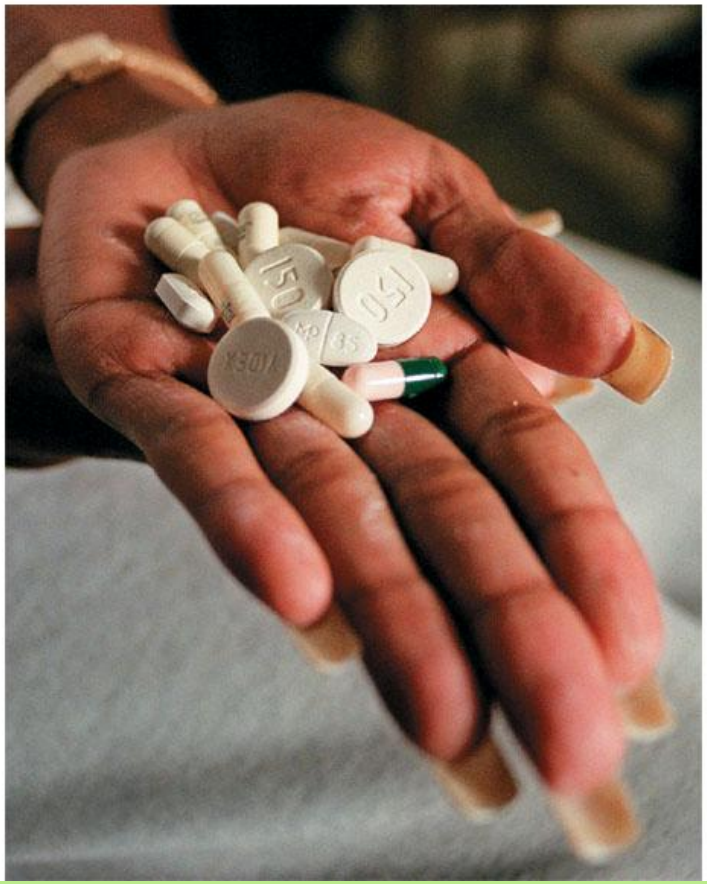
Foundations in Microbiology

Fifth Edition

Talaro

Chapter

12



Drugs, Microbes, Host – The Elements of Chemotherapy

Chapter 12

TABLE 12.1

Characteristics of the Ideal Antimicrobial Drug

- Selectively toxic to the microbe but nontoxic to host cells
- Microbicidal rather than microbistatic
- Relatively soluble and functions even when highly diluted in body fluids
- Remains potent long enough to act and is not broken down or excreted prematurely
- Not subject to the development of antimicrobial resistance
- Complements or assists the activities of the host's defenses
- Remains active in tissues and body fluids
- Readily delivered to the site of infection
- Not excessive in cost
- Does not disrupt the host's health by causing allergies or predisposing the host to other infections

TABLE 12.2

Terminology of Chemotherapy

Chemotherapeutic drug	Any chemical used in the treatment, relief, or prophylaxis of a disease
Prophylaxis*	Use of a drug to prevent imminent infection of a person at risk
Antimicrobial chemotherapy*	The use of chemotherapeutic drugs to control infection
Antimicrobics	All-inclusive term for any antimicrobial drug, regardless of its origin
Antibiotics*	Substances produced by the natural metabolic processes of some microorganisms that can inhibit or destroy other microorganisms
Semisynthetic drugs	Drugs which are chemically modified in the laboratory after being isolated from natural sources
Synthetic drugs	The use of chemical reactions to synthesize antimicrobial compounds in the laboratory
Narrow spectrum (limited spectrum)	Antimicrobics effective against a limited array of microbial types—for example, a drug effective mainly on gram-positive bacteria
Broad spectrum (extended spectrum)	Antimicrobics effective against a wide variety of microbial types—for example, a drug effective against both gram-positive and gram-negative bacteria

Origins of antimicrobial drugs

- Antibiotics are common metabolic products of aerobic spore-forming bacteria & fungi.
  - bacteria in genera *Streptomyces* & *Bacillus*
  - molds in genera *Penicillium* & *Cephalosporium*
- By inhibiting the other microbes in the same habitat, antibiotic producers have less competition for nutrients & space.

