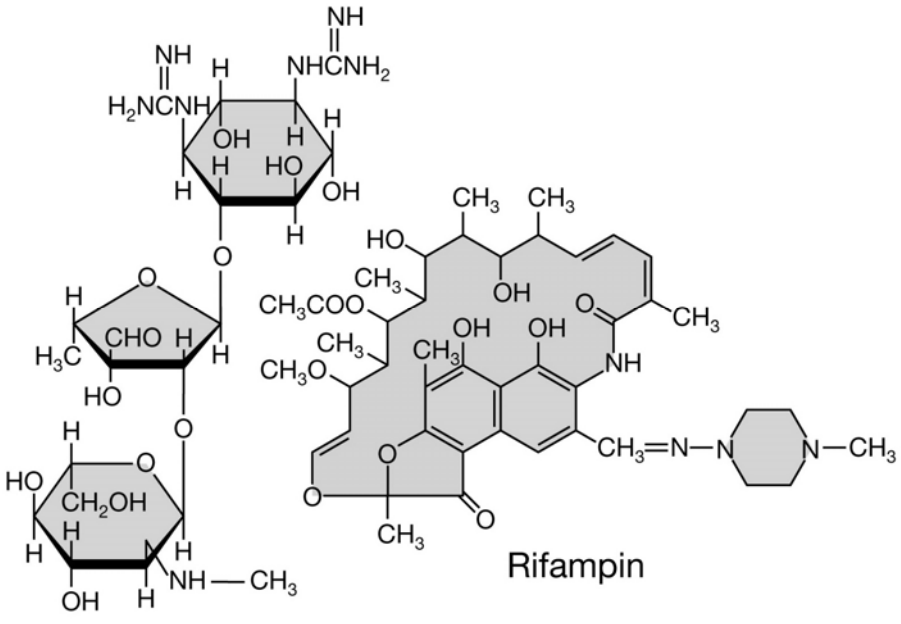
**Classification of Antibiotics:**

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

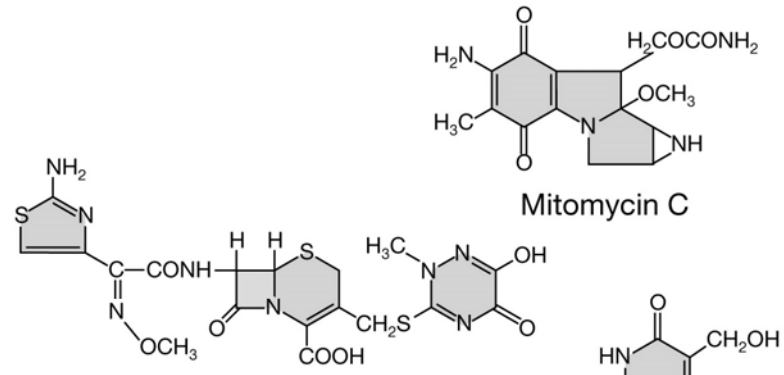
2. Broad and Narrow spectrum

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

**Representative structure**



**Representative structure**

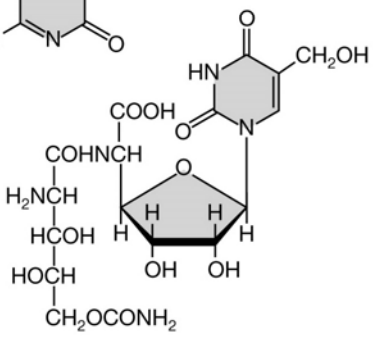


Mitomycin C



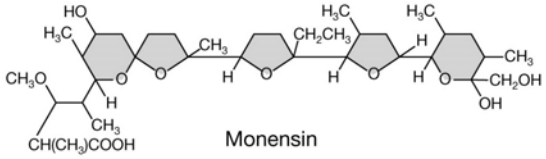
Ceftriaxone

Fancy synthetic cephalosporin,
Note β-lactam box

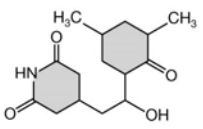


