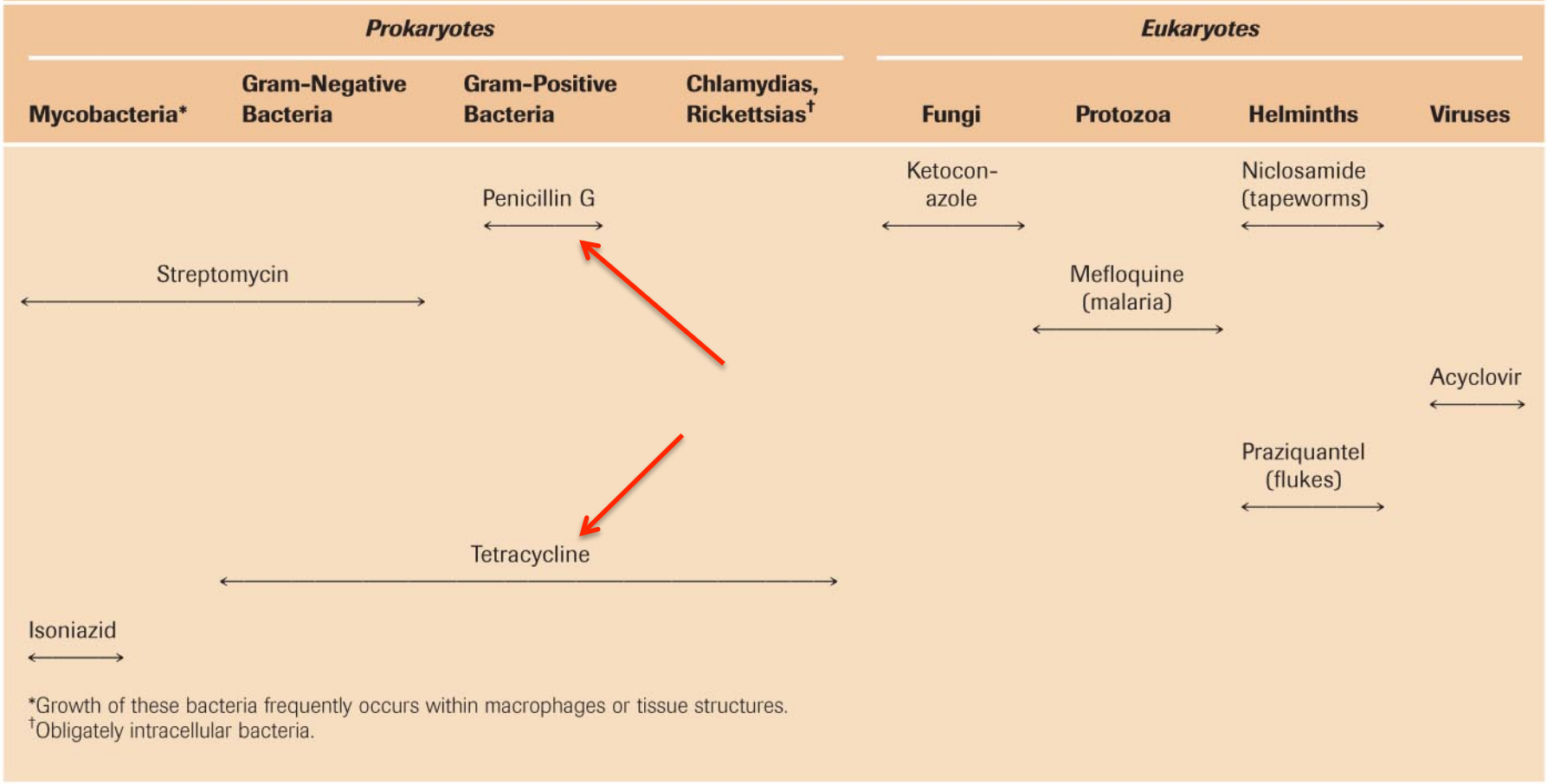
Chemical Control Methods

Chemotherapy

The Spectrum of Antimicrobial Activity

- = range of organisms affected by a drug
- Broad spectrum antibacterial drug affects both gram + and gram – organisms
- Narrow spectrum drug affects one or the other
- See table 20.2

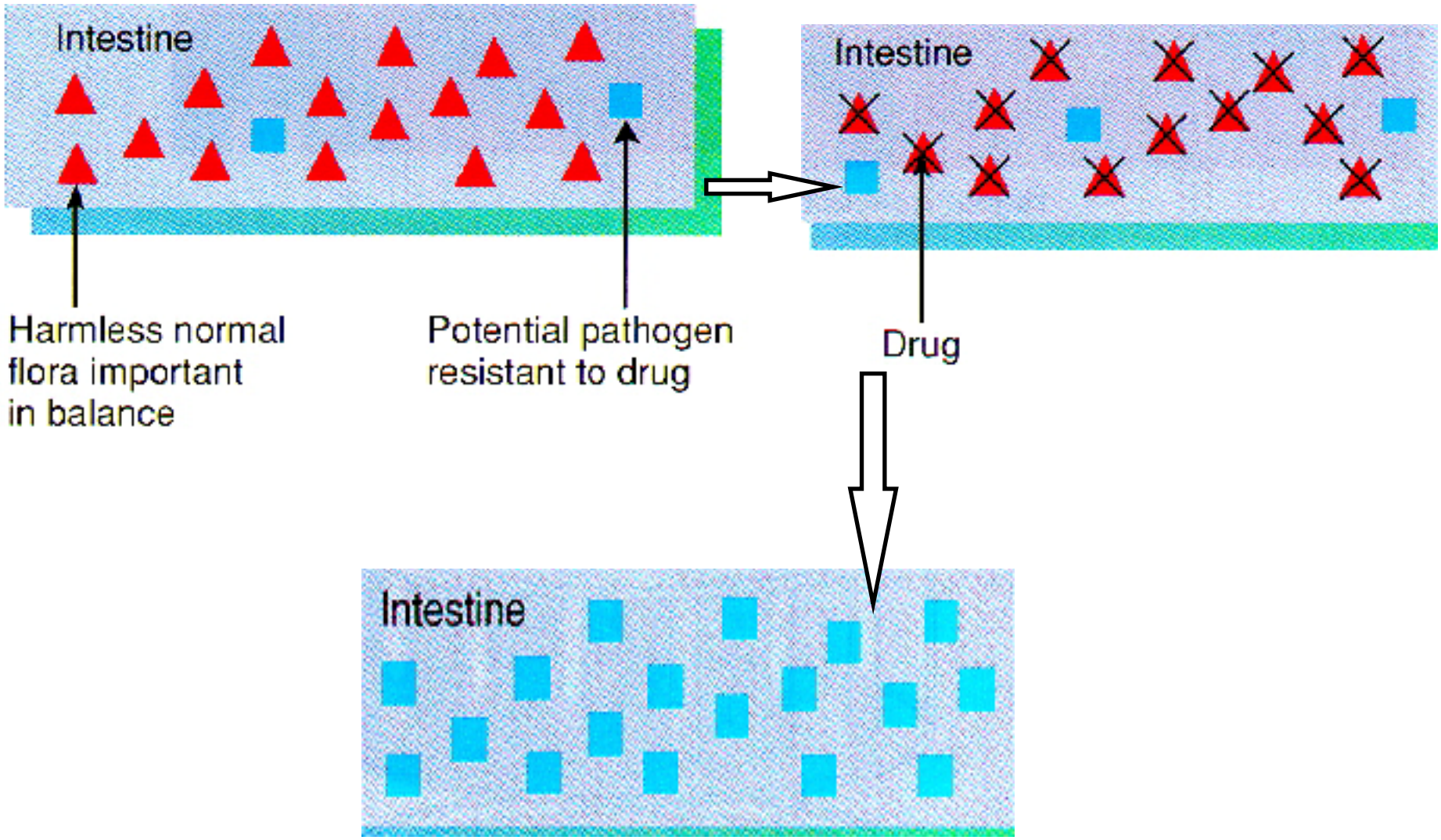
Table 20.2 The Spectrum of Activity of Antibiotics and Other Antimicrobial Drugs



*Growth of these bacteria frequently occurs within macrophages or tissue structures.
†Obligately intracellular bacteria.