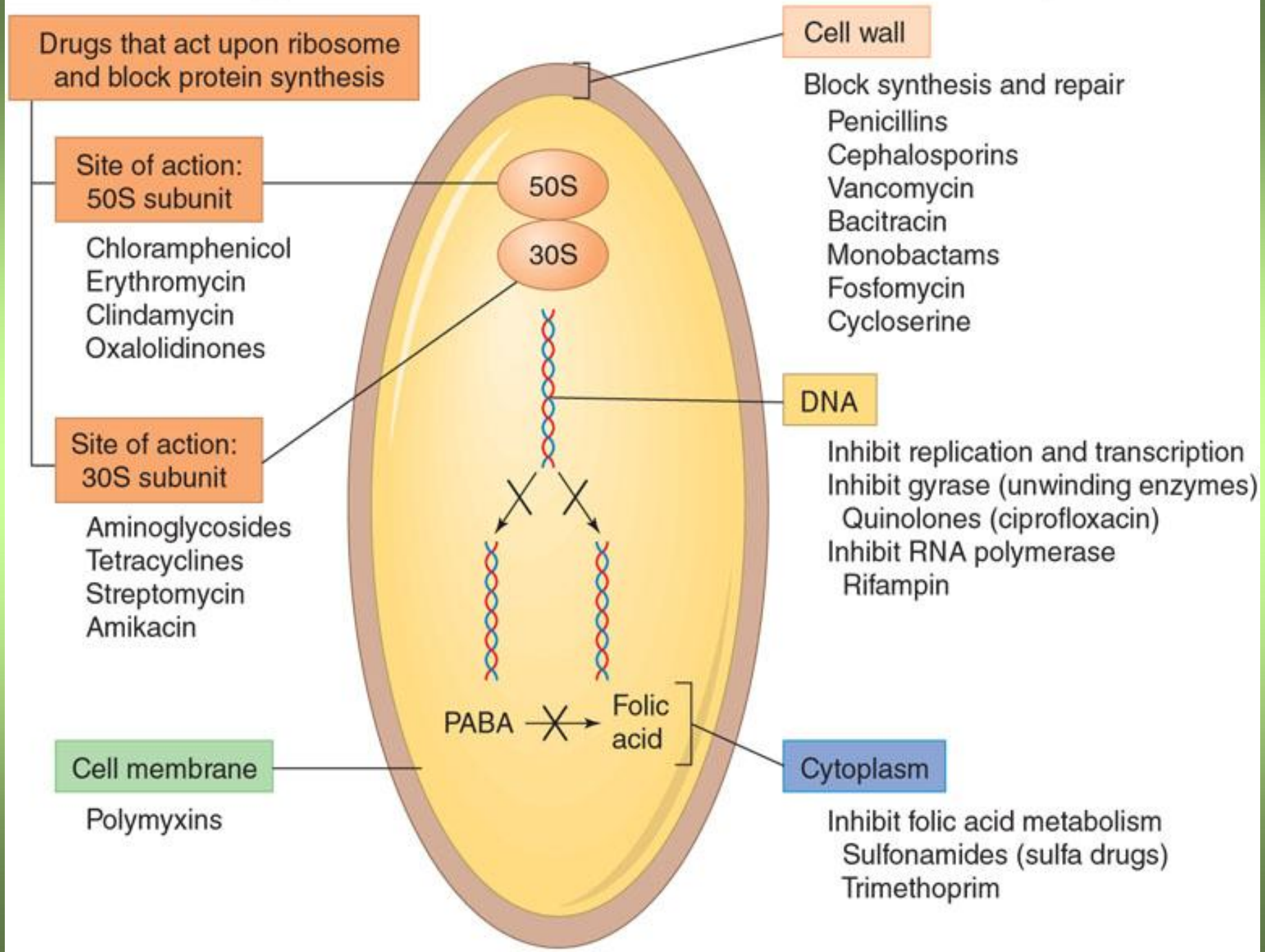
Streptomyces

Selectively toxic

- Drugs should kill or inhibit microbial cells without simultaneously damaging host tissues.
- As the characteristics of the infectious agent become more similar to the vertebrate host cell, complete selective toxicity becomes more difficult to achieve & more side effects are seen.

Targets of antimicrobial drugs

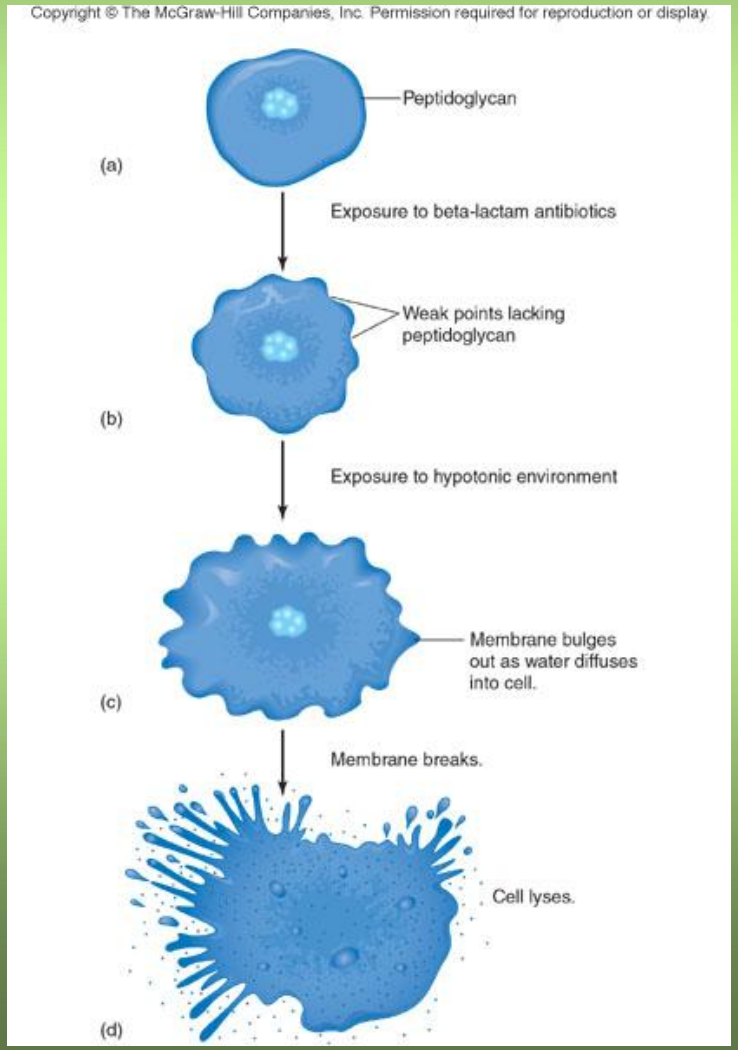
1. Inhibition of cell wall synthesis
2. Inhibition of nucleic acid synthesis, structure or function
3. Inhibition of protein synthesis
4. Disruption of cell membrane structure or function
5. Cell Membrane disruption



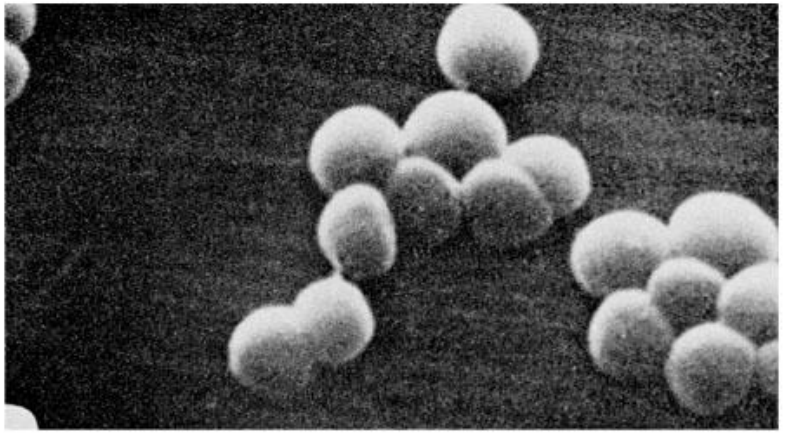
1. Drugs that affect the bacterial cell wall

- Most bacterial cell walls contain a rigid girdle of peptidoglycan.
- Penicillin and cephalosporin block synthesis of peptidoglycan, causing the cell wall to lyse.
- Penicillins do not penetrate the outer membrane and are less effective against gram-negative bacteria.
- Broad spectrum penicillins and cephalosporins can cross the cell walls of gram-negative bacteria.

1. Drugs that affect the bacterial cell wall



1. Drugs that affect the bacterial cell wall



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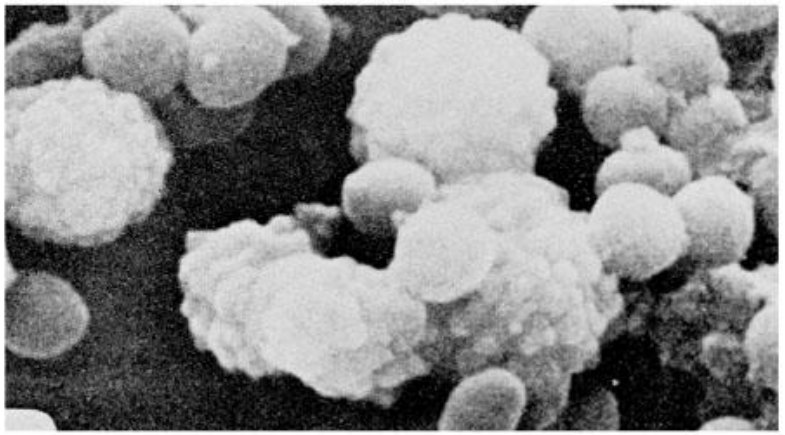