Polyoxin B

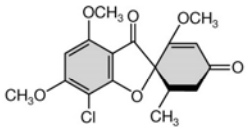
**Representative structure**



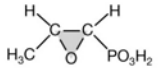
Monensin



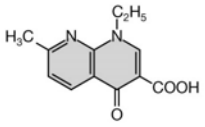
Cycloheximide



Griseofulvin



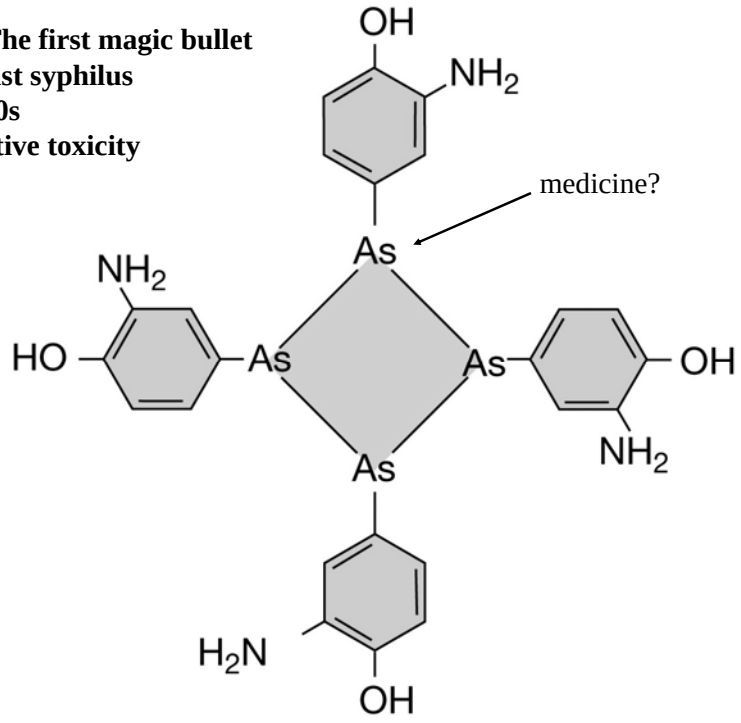
Fosfomycin

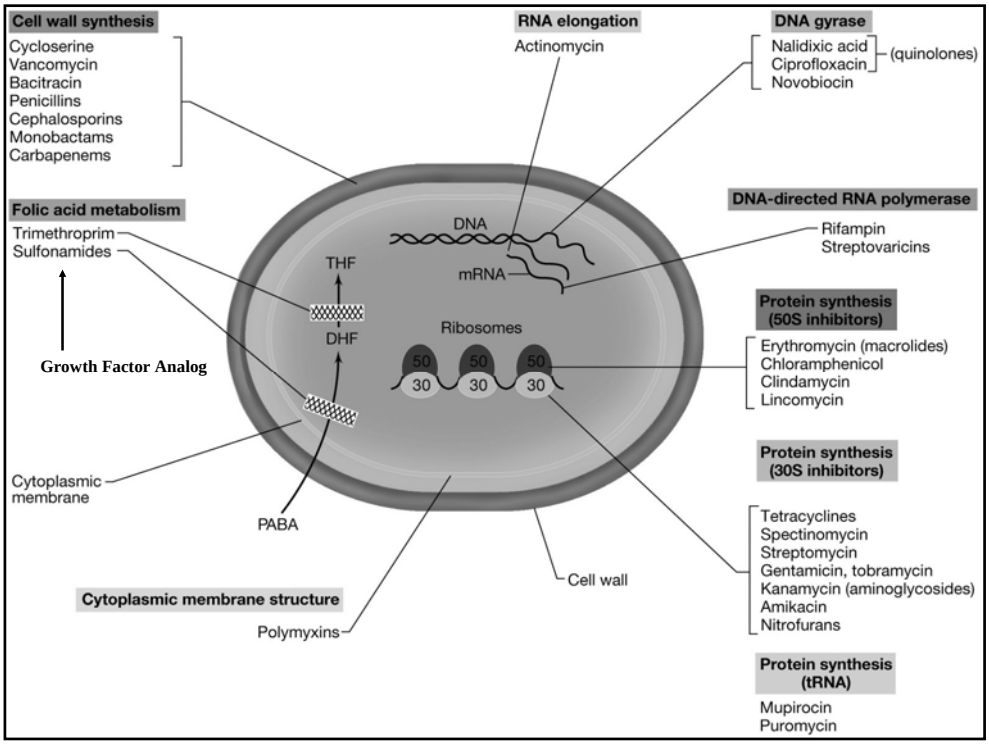


Nalidixic acid

2-Oxazolidinone

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



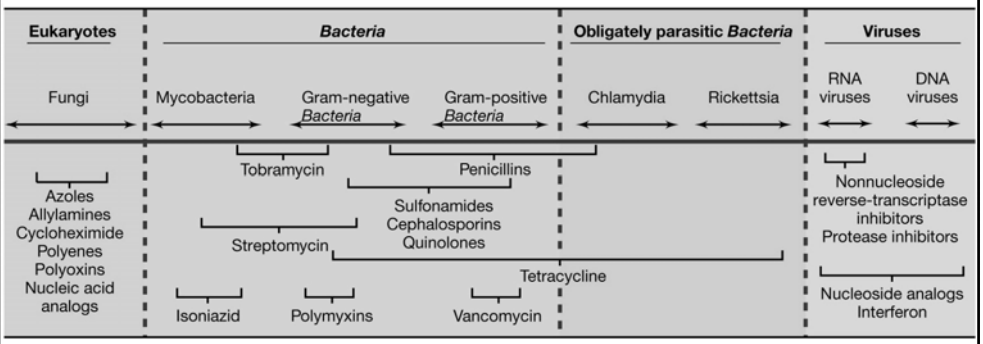
**Antibiotics Affecting Replication, Transcription, & Translation**

