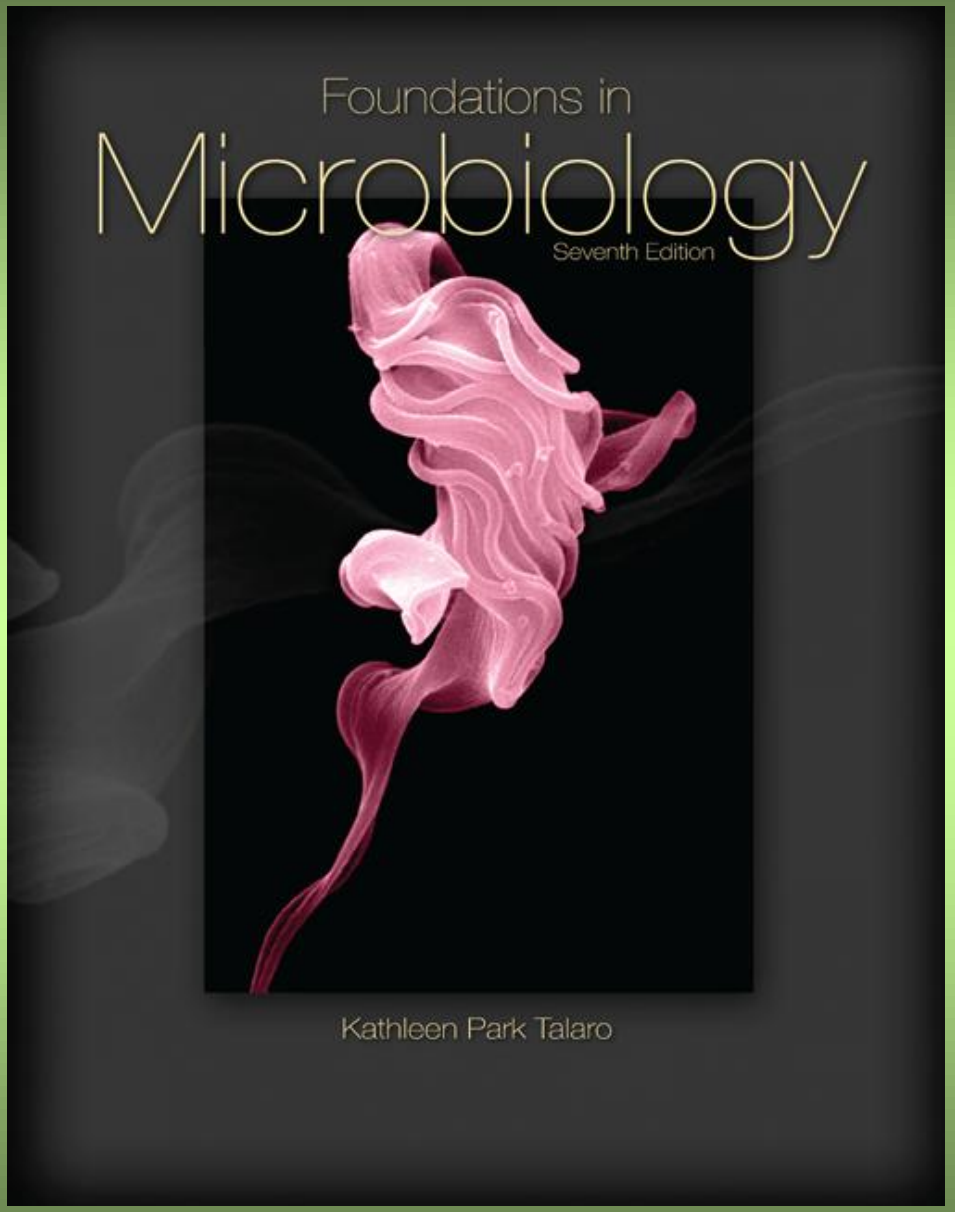
Foundations in Microbiology

Seventh Edition

Talaro

Chapter 12

Drugs, Microbes, Host – The Elements of Chemotherapy



Principles of Antimicrobial Therapy

- Administer a drug to an infected person that destroys the infective agent without harming the host's cells.
- Antimicrobial drugs are produced naturally or synthetically.

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; functions even when highly diluted in body fluids
- Remains potent long enough to act and is not broken down or excreted prematurely
- Doesn't lead 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
- Reasonably priced
- Does not disrupt the host's health by causing allergies or predisposing the host to other infections

Origins of Antimicrobial Drugs

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

Streptomyces

Interactions Between Drug and Microbe

- Antimicrobial drugs should be **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 and more side effects are seen.