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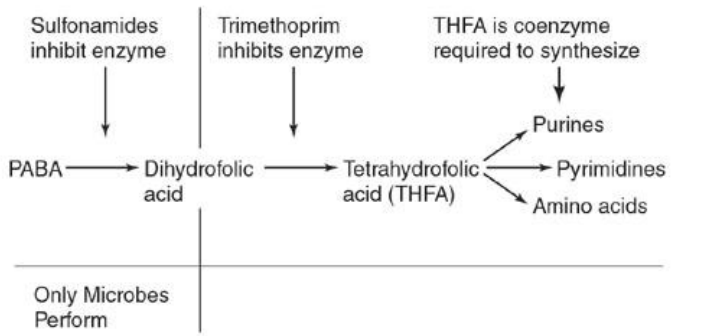
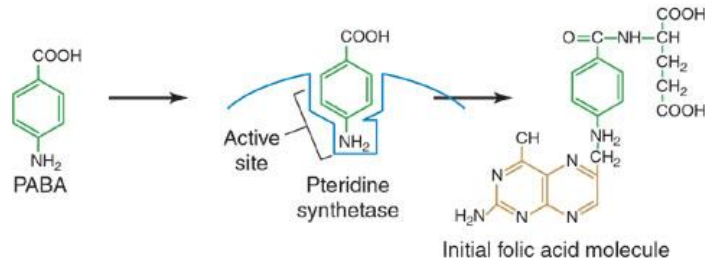
2. Drugs that inhibit nucleic acid synthesis

- may block synthesis of nucleotides, inhibit replication, or stop transcription
- Sulfonamides and trimethoprim block enzymes required for tetrahydrofolate synthesis needed for DNA & RNA synthesis.
- **competitive inhibition** – drug competes with normal substrate for enzyme's active site
- **synergistic effect** – an additive effect, achieved by multiple drugs working together, requiring a lower dose of each

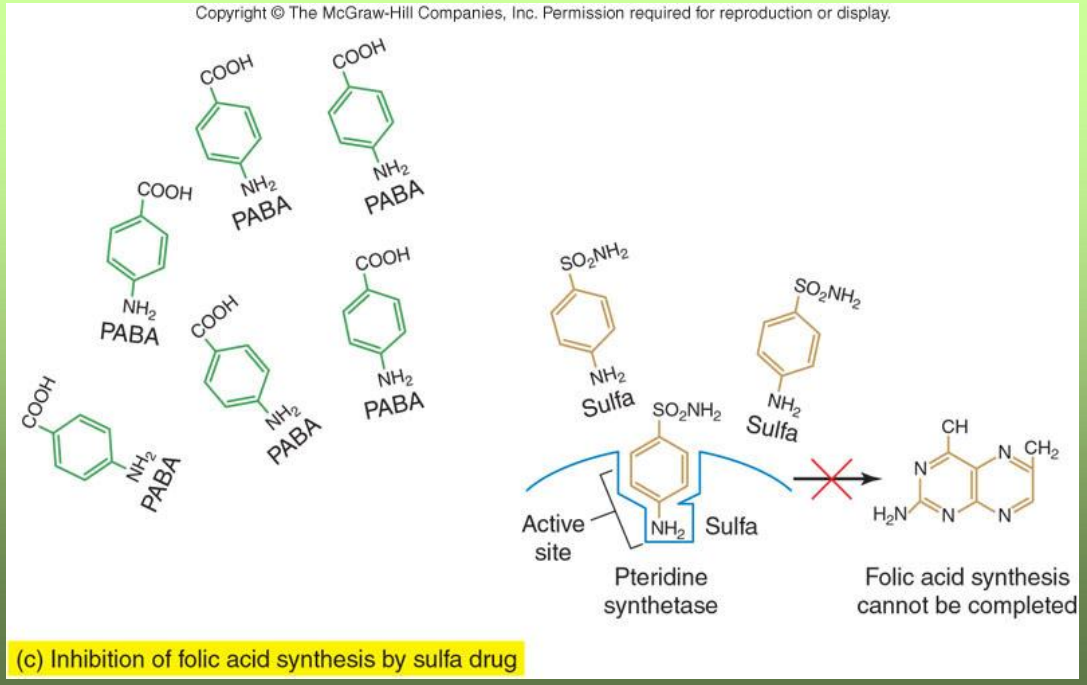
2. Drugs that inhibit nucleic acid synthesis



(a) Normal metabolic pathway



(b) Normal folic acid synthesis



(c) Inhibition of folic acid synthesis by sulfa drug

3. Drugs that block protein synthesis

- Ribosomes of eucaryotes differ in size and structure from procaryotes, so antimicrobics usually have a selective action against procaryotes. But they can also damage the eucaryotic mitochondria.
- Aminoglycosides (streptomycin, gentamicin) insert on sites on the 30S subunit and cause misreading of mRNA.
- Tetracyclines block attachment of tRNA on the A acceptor site and stop further synthesis.