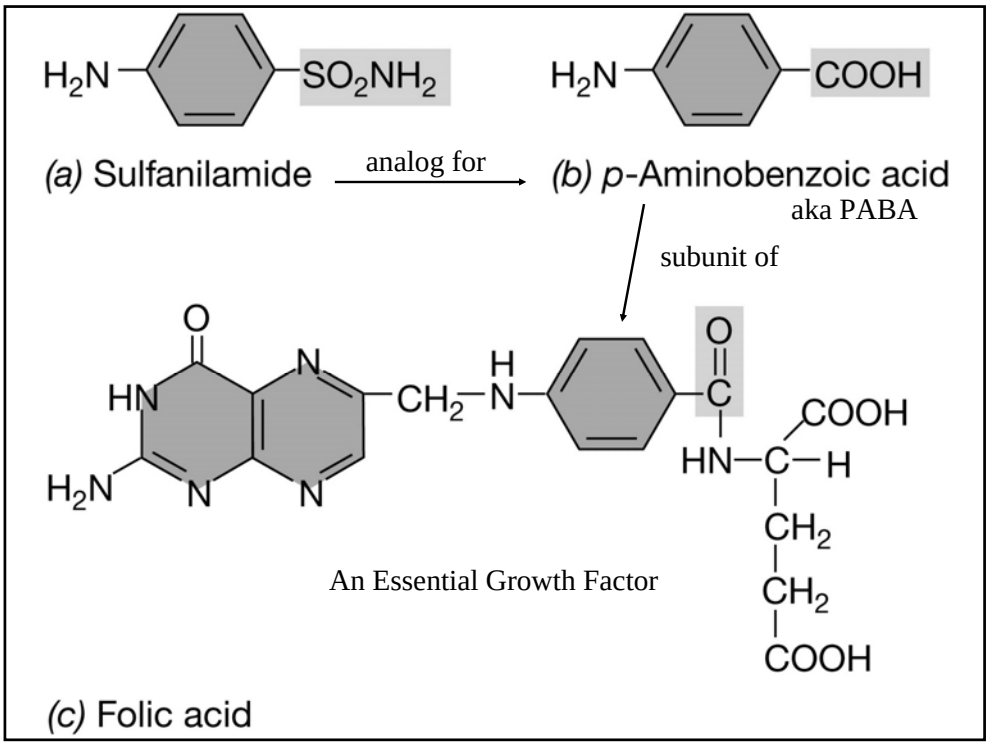
**DNA replication:**
Nalidixic Acid & Novobiocin – Inhibits DNA gyrase

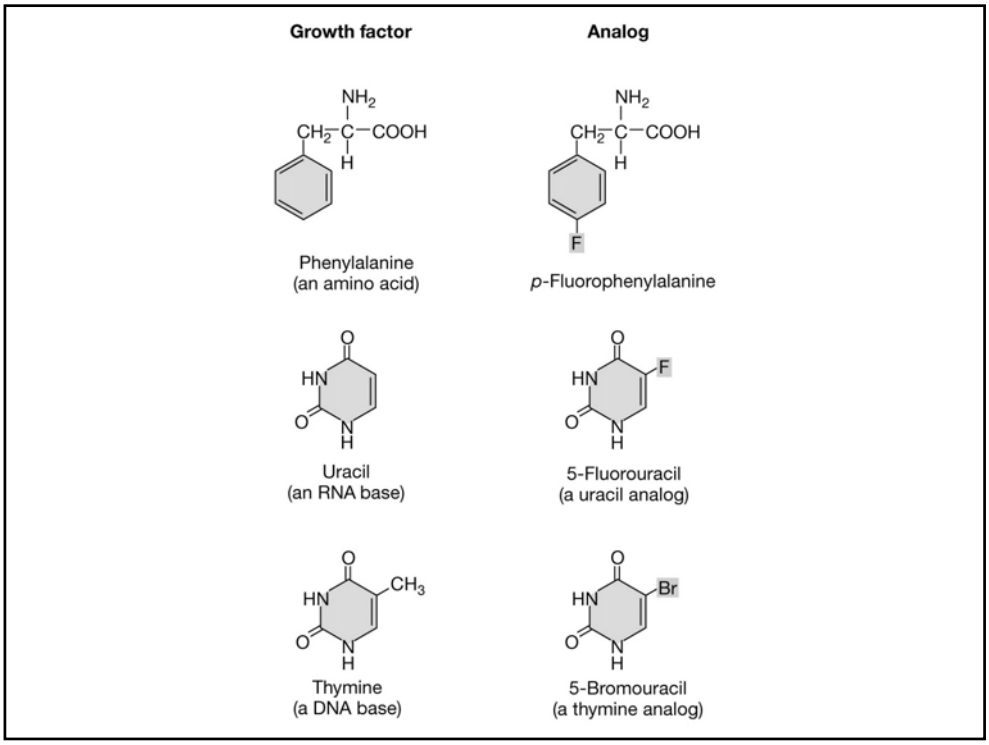
**Transcription:**
Rifampin – Beta subunit of RNA polymerase
Actinomycin – DNA binding, blocks elongation

**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

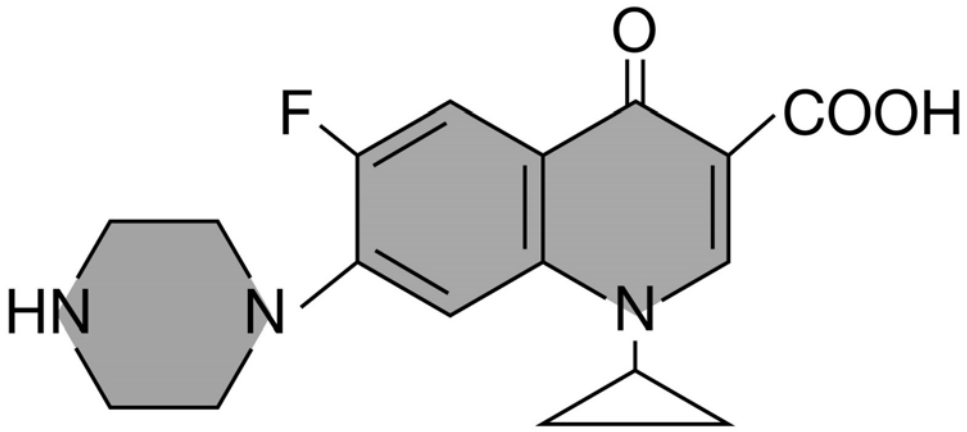
**Antimicrobial spectrum of action for selected chemotherapeutics**