Broad vs. Narrow

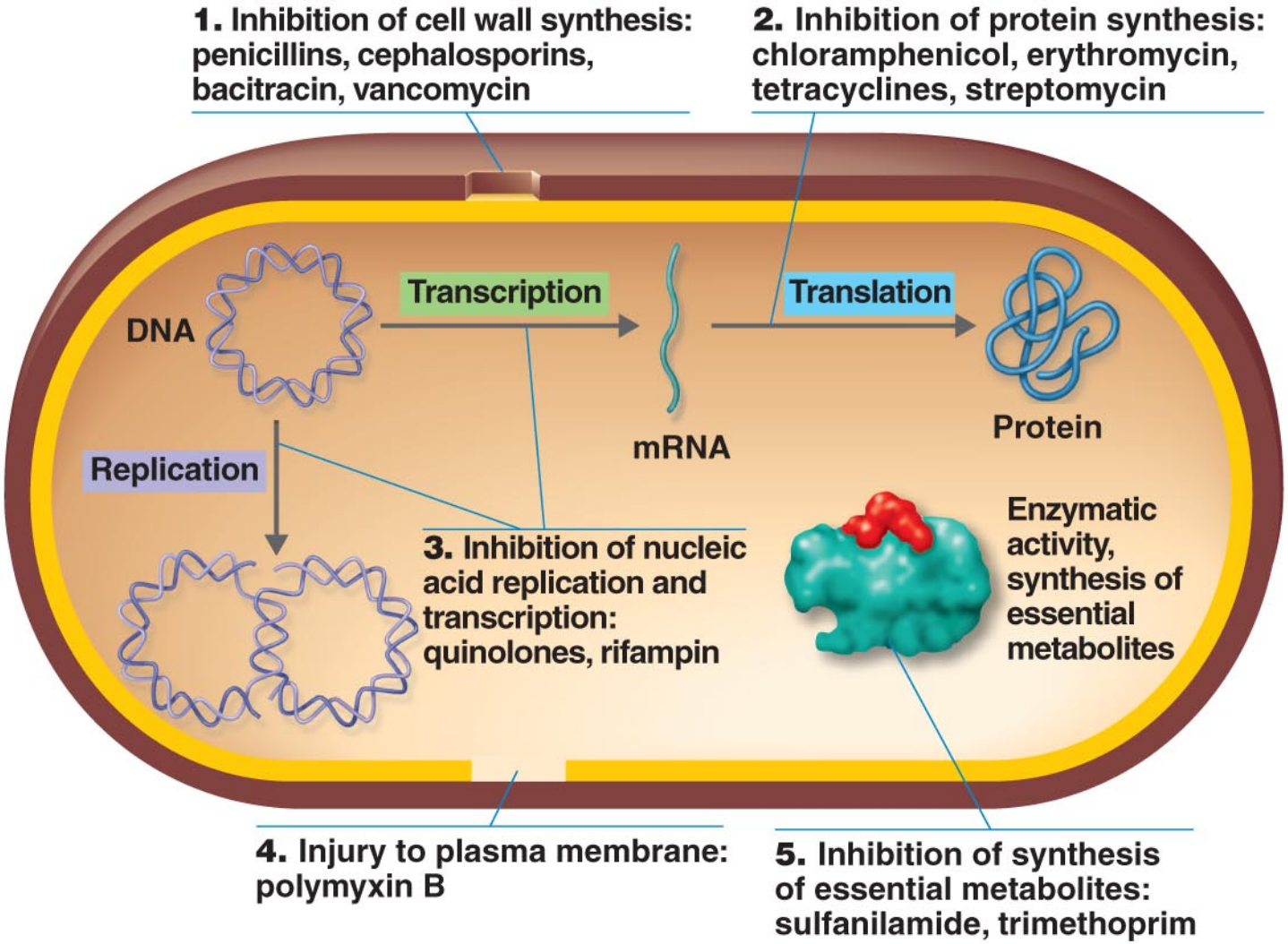
- advantage of broad spectrum: more likely to affect an unidentified pathogen
- disadvantage of broad spectrum: more damage to beneficial normal flora; greater chance of superinfection (infection by a second pathogen)



- Competition, Predator/Prey Models

Concept of selective toxicity

- the obvious part: a drug must be more toxic to the pathogen than to the host
- HOW? Drug affects some aspect of the pathogen's physiology that is not part of the host's physiology
  examples: block an enzyme that only the pathogen has; block formation of cell wall (we have none)
- some common actions:



Key Concept

Antimicrobial drugs function in one of the following five ways: inhibiting cell wall synthesis, inhibiting protein synthesis, inhibiting nucleic acid synthesis, injuring the plasma membrane, or inhibiting synthesis of essential metabolites.

1. Inhibitors of Cell Wall Synthesis

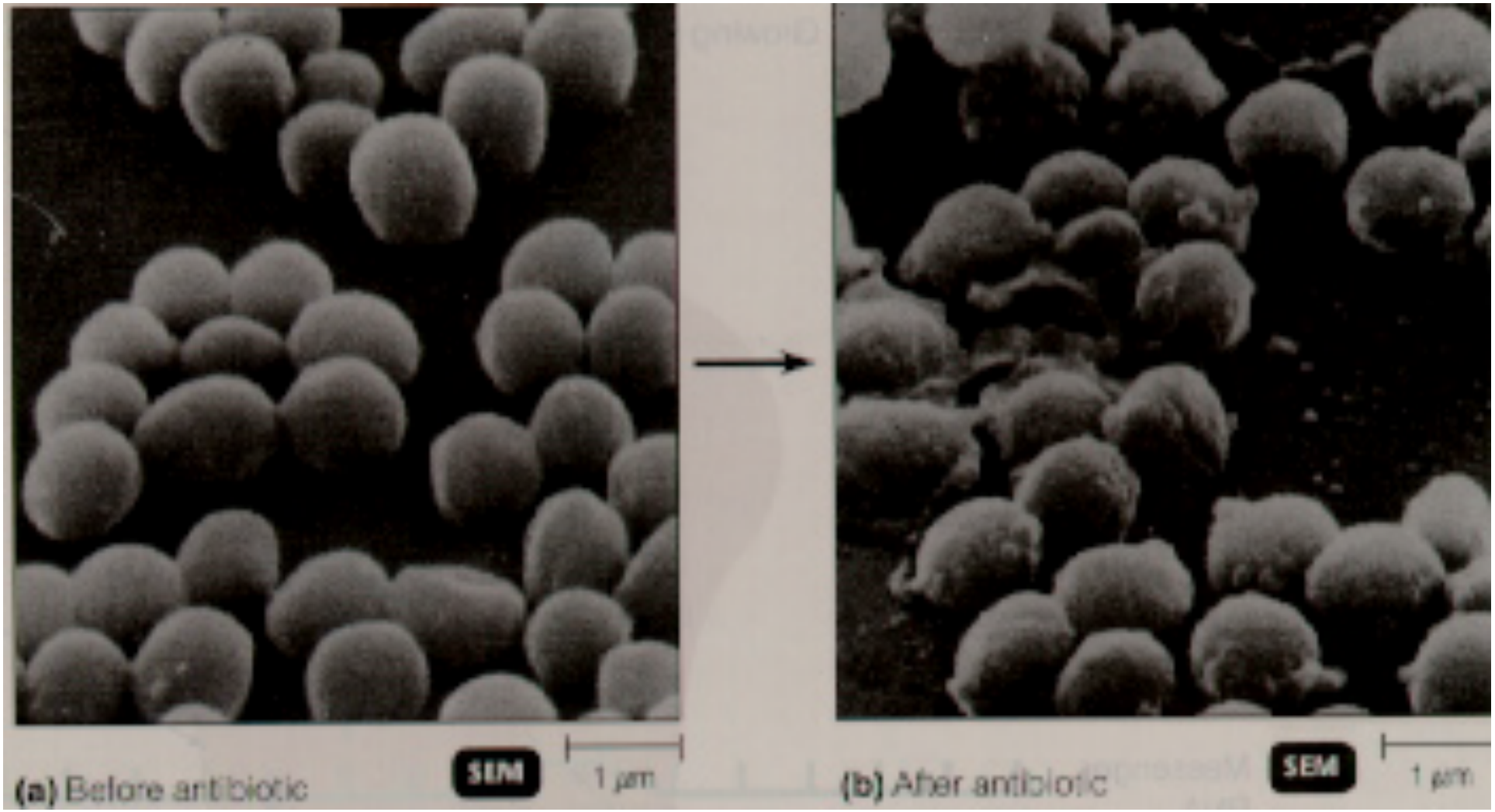
Table 20.3 Antibacterial Drugs

Drugs by Mode of Action	Comments
INHIBITORS OF CELL WALL SYNTHESIS	
Natural Penicillins	
Penicillin G	Against gram-positive bacteria, requires injection
Penicillin V	Against gram-positive bacteria, oral administration
Semisynthetic Penicillins	
Oxacillin	Resistant to penicillinase
Ampicillin	Broad spectrum
Amoxicillin	Broad spectrum; combined with inhibitor of penicillinase
Aztreonam	A monobactam; effective for gram-negative bacteria, including *Pseudomonas* spp.
Imipenem	A carbapenem; very broad spectrum
Cephalosporins	
Cephalothin	First-generation cephalosporin; activity similar to penicillin; requires injection
Cefixime	Fourth-generation cephalosporin; oral administration
Polypeptide Antibiotics	
Bacitracin	Against gram-positive bacteria; topical application
Vancomycin	A glycopeptide type; penicillinase-resistant; against gram-positive bacteria
Antimycobacterial Antibiotics	
Isoniazid	Inhibits synthesis of mycolic acid component of cell wall of *Mycobacterium* spp.
Ethambutol	Inhibits incorporation of mycolic acid into cell wall of *Mycobacterium* spp.