3. Drugs that block protein synthesis

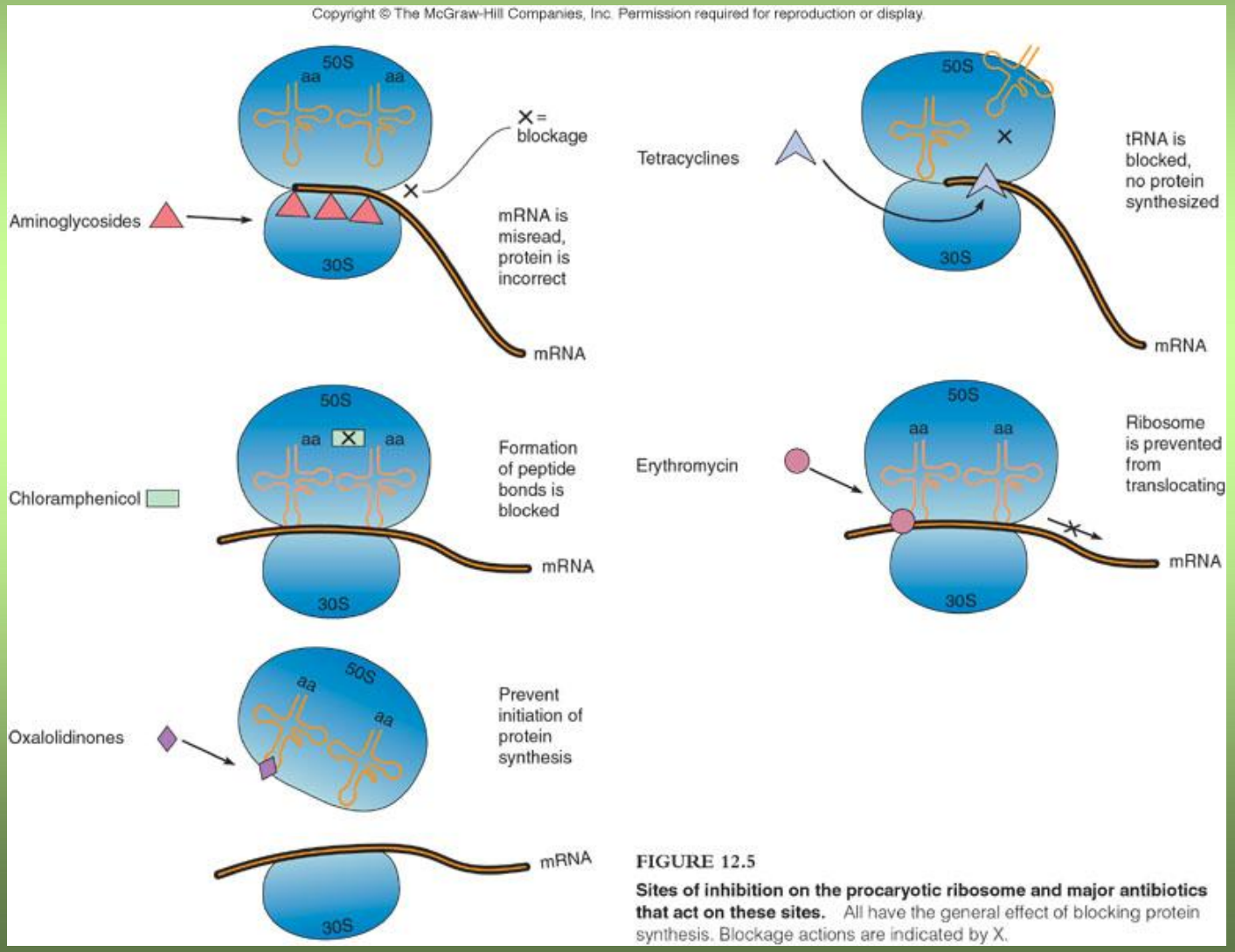


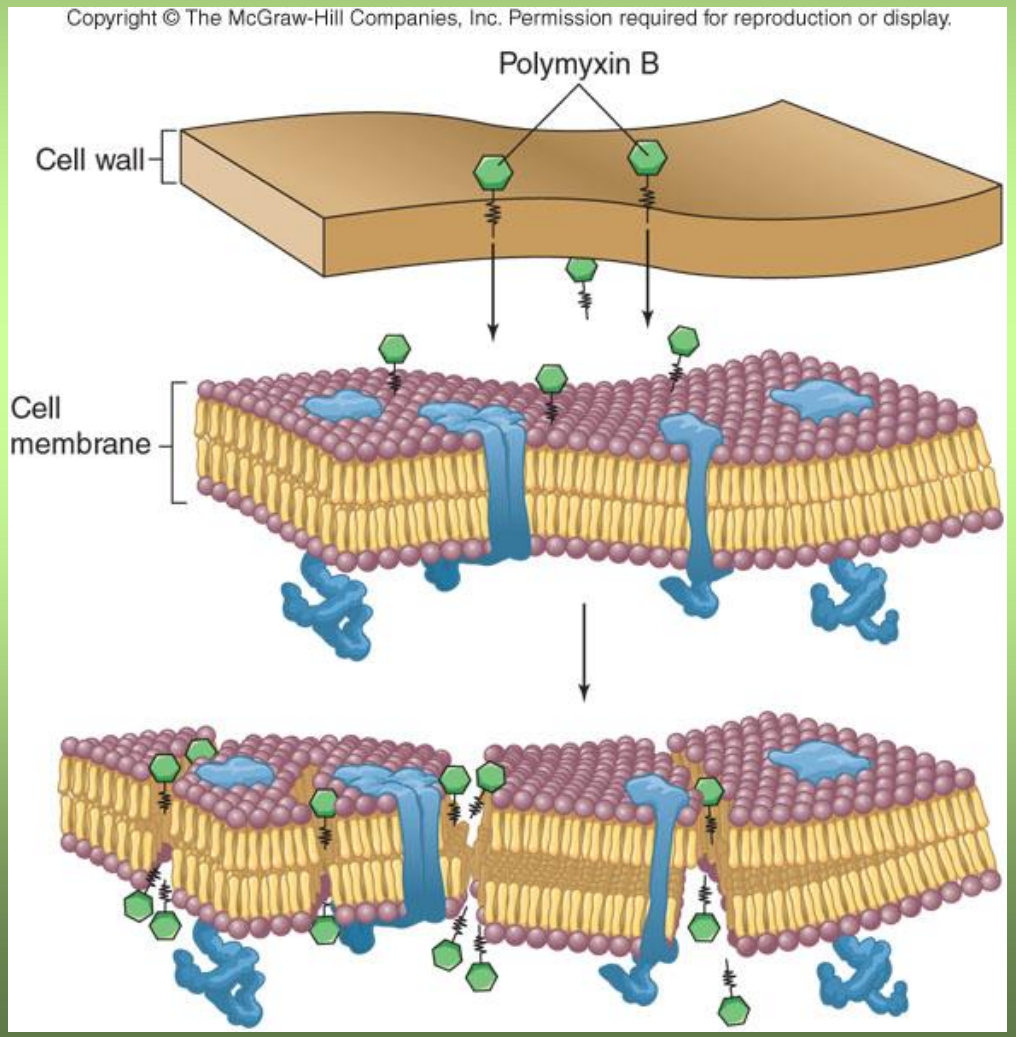
FIGURE 12.5

Sites of inhibition on the procaryotic ribosome and major antibiotics that act on these sites. All have the general effect of blocking protein synthesis. Blockage actions are indicated by X.

4. Drugs that disrupt cell membrane function

- A cell with a damaged membrane dies from disruption in metabolism or lysis.
- These drugs have specificity for a particular microbial group, based on differences in types of lipids in their cell membranes.
- Polymyxins interact with phospholipids and cause leakage, particularly in gram-negative bacteria
- Amphotericin B and nystatin form complexes with sterols on fungal membranes which causes leakage.

4. Drugs that disrupt cell membrane function



Survey of major antimicrobial drug groups

- Antibacterial drugs
  - Antibiotics
  - Synthetic drugs
- Antifungal drugs
- Antiparasitic drugs
- Antiviral drugs

About 260 different antimicrobial drugs are classified in 20 drug families.