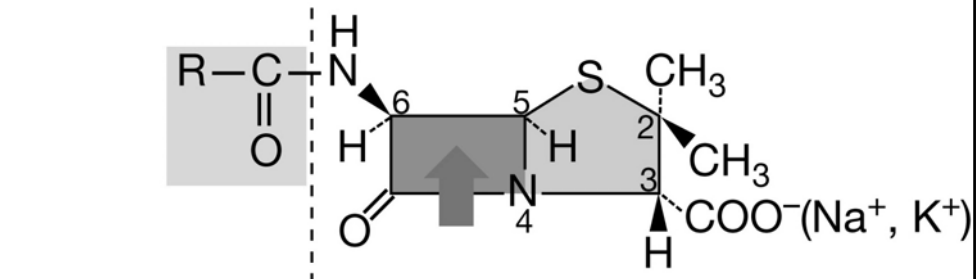

(a) Sulfanilamide
analog for
(b) p-Aminobenzoic acid
aka PABA
subunit of
An Essential Growth Factor
(c) Folic acid


Growth factor
Analog
Phenylalanine
(an amino acid)
p-Fluorophenylalanine
Uracil
(an RNA base)
5-Fluorouracil
(a uracil analog)
Thymine
(a DNA base)
5-Bromouracil
(a thymine analog)

**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**




β-Lactam ring

Thiazolidine ring

*N*-Acyl group

6-Aminopenicillanic acid

**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.

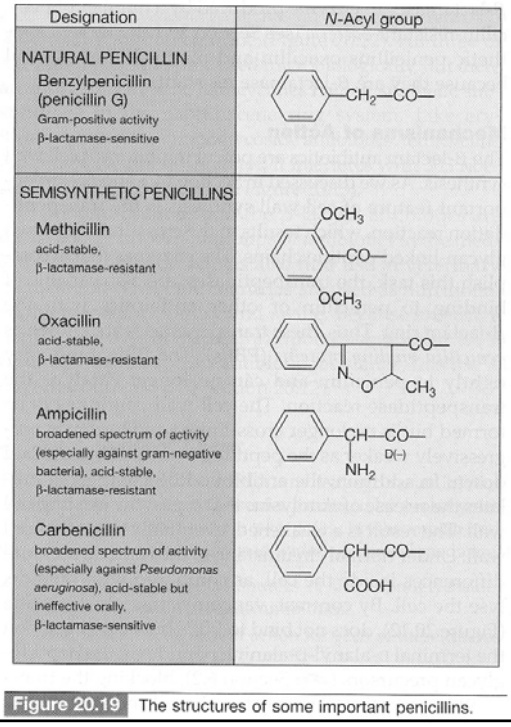
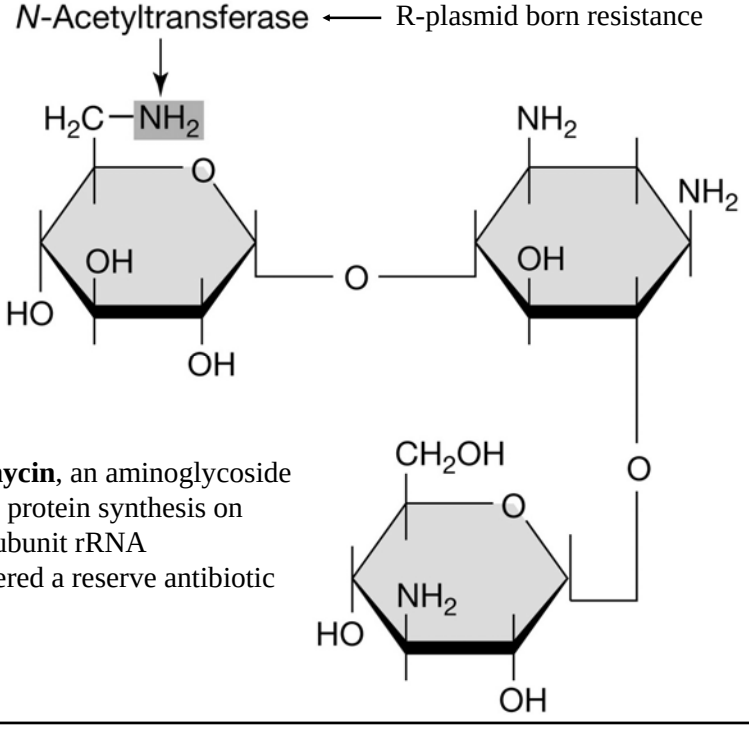
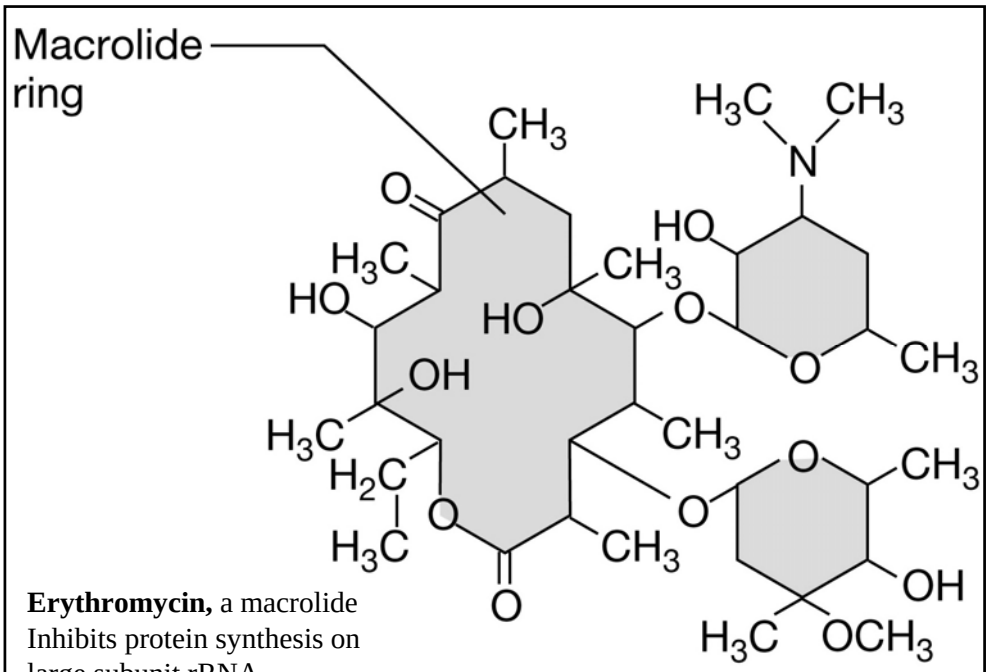