cell wall damage by antibiotic

- before antibiotic

after antibiotic



Remember the definition for antibiotic?

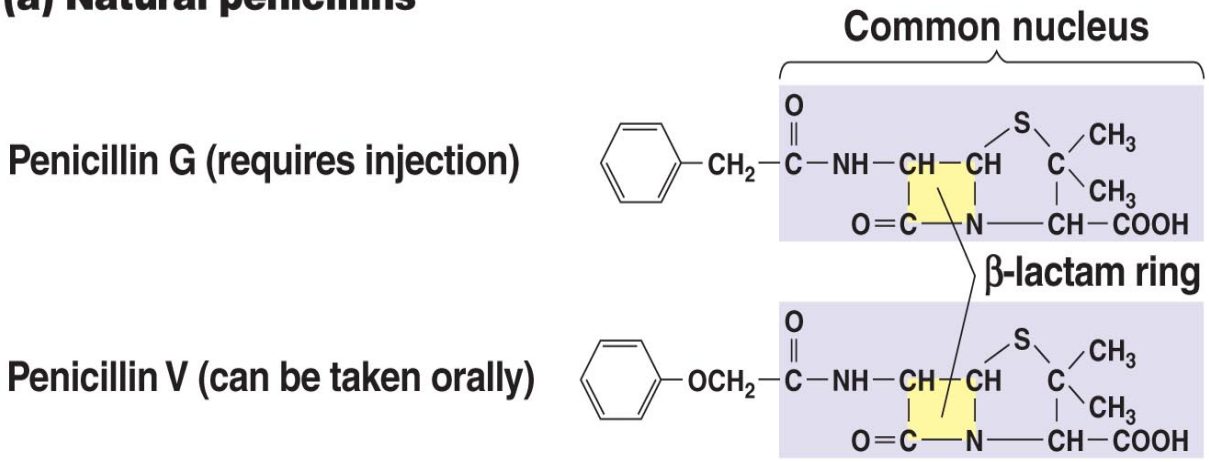
- A substance produced by microbes that in small amounts inhibits another microbe
- See table 20.1

Table 20.1 Representative Sources of Antibiotics

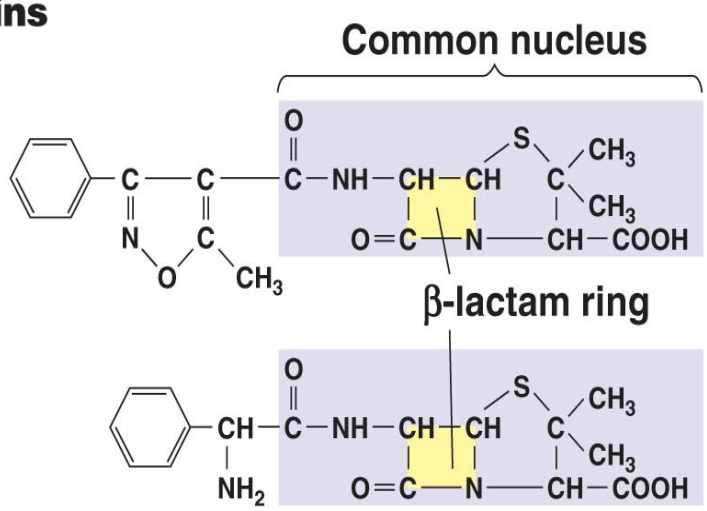
Microorganism	Antibiotic
Gram-Positive Rods	
Bacillus subtilis	Bacitracin
Paenibacillus polymyxa	Polymyxin
Actinomycetes	
Streptomyces nodosus	Amphotericin B
Streptomycems venezuelae	Chloramphenicol
Streptomyces aureofaciens	Chlortetracycline and tetracycline
Saccharopolyspora erythraea	Erythromycin
Streptomyces fradiae	Neomycin
Streptomyces griseus	Streptomycin
Micromonospora purpurea	Gentamicin
Fungi	
Cephalosporium spp.	Cephalothin
Penicillium griseofulvum	Griseofulvin
Penicillium chrysogenum	Penicillin