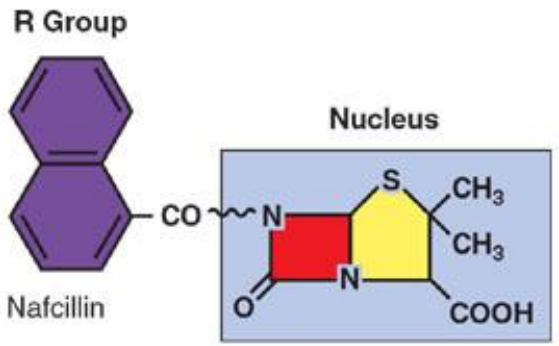
Antibacterial antibiotics

- Penicillins
- Cephalosporins
- Other beta-lactam antibiotics
- Aminoglycosides
- Tetracycline antibiotics
- Chloramphenicol
- Other *Streptomyces* antibiotics
- The *Bacillus* antibiotics
- New classes

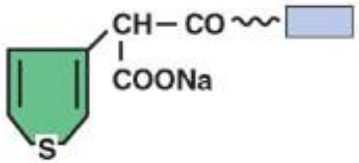
Penicillins

- Large diverse group of compounds
- Could be synthesized in the laboratory
- more economical to obtain natural penicillin through microbial fermentation and modify it to semi-synthetic forms
- *Penicillium chrysogenum* – major source
- All consist of 3 parts
  - thiazolidine ring
  - beta-lactam ring
  - variable side chain dictates microbial activity

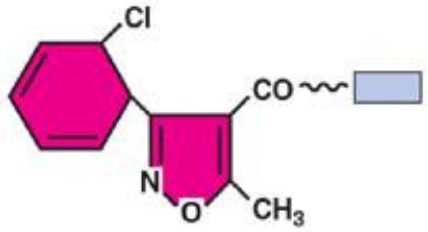
Penicillins



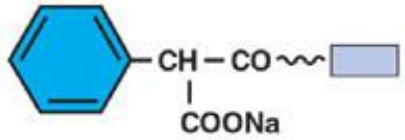
Nafcillin



Ticarcillin



Cloxacillin



Carbenicillin

Penicillins Video

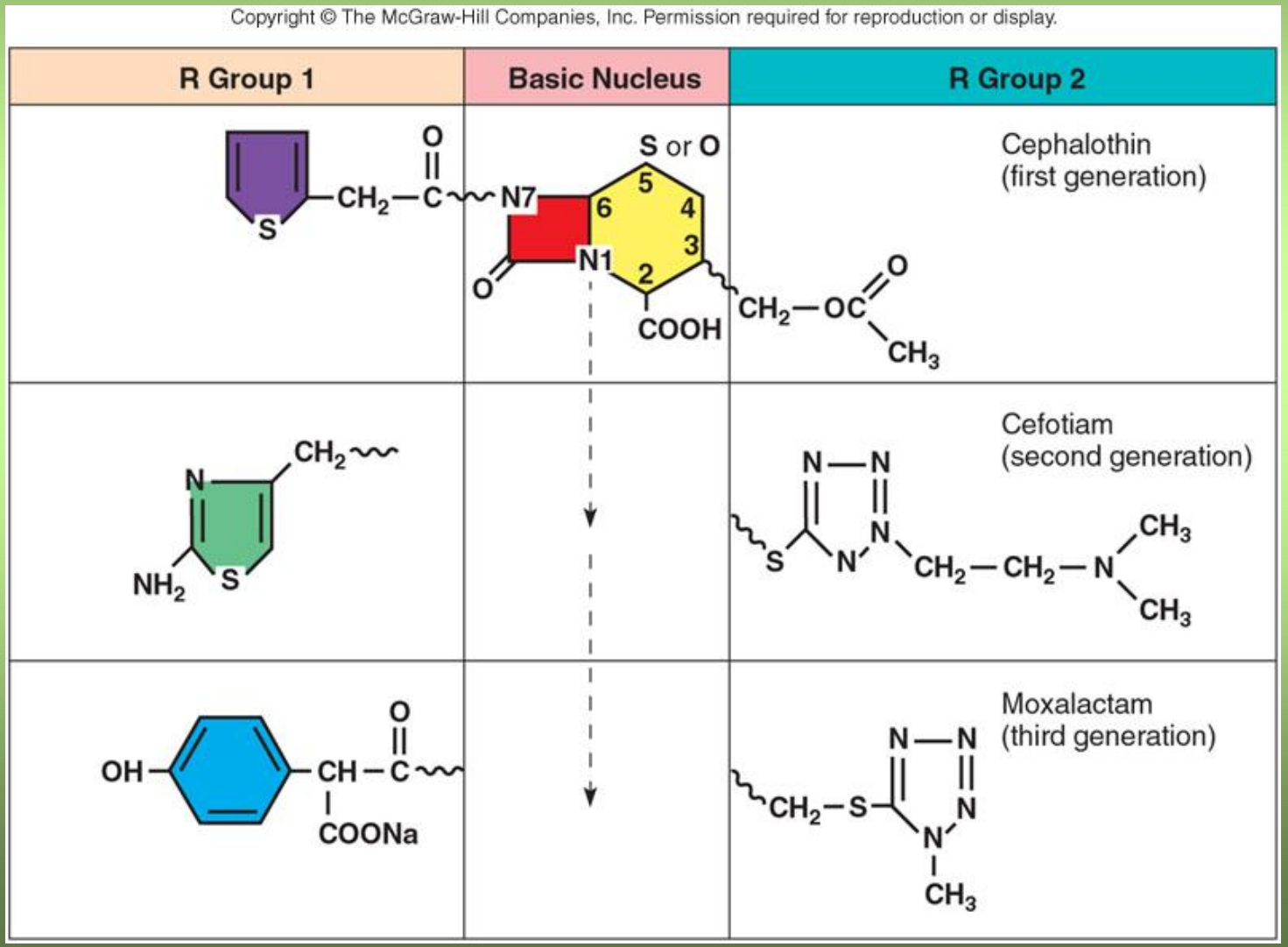
- Penicillins G and V most important natural forms
- Penicillin is the drug of choice for gram-positive cocci (streptococci) and some gram-negative bacteria (meningococci and syphilis spirochete)
- Semisynthetic penicillins – **ampicillin**, carbenicillin & amoxicillin have broader spectra – gram negative enterics rods
- Penicillinase-resistant – **methicillin, nafcillin, cloxacillin**
- Primary problems – allergies and resistant strains of bacteria


YOU KNOW, CLAUDIA, WHEN THEY MADE YOU, THEY BROKE THE MOLD.
PENICILLIN
PENICILLIN
9-3
©2004 CREATORS SYNDICATE, INC. WWW.CREATORS.COM DEEDY

Cephalosporins

- Account for majority of all antibiotics administered
- Isolated from *Cephalosporium acremonium* mold
- Beta-lactam ring that can be altered
- Relatively broad-spectrum, resistant to most penicillinases, & cause fewer allergic reactions
- Some are given orally, many must be administered parenterally