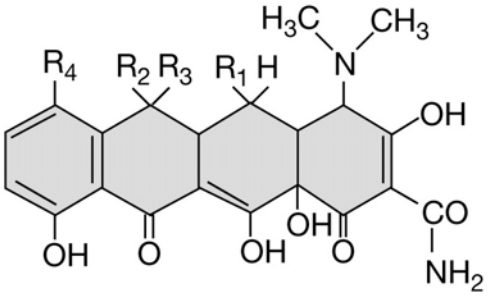

**Figure 20.19** The structures of some important penicillins.




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



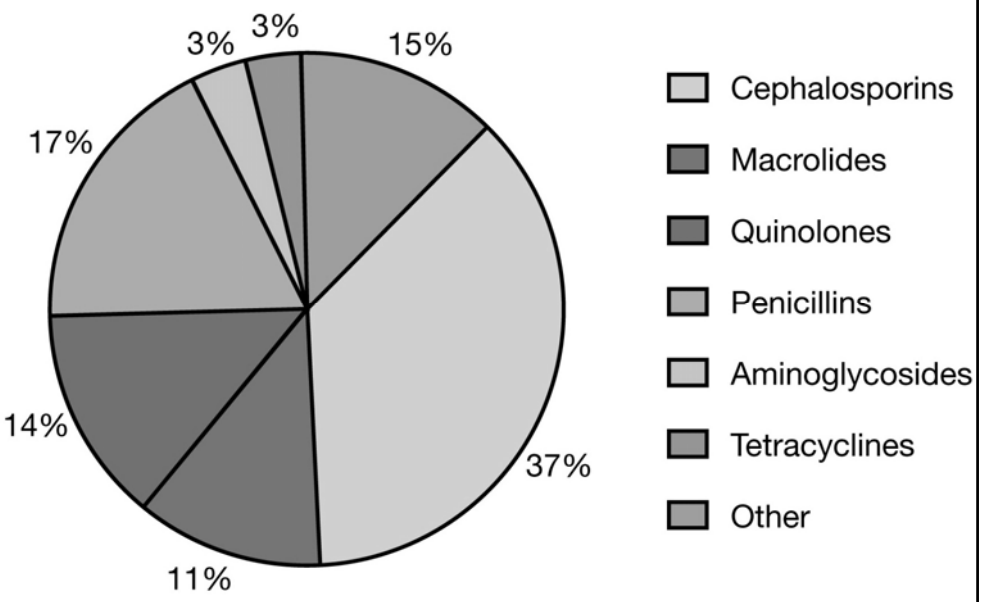

**Erythromycin,** a macrolide
Inhibits protein synthesis on large subunit rRNA
Often works when allergic to β-lactams




**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

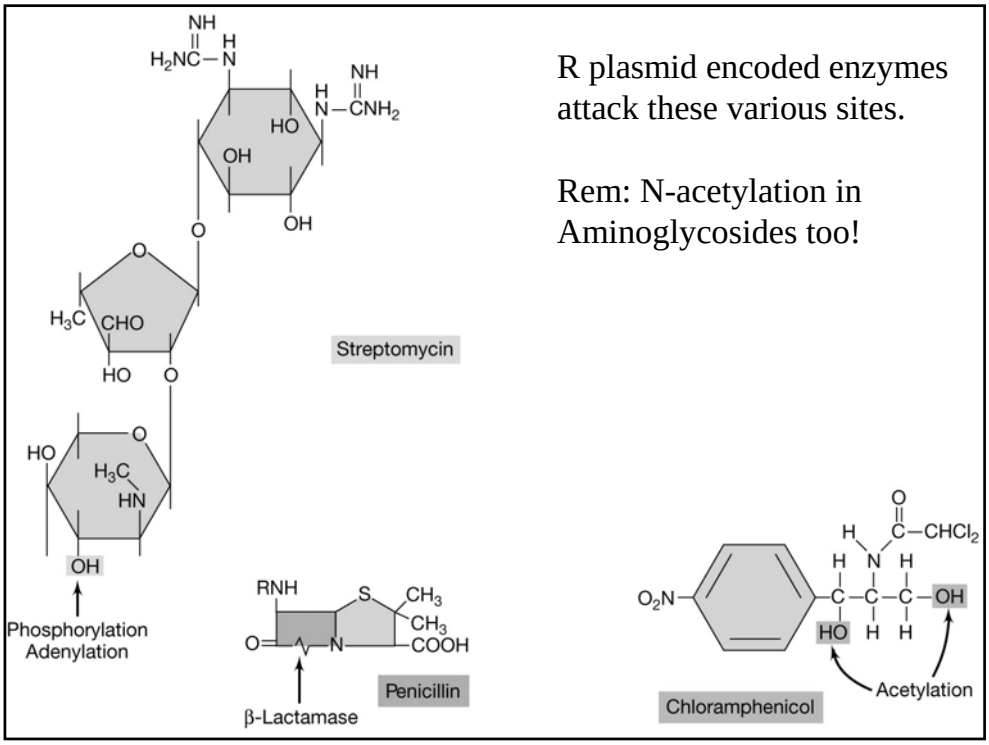
4. Modifies the target of the antibiotic

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

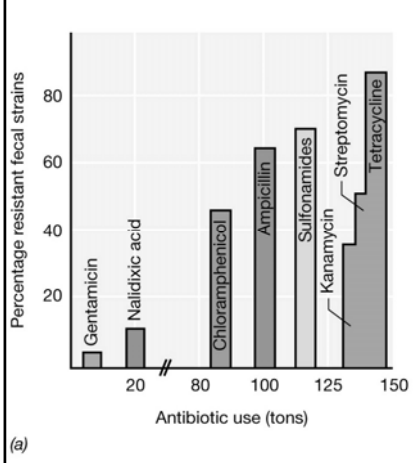