Penicillin as an example

(a) Natural penicillins



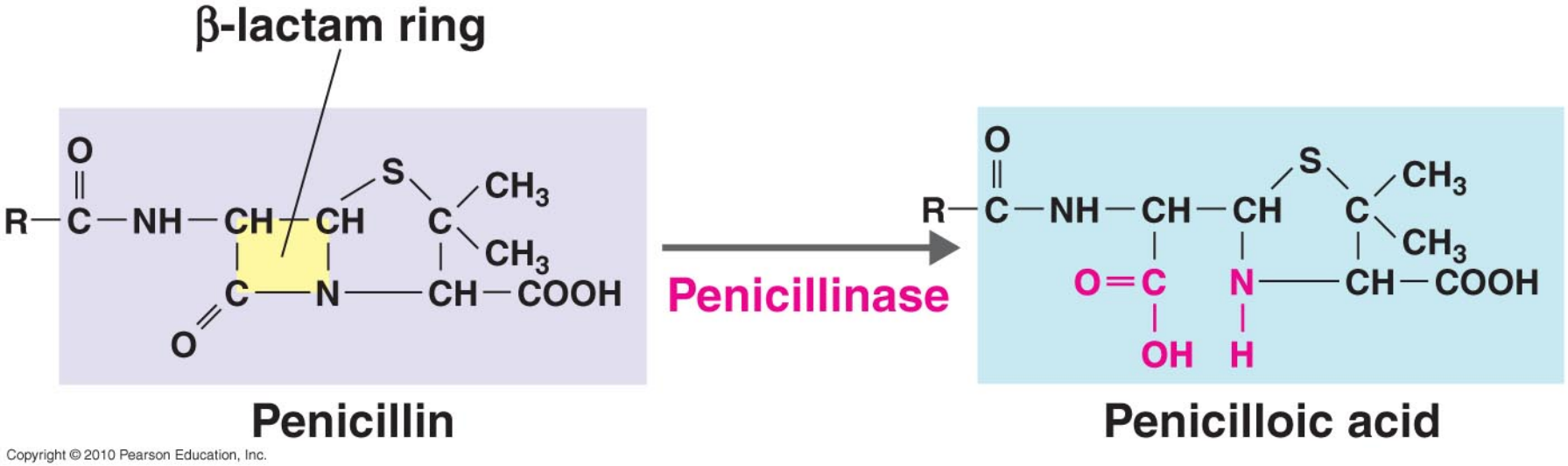
(b) Semisynthetic penicillins



Oxacillin:
Narrow spectrum, only gram-positives, but resistant to penicillinase

Ampicillin:
Extended spectrum, many gram-negatives

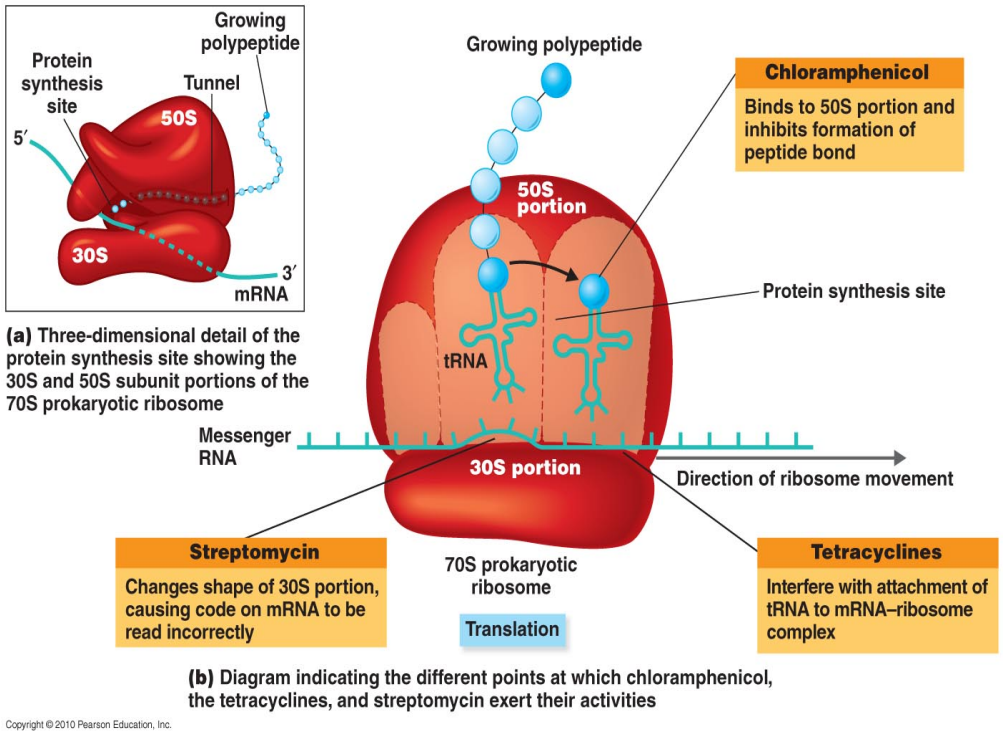
Penicillinases (beta-lactamases)



- Semisynthetic penicillins are made to resist penicillinases and have a broader spectrum of activity than natural (fungal made) penicillins

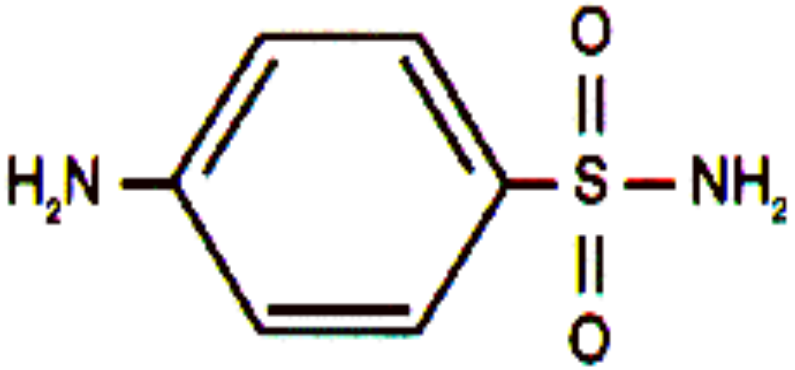
2. Inhibitors of Protein Synthesis

- Tetracyclines as the example
  - Broad-spectrum antibiotics produced by *Streptomyces* spp.
  - 70S prokaryotic ribosome that tetracycline targets!

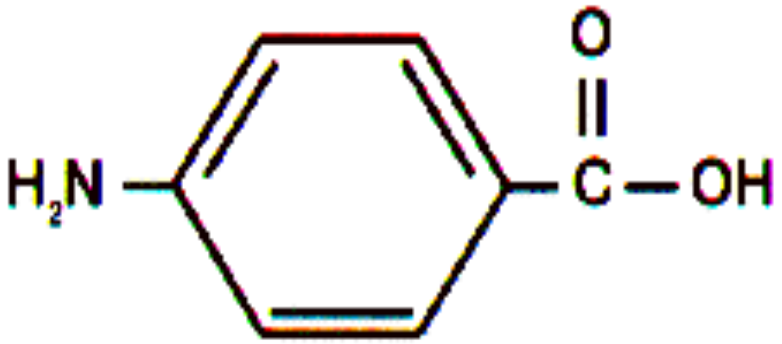


3. Competitive Inhibitors of bacterial enzyme function

- Let's use sulfonamides (sulfa drugs) as the example
- First synthetic antimicrobial drugs used to treat microbial diseases



Sulfanilamide



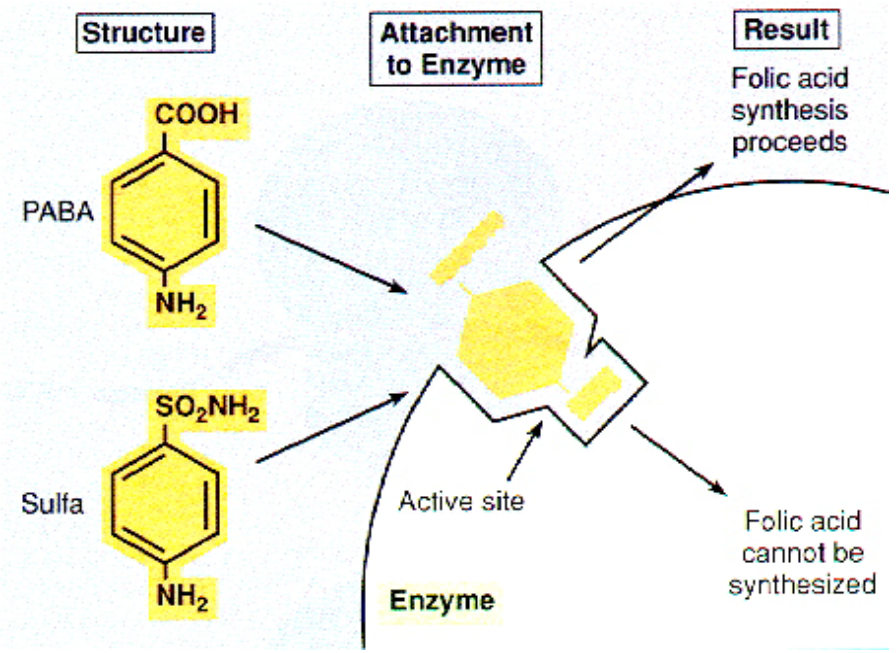
p-aminobenzoic acid

sulfonamide action

- in bacteria but not in people:

PABA ⟹ Folic acid (vitamin)