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 potential for infection of a person at risk
Antimicrobial chemotherapy*	The use of chemotherapeutic drugs to control infection
Antimicrobials	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 that 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)	Antimicrobials effective against a limited array of microbial types—for example, a drug effective mainly on gram-positive bacteria
Broad spectrum (extended spectrum)	Antimicrobials effective against a wide variety of microbial types—for example, a drug effective against both gram-positive and gram-negative bacteria

* *prophylaxis* (proh″-fih-lak′-sis) Gr. *prophylassein,* to keep guard before. A process that prevents infection or disease in a person at risk.

* *chemotherapy* (kee″-moh-ther′-uh-pee) Gr. *chemieia,* chemistry, and *therapeia,* service to the sick. Use of drugs to treat disease.

* *antibiotic* (an-tee′-by-aw″-tik) Gr. *anti,* against, and *bios,* life.

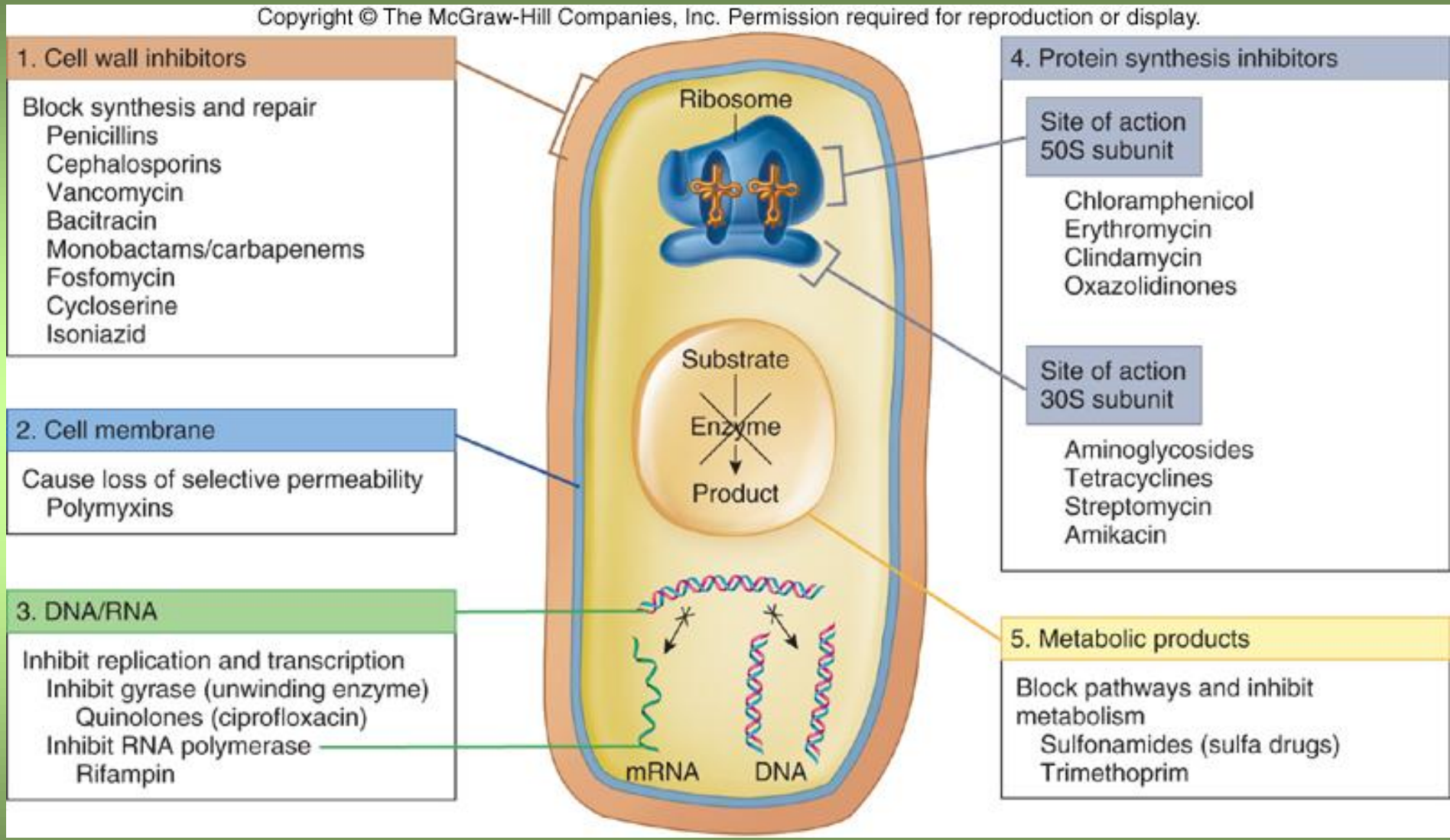
Mechanisms of Drug Action

1. Inhibition of cell wall synthesis
2. Disruption of cell membrane structure or function
3. Inhibition of nucleic acid synthesis, structure or function
4. Inhibition of protein synthesis
5. Blocks on key metabolic pathways