| Resistance mechanism | Antibiotic example | Genetic basis of resistance | Mechanism present in: |
|---|---|---|---|
| Reduced permeability | Penicillins | Chromosomal | *Pseudomonas aeruginosa*<br>Enteric *Bacteria* |
| Inactivation of antibiotic (for example, penicillinase; modifying enzymes | Penicillins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

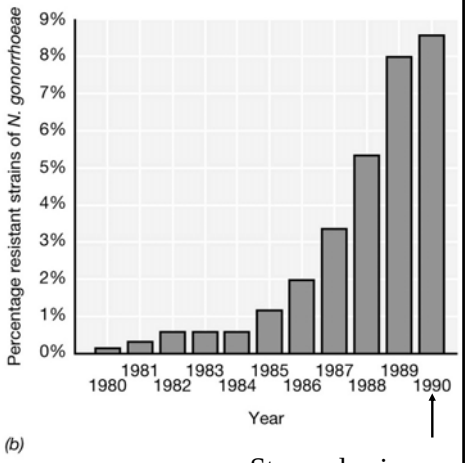



R plasmid encoded enzymes attack these various sites.

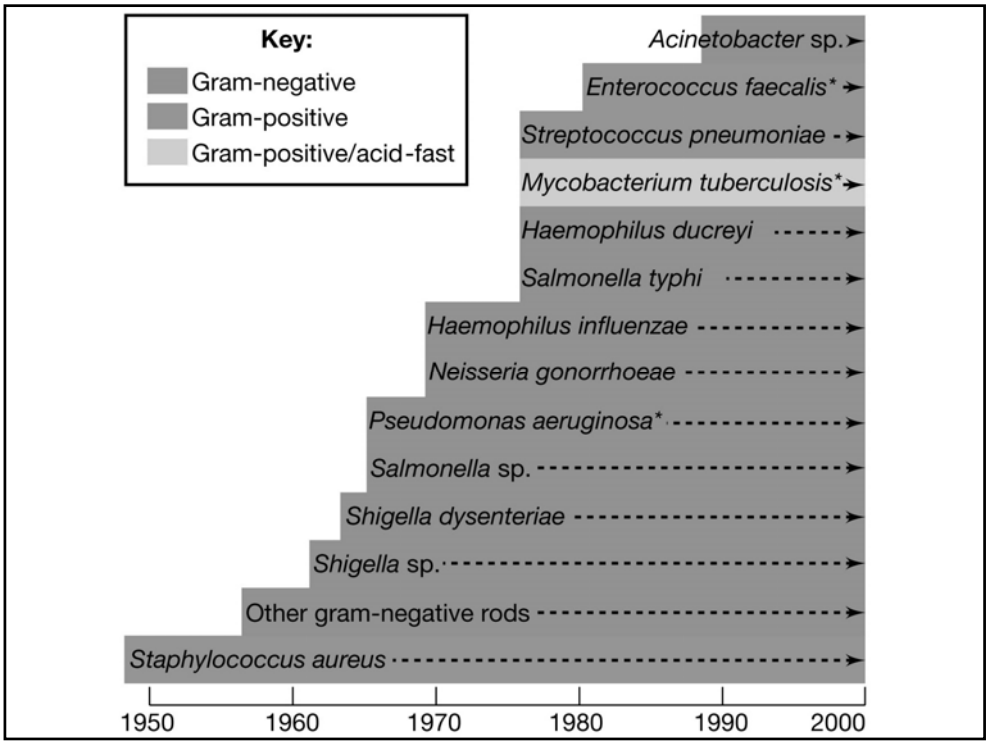
Rem: N-acetylation in Aminoglycosides too!