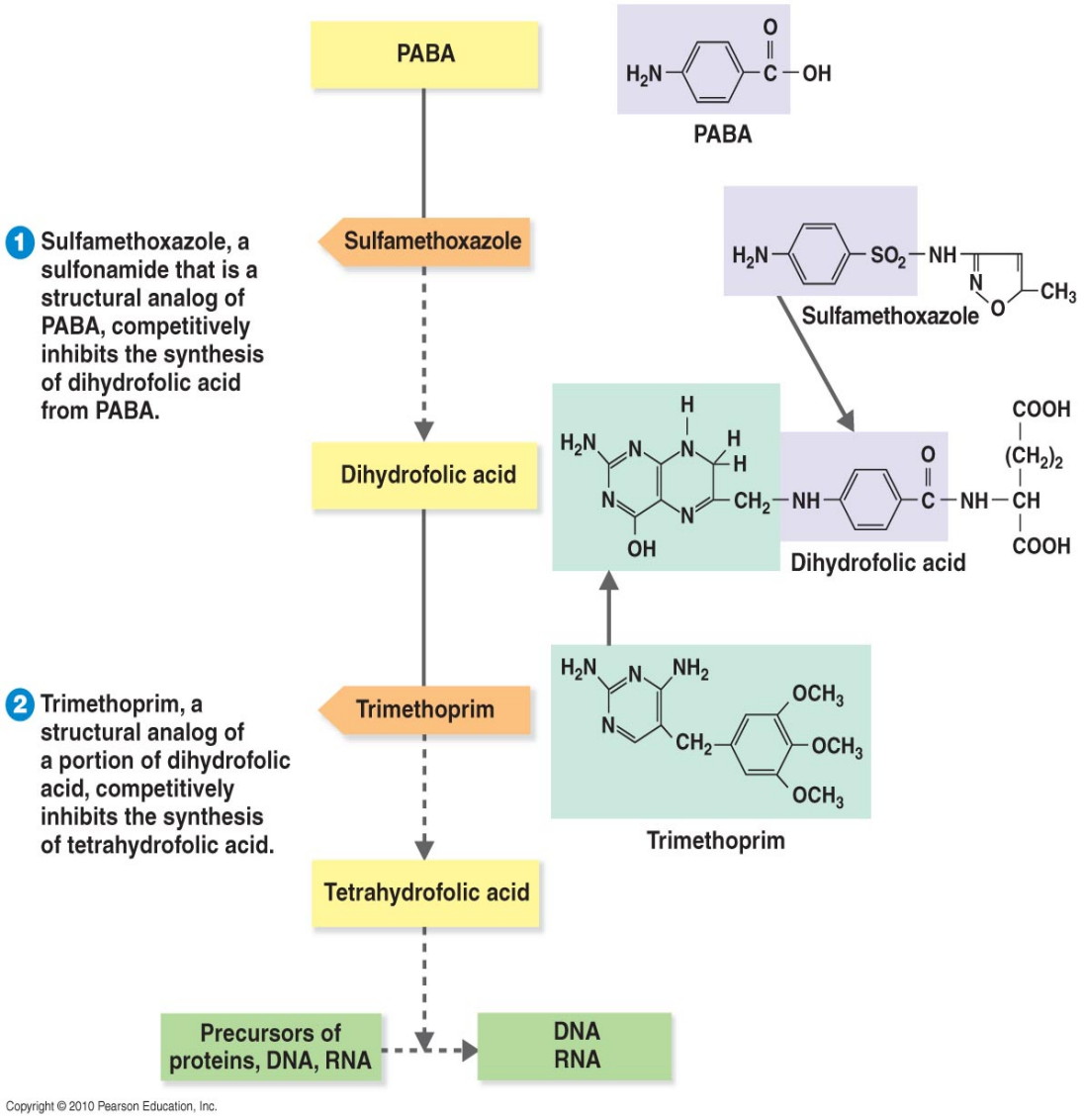
enzyme:
blocked by sulfonamide



Synergism and antagonism

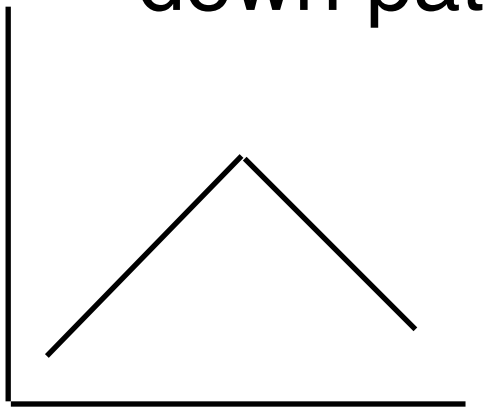
- _____: = combined effect of two drugs used at same time is greater than the sum of their individual effects: *2 + 2 = 8 (next slide example)*
- _____: = combined effect of two drugs used at same time is less than the sum of their individual effects: 2 + 2 = 0
  - E.g. Tetracycline is bacteriostatic and interferes with the action of penicillin….why?

TMP-SMZ : Sulfa drug synergism

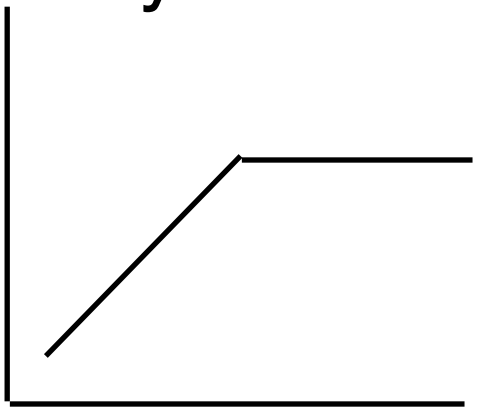


-cidal vs -static

- -cide or -cidal refers to killing, e.g.:
- -stasis or -static refers to inhibition without killing, e.g.
- static effect often adequate: drug slows down pathogen; body defenses clean it up



cidal effect



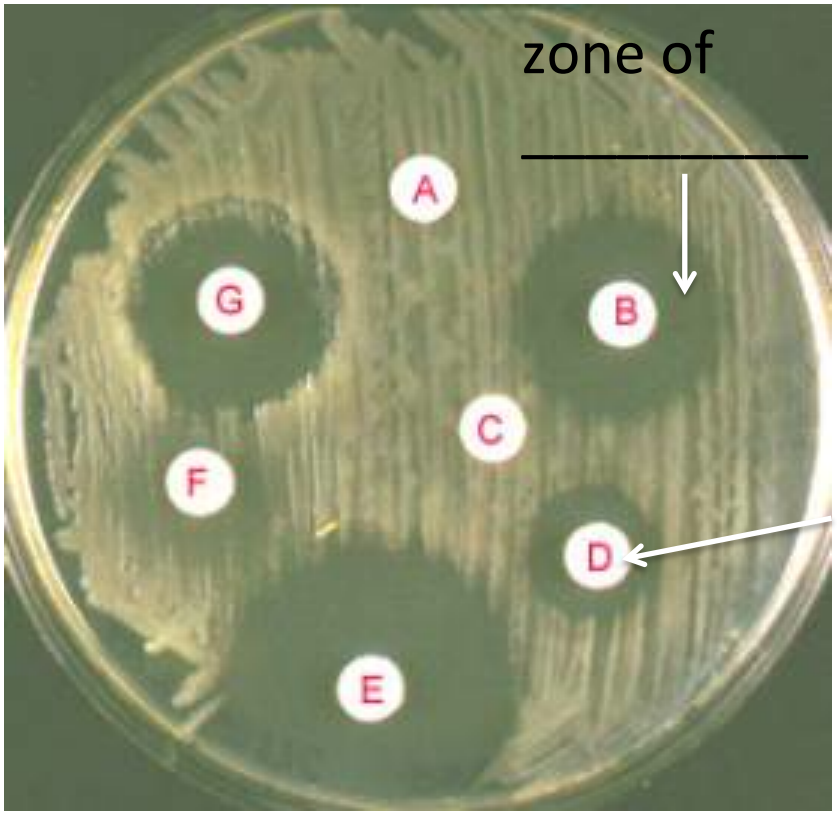
static effect

Susceptibility testing

- done to determine which drugs might control an infection
- several methods. This is the Kirby-Bauer disk-diffusion method:

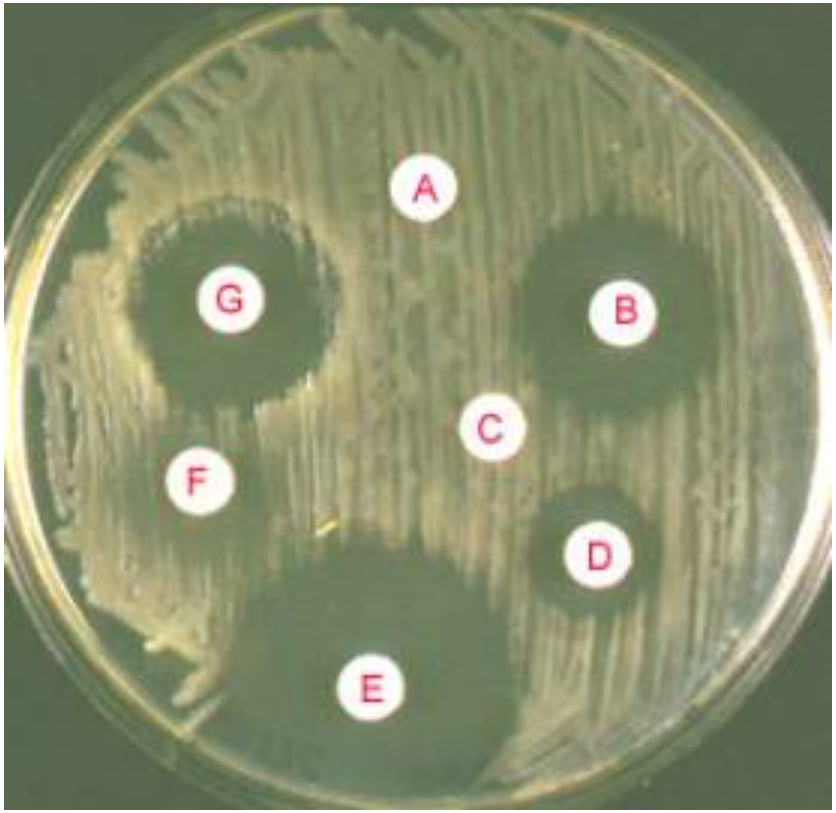
Kirby-Bauer : test to guide chemotherapy

Petri plate with pure culture of pathogen:



- Results reported as:
  - ___ (sensitive) = drug worked well
  - ___ (intermediate) or MS (moderately susceptible) = drug worked a little
  - ___ (resistant) = drug did not affect organism

- Simple and inexpensive but has limitations



Which Drug is the **most** effective?