Cephalosporins



Cephalosporins

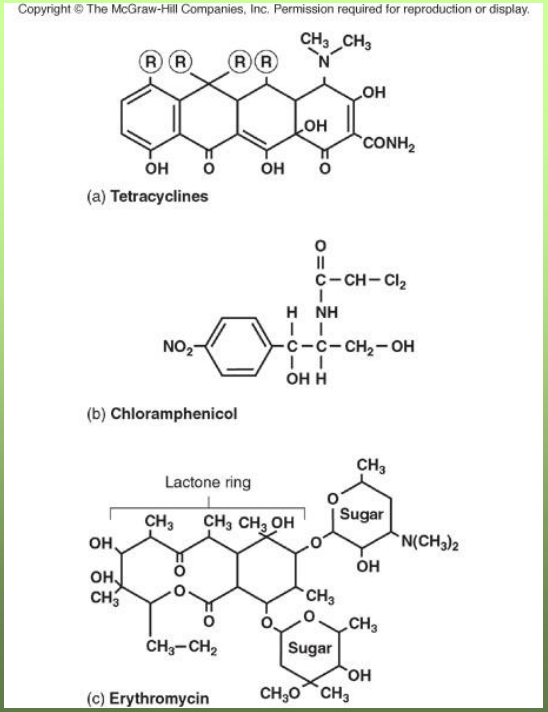
- 3 generations exist
- **First generation** – cephalothin, cefazolin – most effective against gram-positive cocci
- **Second generation** – cefaclor, cefonacid – more effective against gram-negative bacteria
- **Third generation** – cephalexin, cefotaxime – broad-spectrum activity against enteric bacteria with beta-lactamases
- Ceftriaxone – new semisynthetic broad-spectrum drug for treating wide variety of infections

Aminoglycosides

- products of various species of soil actinomycetes in genera *Streptomyces* & *Micromonospora*
- Broad-spectrum, inhibit protein synthesis, especially useful against aerobic gram-negative rods & certain gram-positive bacteria
  - **Streptomycin** – bubonic plague, tularemia, TB
  - **Gentamicin** – less toxic, used against gram-negative rods
  - Newer – **Tobramycin** & **amikacin** gram-negative bacteria

Tetracycline antibiotics

- Broad-spectrum, block protein synthesis
- **Doxycycline** & **minocycline** – oral drugs taken for STDs, Rocky Mountain spotted fever, Lyme disease, typhus, acne & protozoa



Chloramphenicol

- Isolated from *Streptomyces venezuelae*
- Potent broad-spectrum drug with unique nitrobenzene structure
- Blocks peptide bond formation
- No longer derived from natural source
- Very toxic, restricted uses, can cause irreversible damage to bone marrow
- Typhoid fever, brain abscesses, rickettsial & chlamydial infections

Other *Streptomyces* antibiotics

- **Erythromycin** – macrolide, large lactone ring with sugars
- Broad-spectrum, fairly low toxicity
- Attaches to ribosome
- Taken orally for Mycoplasma pneumonia, legionellosis, Chlamydia, pertussis, diptheria and as a prophylactic prior to intestinal surgery
- For **penicillin-resistant** – gonococci, syphilis, acne
- Newer semi-synthetic **macrolides – clarithomycin, azithromycin**

Other *Streptomyces* antibiotics

- **Clindamycin** – broad-spectrum, serious abdominal anaerobic infections
- **Vancomycin** –narrow-spectrum, effective against penicillin & methicillin resistant staphylococcal infections; very toxic, hard to administer
- **Rifampin** – limited spectrum, cannot pause through many cell membranes, used to treat gram-positive bacteria, TB, leprosy

Miscellaneous antibacterial drugs

- Isoniazid –used with **rifampicin** to treat TB
- Oxazolidinones- new class of antibacterial drugs inhibit initiation of protein synthesis (50S ribosome)
  - **Linezolid** – MRSA, VRE
- Quinolones (Fluoroquinolones) –broad-spectrum, potent
  - **norfloxacin**, **ciprofloxacin** – UTI, STD, GI, osteomyletitis, respiratory & soft tissue infections
  - **sparofloxacin, levofloxacin** – pneumonia, bronchitis, sinusitis

Antifungal drugs

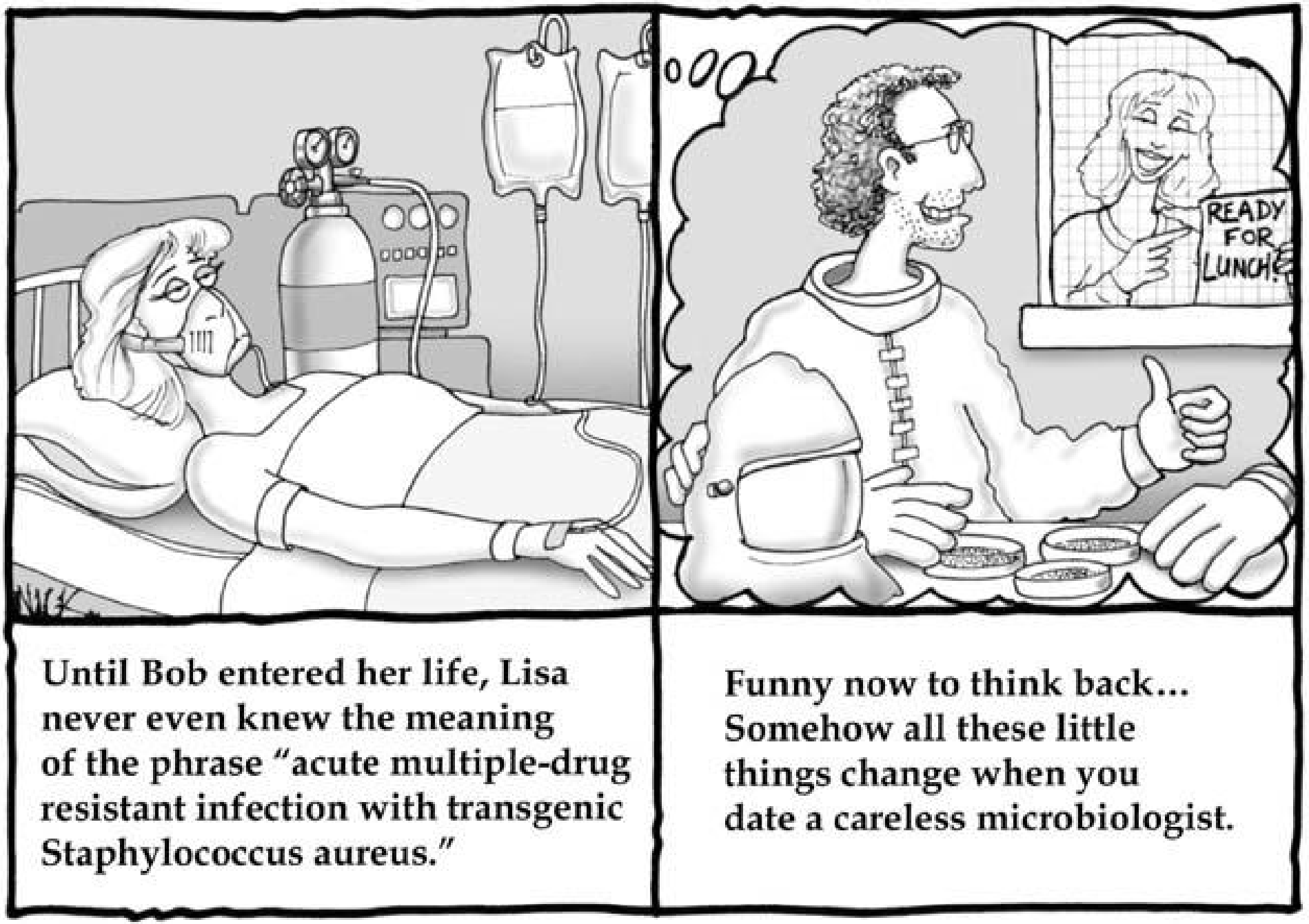
- Macrolide polyene
  - **Amphotericin B** –mimic lipids, most versatile & effective, topical & systemic treatments
  - **Nystatin** – topical treatment
- **Griseofulvin** – stubborn cases of dermatophyte infections, nephrotoxic
- Synthetic azoles – broad-spectrum; **ketoconazole, clotrimazole, miconazole**
- **Flucytosine** – analog of cytosine; cutaneous mycoses or in combination with amphotericin B for systemic mycoses