The emergence of antimicrobial drug-resistant bacteria

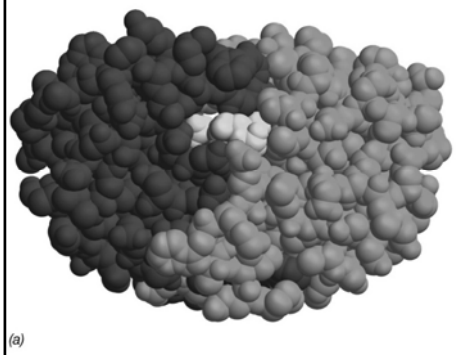


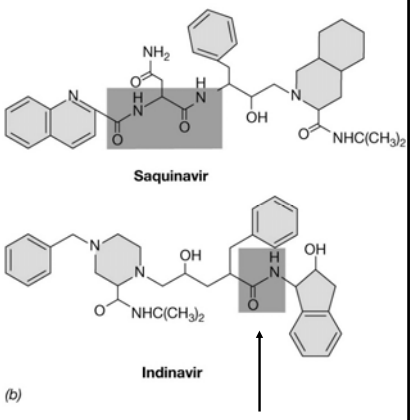

Stopped using penicillin



## Computerized Drug Design




HIV protease homodimer
required for HIV maturation




Peptide bond analogs &
non-nucleoside RT inhibitors

## Microbial Sources of Antibiotics

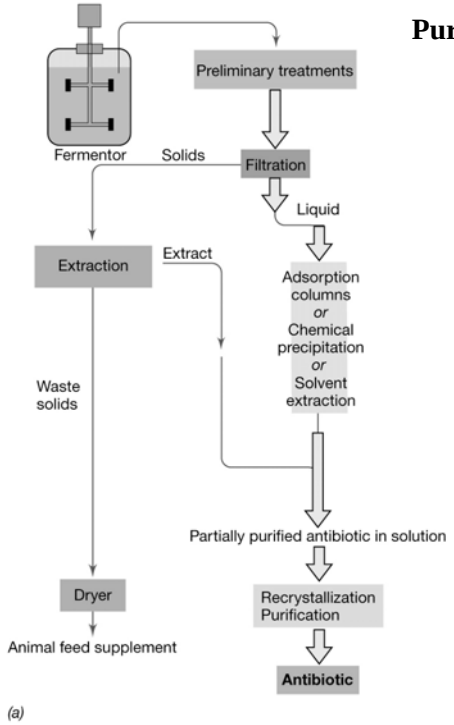
| **Microorganism** | **Antibiotic** |
|---|---|
| **Bacteria:** | |
| ***Streptomyces* spp.** | **chloramphenicol**<br>**erythromycin**<br>**kanamycin**<br>**rifampin**<br>**streptomycin**<br>**tetracyclines** |
| ***Bacillus* spp.** | **bacitracin**<br>**polymyxin** |
| **Fungi:** | |
| ***Penicillium*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