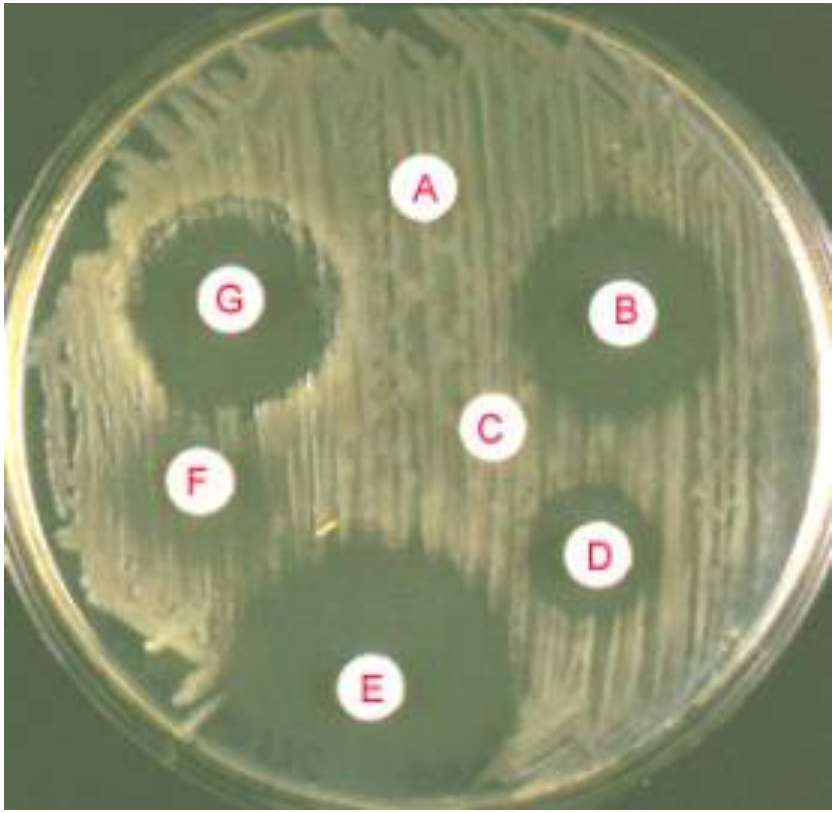
A)

B)

C)

D)

E)



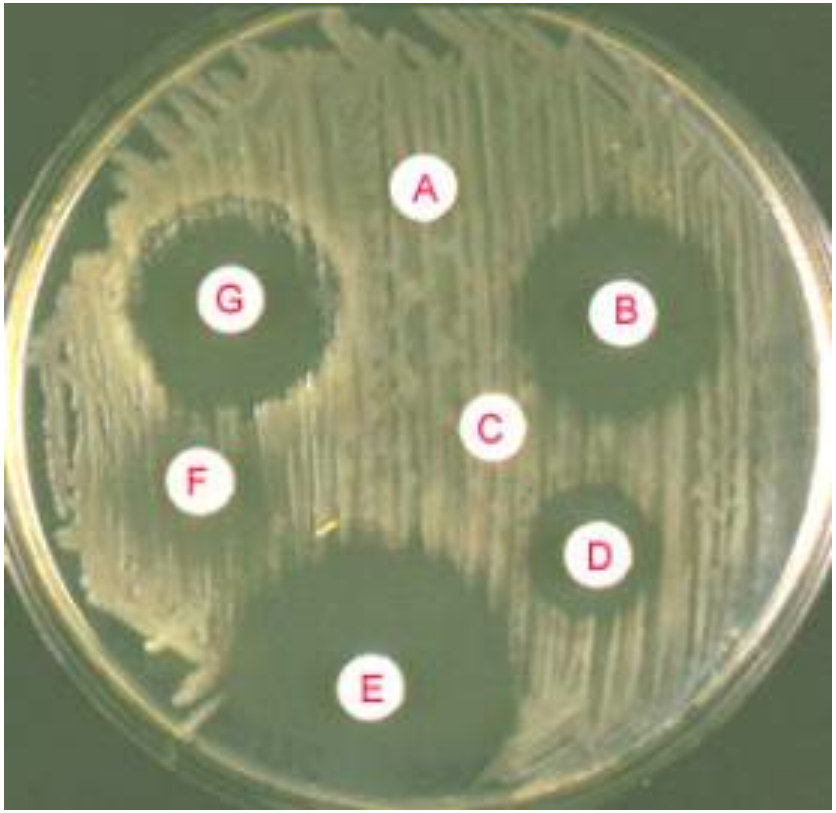
Which drug is NOT effective?

B)

C)

D)

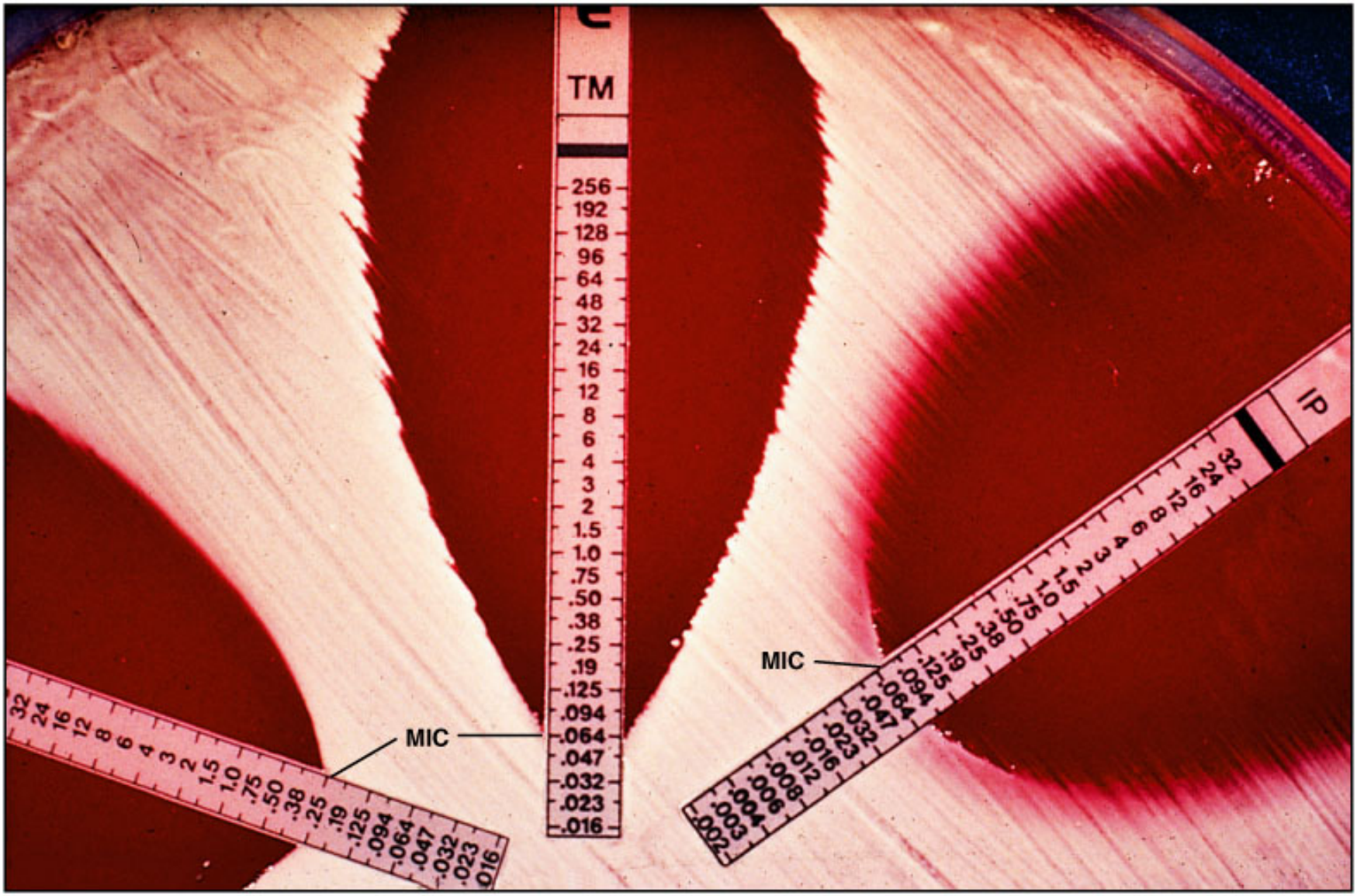
E)