Antiparasitic drugs

- Antimalarial drugs – **quinine, chloroquinine, primaquine, mefloquine**
- Antiprotozoan drugs - **Metronidazole (Flagyl), quinicrine, sulfonamides, tetracyclines**
- Antihelminthic drugs – immobilize, disintegrate, or inhibit metabolism
  - **mebendazole, thiabendazole-** broad-spectrum – inhibit function of microtubules, interfers with glucose utilization & disables them
  - **pyrantel, piperazine-** paralyze muscles
  - **niclosamide** – destroys scolex

Antiviral drugs

- Block penetration into host cell
- Block transcription or translation
  - Nucleotide analogs
    - **Acyclovir** – herpesviruses
    - **Ribavirin**- a guanine analog – RSV, hemorrhagic fevers
    - **AZT** – thymine analog - HIV
- Prevent maturation of viral particles
  - Protease inhibitors – HIV
- Interferon - HCV



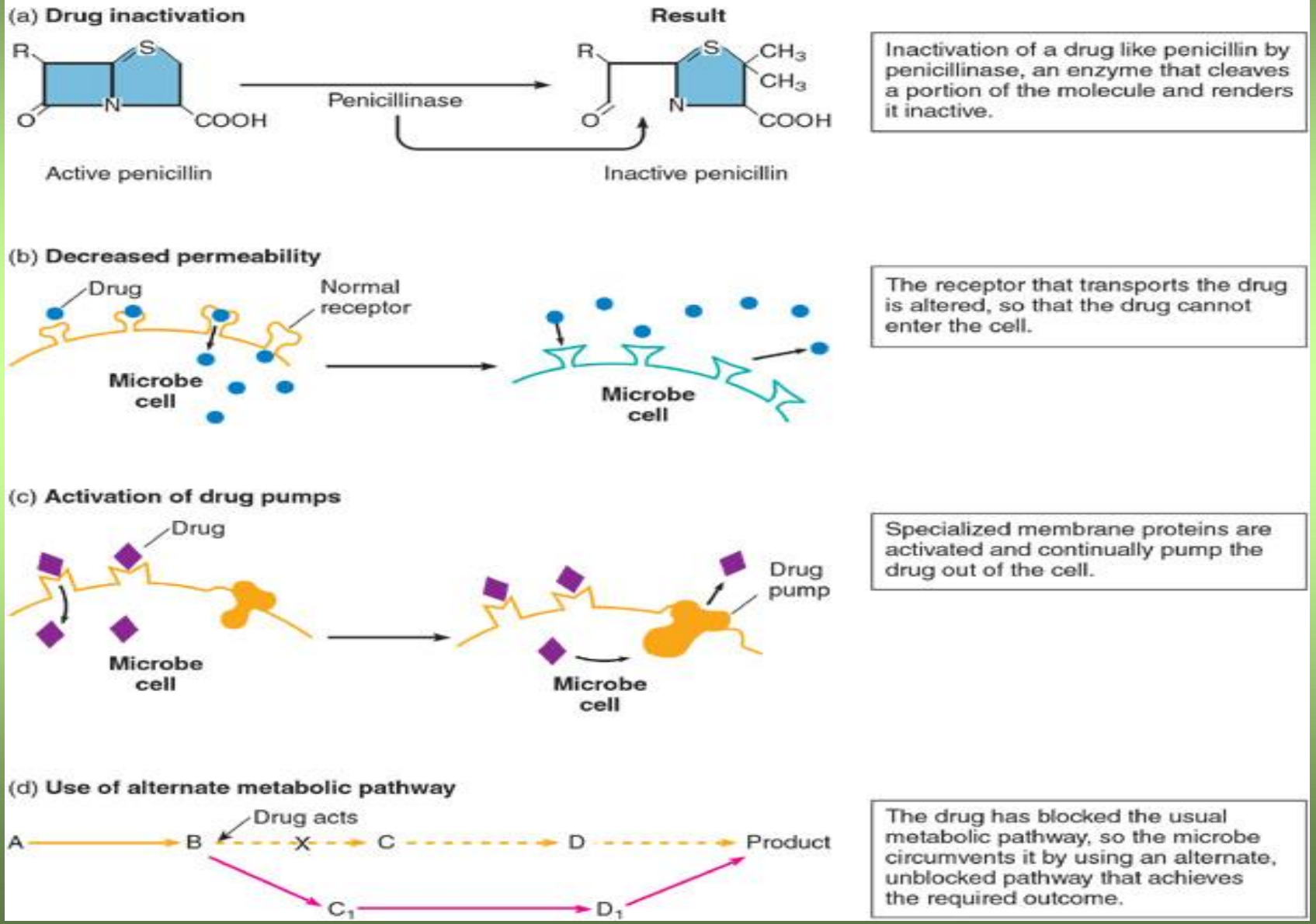
Until Bob entered her life, Lisa never even knew the meaning of the phrase "acute multiple-drug resistant infection with transgenic Staphylococcus aureus."

Funny now to think back... Somehow all these little things change when you date a careless microbiologist.