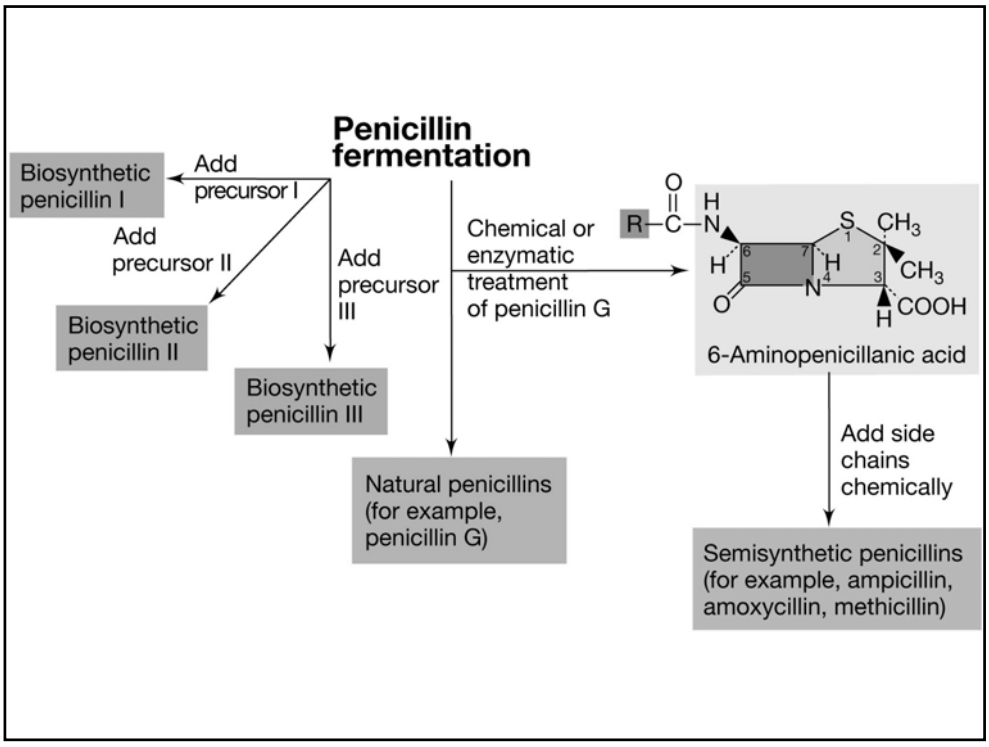
**Production of Antibiotics:**

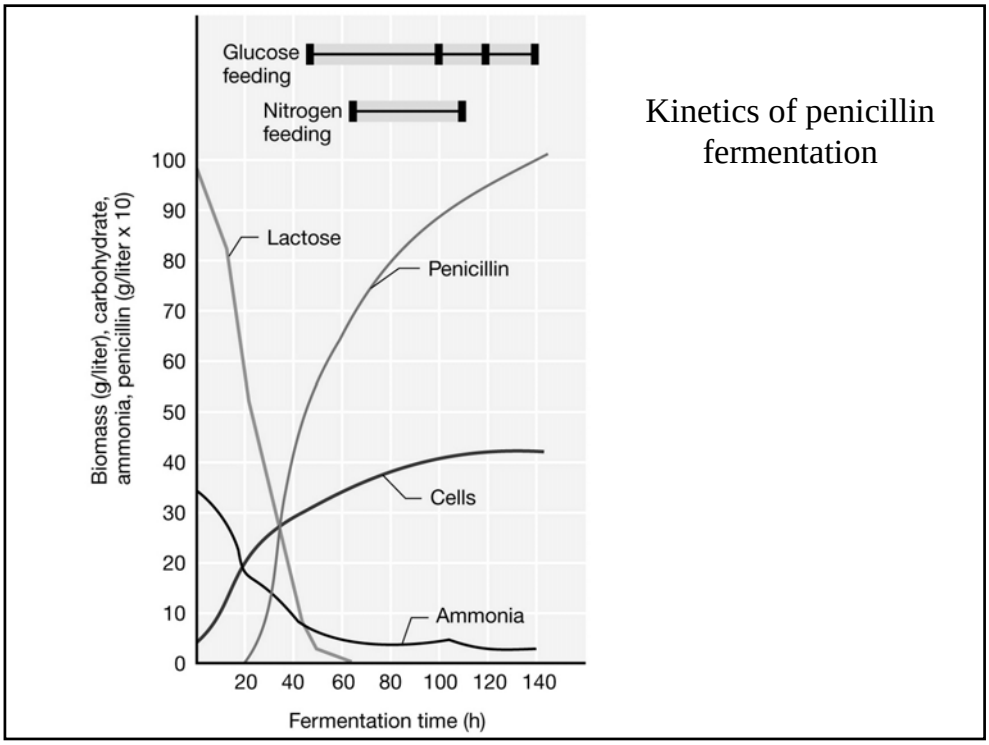
**Secondary Metabolites** produced near the end of a bacterium or fungus life cycle:

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

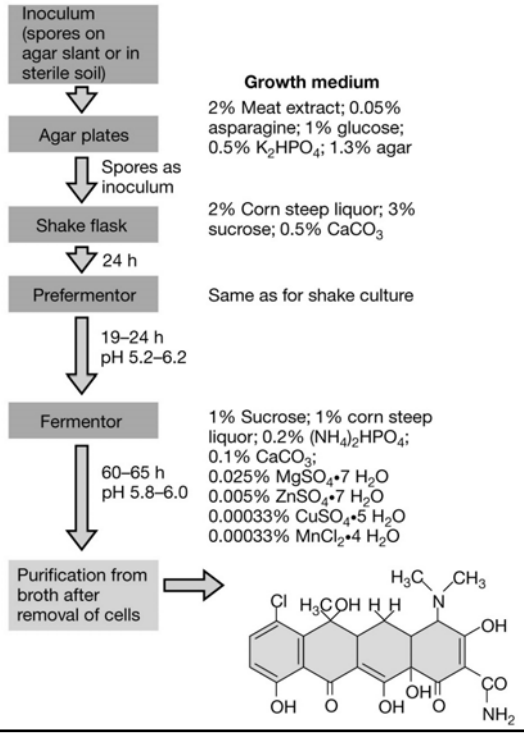
**Purification of an antibiotic**






Kinetics of penicillin fermentation




Production scheme for chlortetracycline

>300 genes involved

~72 intermediate products

Glucose avoided due to catabolite repression