In general the bacteria growing on this plate are___

To drug “A”

A) S
B) R
C) I



Drug Resistance

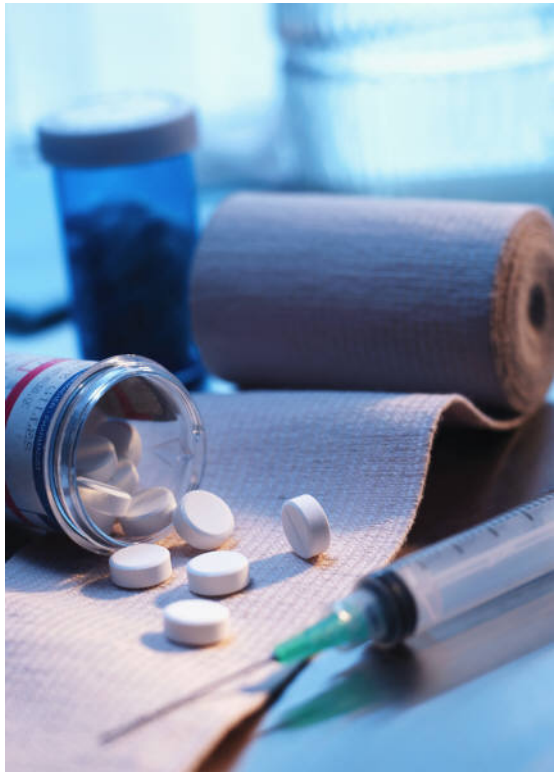
- pathogen is not affected by a drug
  - opposite of susceptibility (a drug affects a pathogen)
- develops with every class of pathogen
- it is the PATHOGEN that changes: not the drug and not the host
  - we (hosts) may develop an allergy, but not a drug resistance

Drug resistance develops in the

- Pathogen

- The lack of susceptibility of a microbe to a chemotherapeutic agent

≠



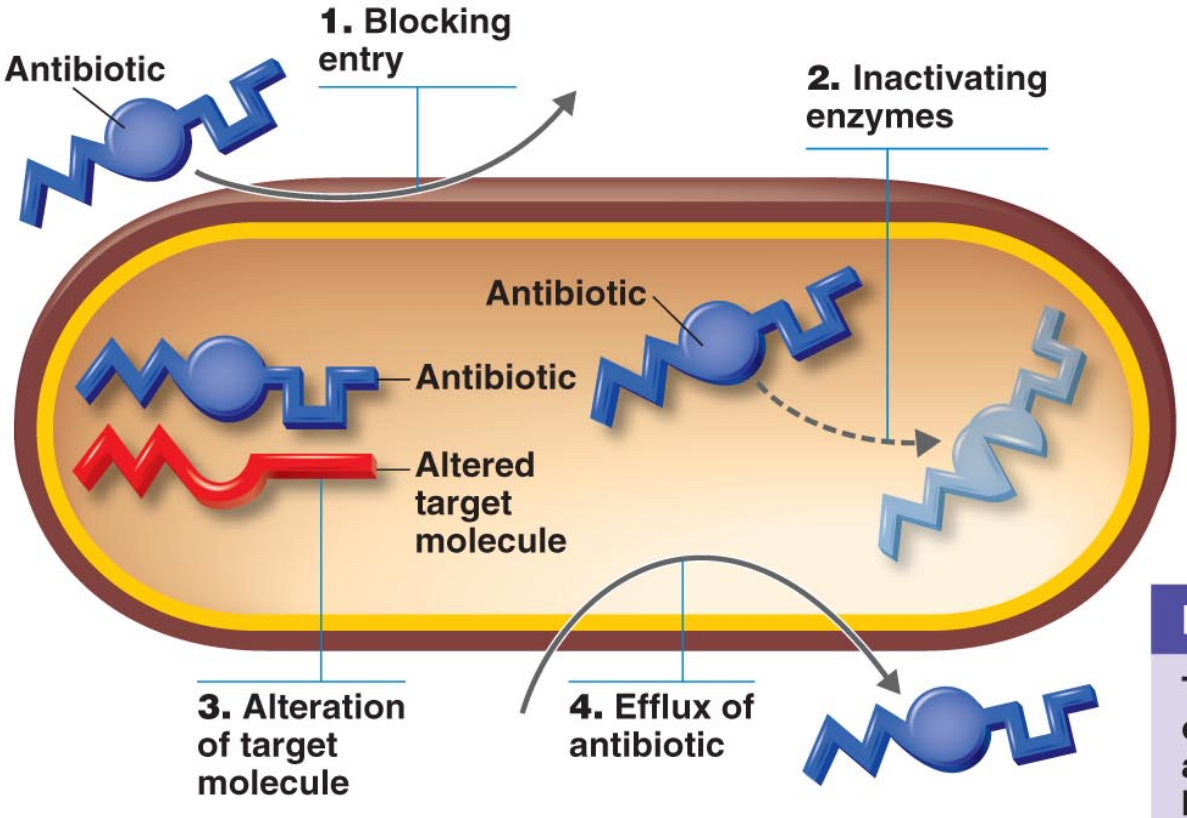
How Drug Resistance Develops

- a. selection & evolution: every time a drug dosage kills less than 100%, the survivors are the most drug resistant individuals (re: genetic variability in initial population)

- b. pathogen changes (mutations) so it is not affected by the drug
  - develops a way to inactivate the drug, such as penicillinase (beta-lactamase)
  - prevents the drug from reaching its target site within the pathogen
  - blocks entry of the drug into the cell
  - target site changes, e.g. a new enzyme appears that does same job but is not affected by the drug
  - Rapid efflux (ejection), which pumps the drug out of the cell before it can become effective

- If you are given an antibiotic and you do NOT finish taking your prescribed dosage of the antibiotic, which of the following is most likely to happen?
- A) That antibiotic will not be as effective for fighting future infections because you body will have adapted to the drug.
- B) That antibiotic will not be as effective in several weeks against that same infection (should you relapse) because the bacteria will be more resistant to the drug.
- C) The normal flora of microbes are more likely to evolve and become pathogens because of competition that results from stopping a drug before the initial infection was destroyed.
- D) Nothing will happen. As long as you are feeling better at the time in which you stop taking your antibiotic, your infection will be gone.