TABLE 12.4 Mechanisms of Drug Effects on Major Categories of Pathogens

Infectious Agent	Drug Groups/ Examples	General Targets	Outcome of Drug Action on the Microbe
Bacteria	Penicillins Penicillin, ampicillin	Cell wall synthesis	Lysis of cells
	Cephalosporins Keflex, cefotaxime	Cell wall synthesis	Lysis of cells
	Bacitracin	Cell wall	Lysis of cells
	Aminoglycosides Streptomycin Gentamicin	Prokaryotic ribosomes	Inhibit protein synthesis
	Macrolides	Various targets	
	Erythromycin	Ribosomes	Inhibit protein synthesis
	Vancomycin	Cell wall	Lysis of cells
	Tetracyclines Doxycycline	Prokaryotic ribosomes	Inhibit protein synthesis
	Chloramphenicol	Ribosomes	Inhibits protein synthesis
	Fluoroquinolones Ciprofloxacin Levofloxacin	DNA gyrase	Block replication of DNA
	Rifampin	RNA polymerase	Stops mRNA synthesis
	Sulfa drugs Sulfasoxazole	Metabolic pathway	Inhibit folic acid formation
	Trimethoprim	Metabolic pathway	Inhibits folic acid formation
Fungi	Macrolides Amphotericin B	Fungal cell membrane	Loss of selective permeability
	Azoles Miconazole Fluconazole	Fungal cell membrane	Loss of selective permeability
	Flucytosine	Fungal DNA and RNA synthesis	Stops cell reproduction
Protozoa	Quinines Chloroquine Mefloquine	Nutrition of the malaria parasite	Buildup of toxic wastes in the parasite's cells
	Metronidazole	Anaerobic cells	Buildup of toxic free radicals
Helminths	Bendazoles	Microtubules	Inhibit glucose metabolism
	Diethylcarbamide	Unknown	Kills larval forms
	Piperazine	Worm muscles	Worm is expelled.
	Niclosamide	ATP formation	Loosens worm hold
	Ivermectin	Nerve transmission	Worm is expelled.
Viruses	Amantidine	Host cell membrane	Blocks entry, fusion
	Cyclovirs	DNA synthesis	Stop virus replication
	Azidothymidine	Reverse transcriptase	Blocks DNA formation

Figure 12.2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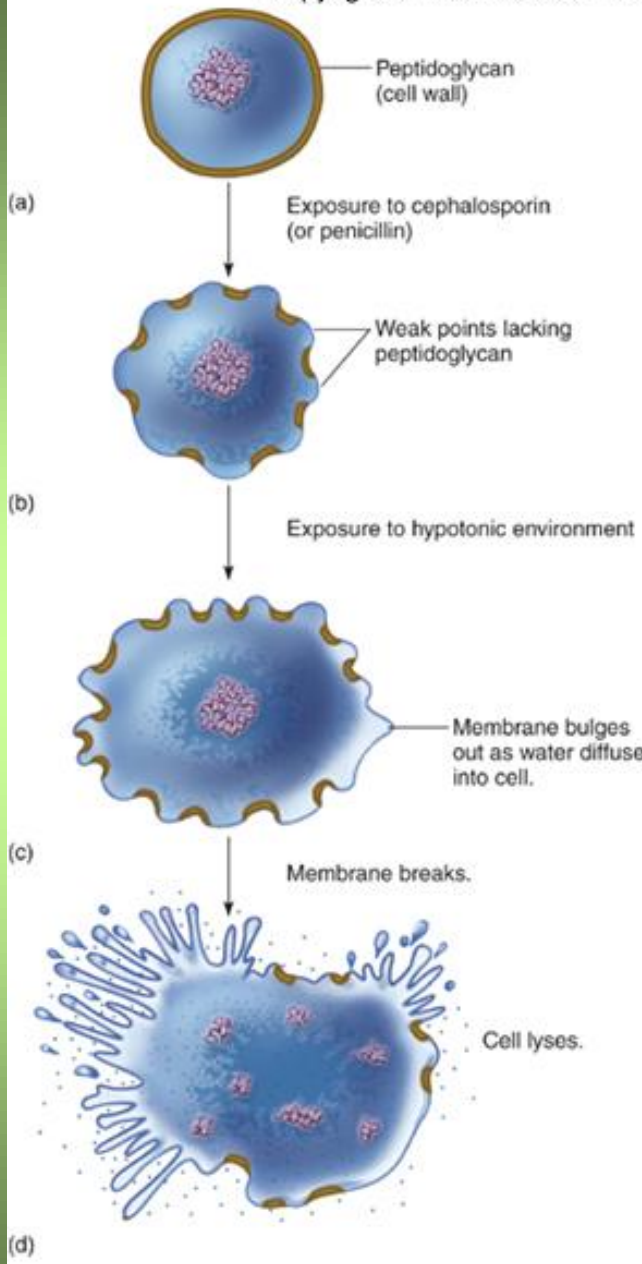
1. Cell wall inhibitors
Block synthesis and repair
Penicillins
Cephalosporins
Vancomycin
Bacitracin
Monobactams/carbapenems
Fosfomycin
Cycloserine
Isoniazid
2. Cell membrane
Cause loss of selective permeability
Polymyxins
3. DNA/RNA
Inhibit replication and transcription
Inhibit gyrase (unwinding enzyme)
Quinolones (ciprofloxacin)
Inhibit RNA polymerase
Rifampin
Ribosome
Substrate
Enzyme
Product
mRNA
DNA
4. Protein synthesis inhibitors
Site of action
50S subunit
Chloramphenicol
Erythromycin
Clindamycin
Oxazolidinones
Site of action
30S subunit
Aminoglycosides
Tetracyclines
Streptomycin
Amikacin
5. Metabolic products
Block pathways and inhibit metabolism
Sulfonamides (sulfa drugs)
Trimethoprim