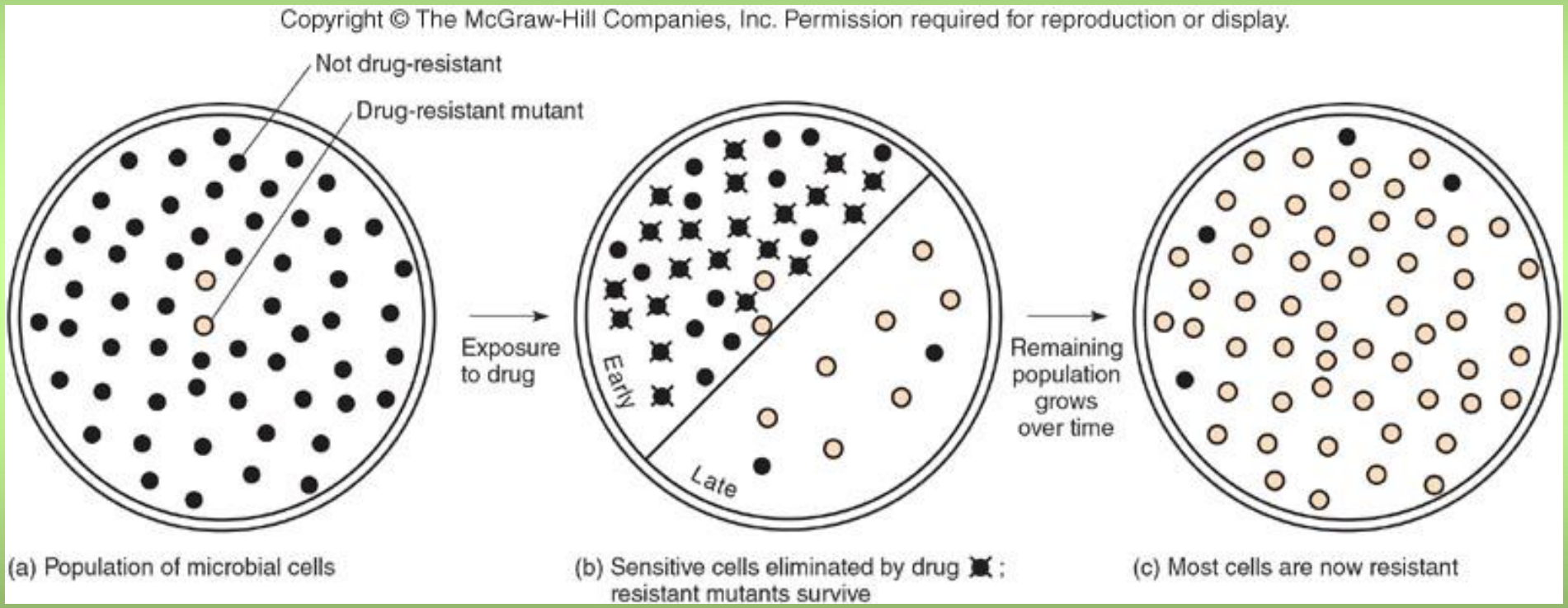
Mechanisms drug resistance

- Drug inactivation – penicillinases
- Decreased permeability to drug or increased elimination of drug from cell
- Change in metabolic patterns
- Change in drug receptors

Mechanisms drug resistance

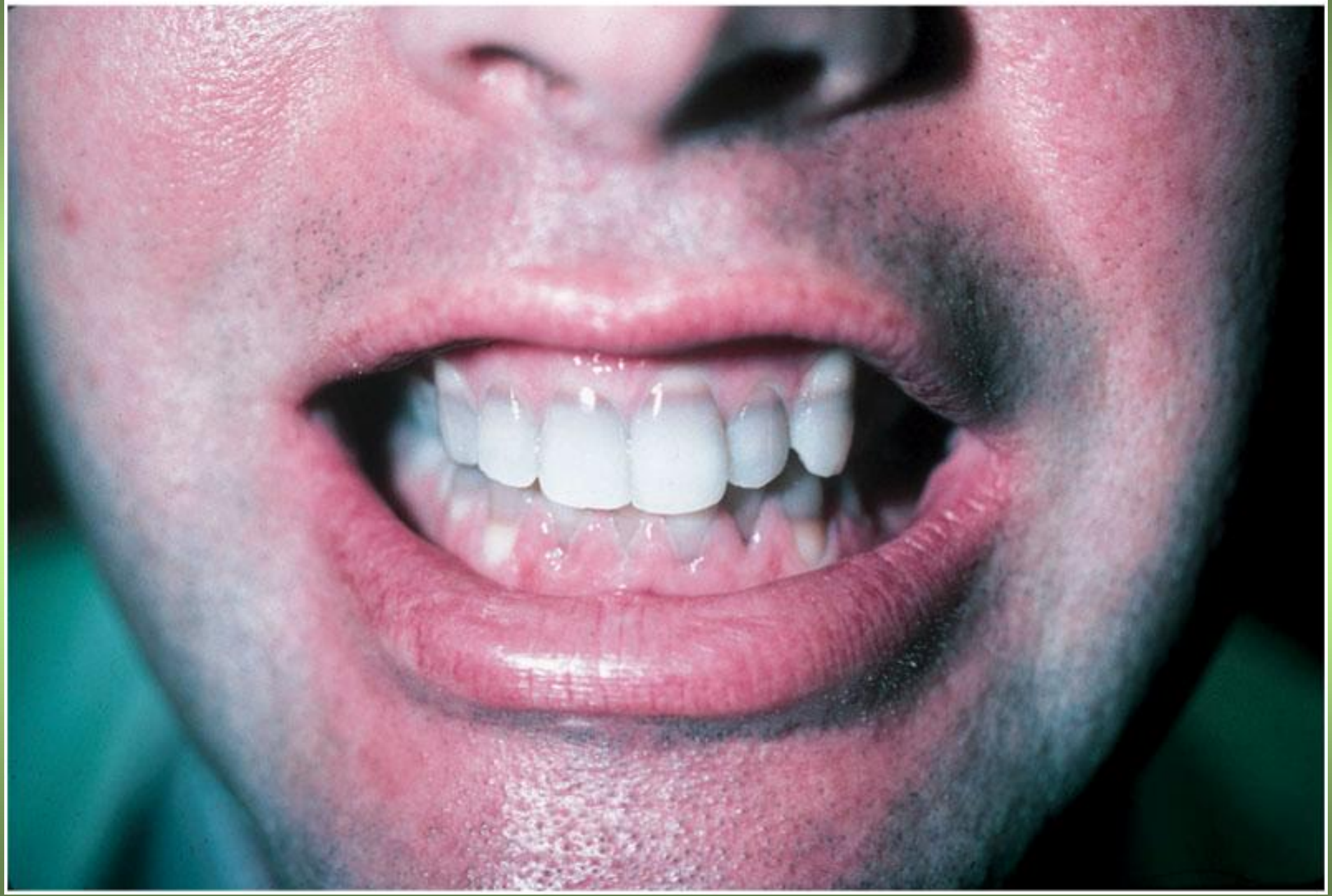


Selection for drug resistance



Side effects of drugs

1. Toxicity to organs
2. Allergic responses
3. Suppression and alteration of microflora



"WOULD YOU LIKE THAT TO BE A STEAK WITH A BROAD-SPECTRUM ANTIBIOTIC, OR ONE WITH A VARIETY OF THERAPEUTIC PROTEINS?"