Figure 20.20

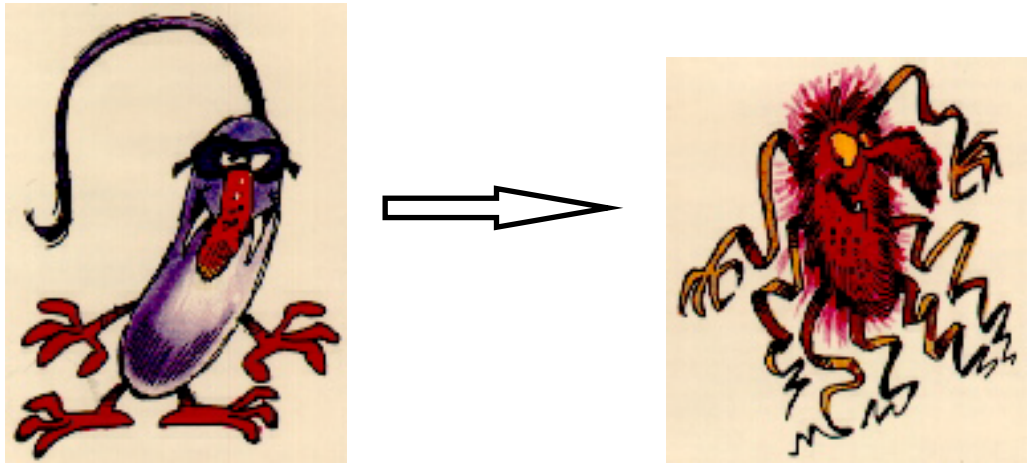


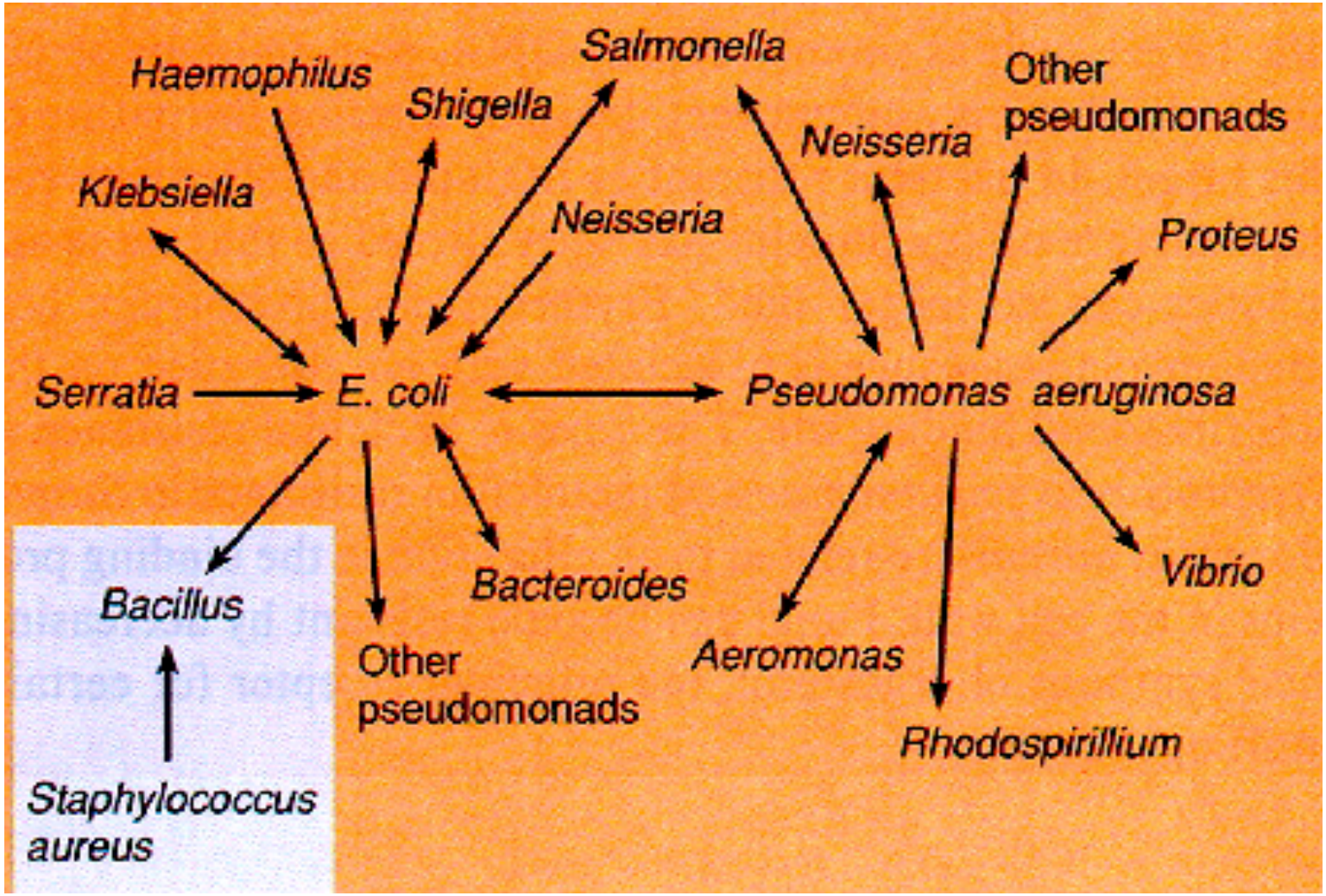
Another great essay!

Key Concept

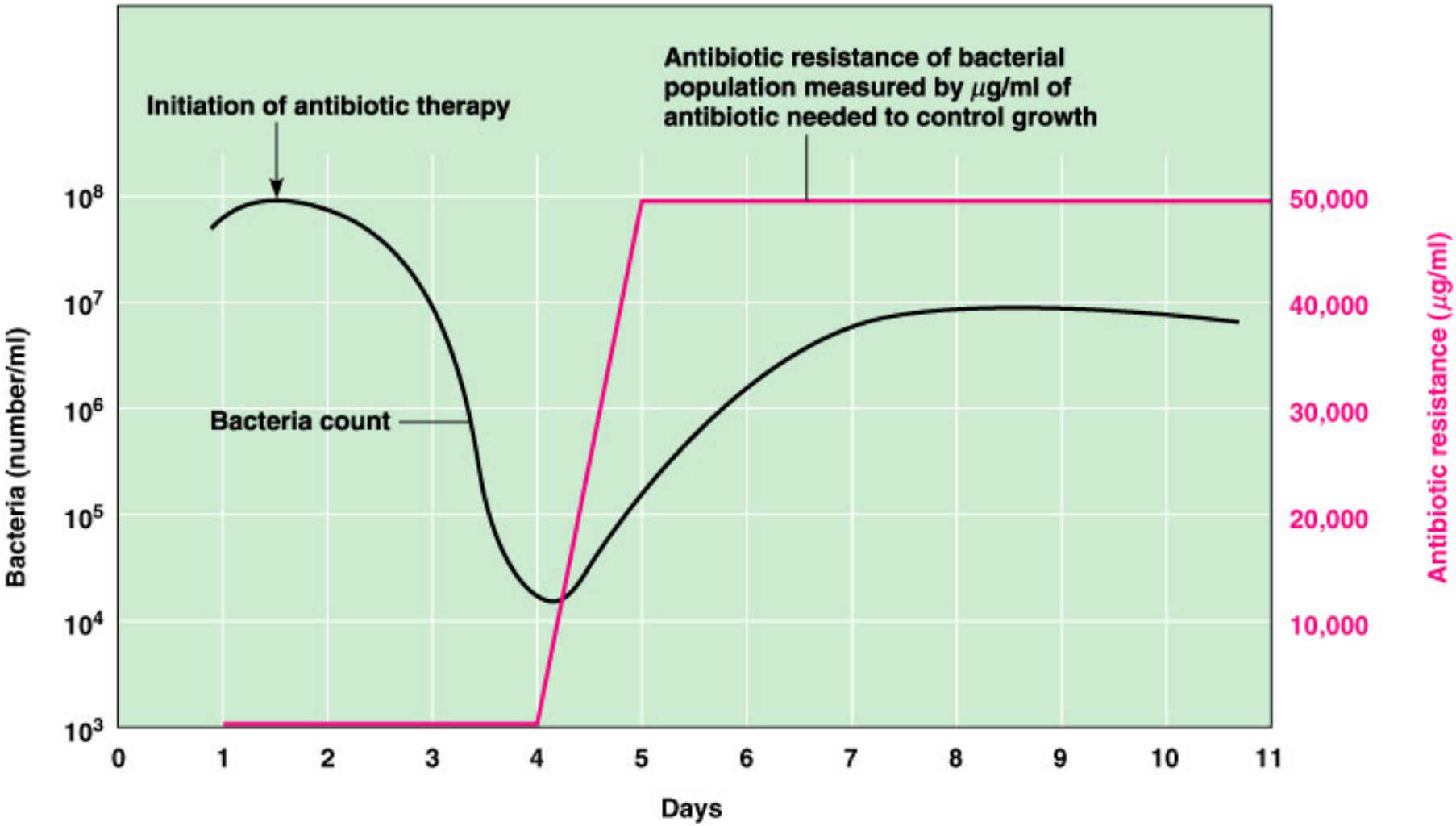
The four main mechanisms of microbial resistance to antimicrobial agents are blocking entry of the drug into the cell, inactivation of the drug by enzymes, alteration of the drug's target sites, and efflux of the drug from the cell.

- c. recombination: drug resistance genes travel from pathogen to pathogen




Haemophilus
Shigella
Salmonella
Other pseudomonads
Neisseria
Klebsiella
Neisseria
Proteus
Serratia
E. coli
Pseudomonas aeruginosa
Bacillus
Bacteroides
Vibrio
Other pseudomonads
Aeromonas
Rhodospirillium
Staphylococcus aureus

Development of an antibiotic-resistant mutant during antibiotic



How to delay resistance

- probably can't prevent, only delay resistance
- a. avoid unnecessary or inappropriate drug use
  - unnecessary: using drug for minor infection that the body defenses would clean up
  - inappropriate: using antibacterial drug for a viral infection
- b. when using a drug, use full dosage (to avoid leaving resistant survivors)
- c. in long-term use, rotate drugs
- d. minimize use of antibiotics in animal feed to promote growth