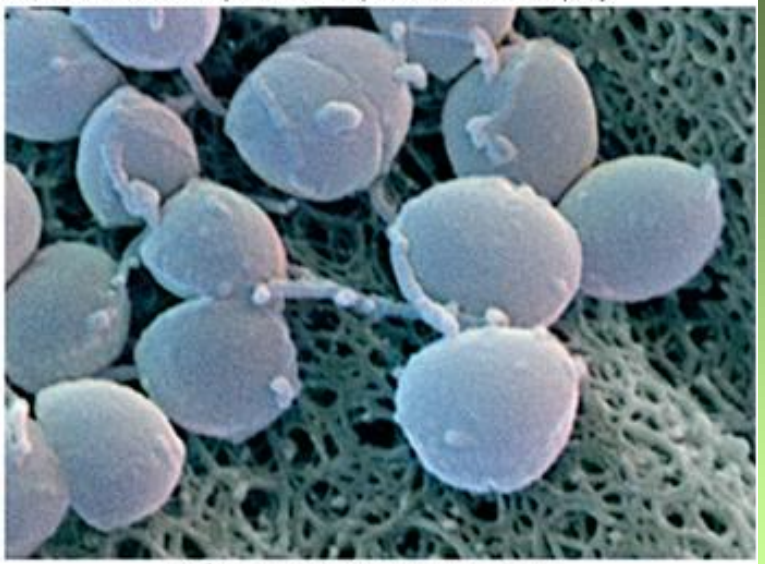
The Spectrum of an Antimicrobic Drug

- Spectrum – range of activity of a drug
  - **narrow-spectrum** – effective on a small range of microbes
    - target a specific cell component that is found only in certain microbes
  - **broad-spectrum** – greatest range of activity
    - target cell components common to most pathogens

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.

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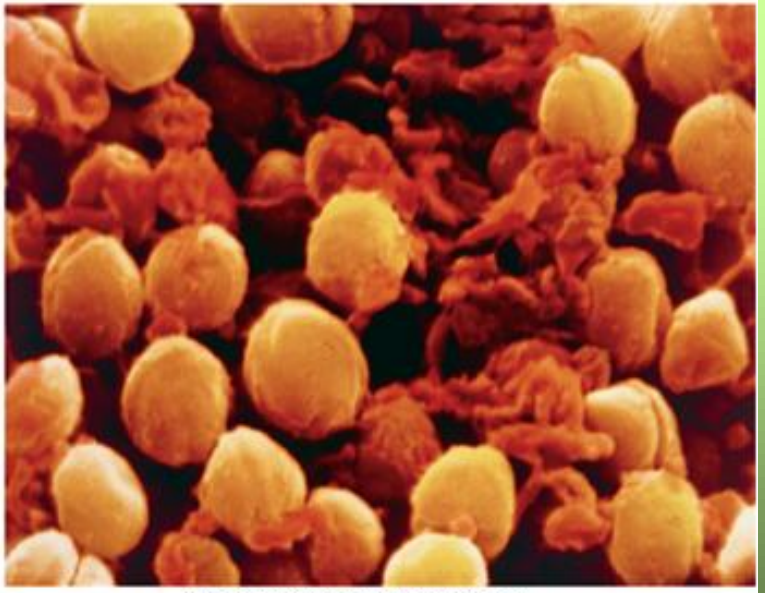
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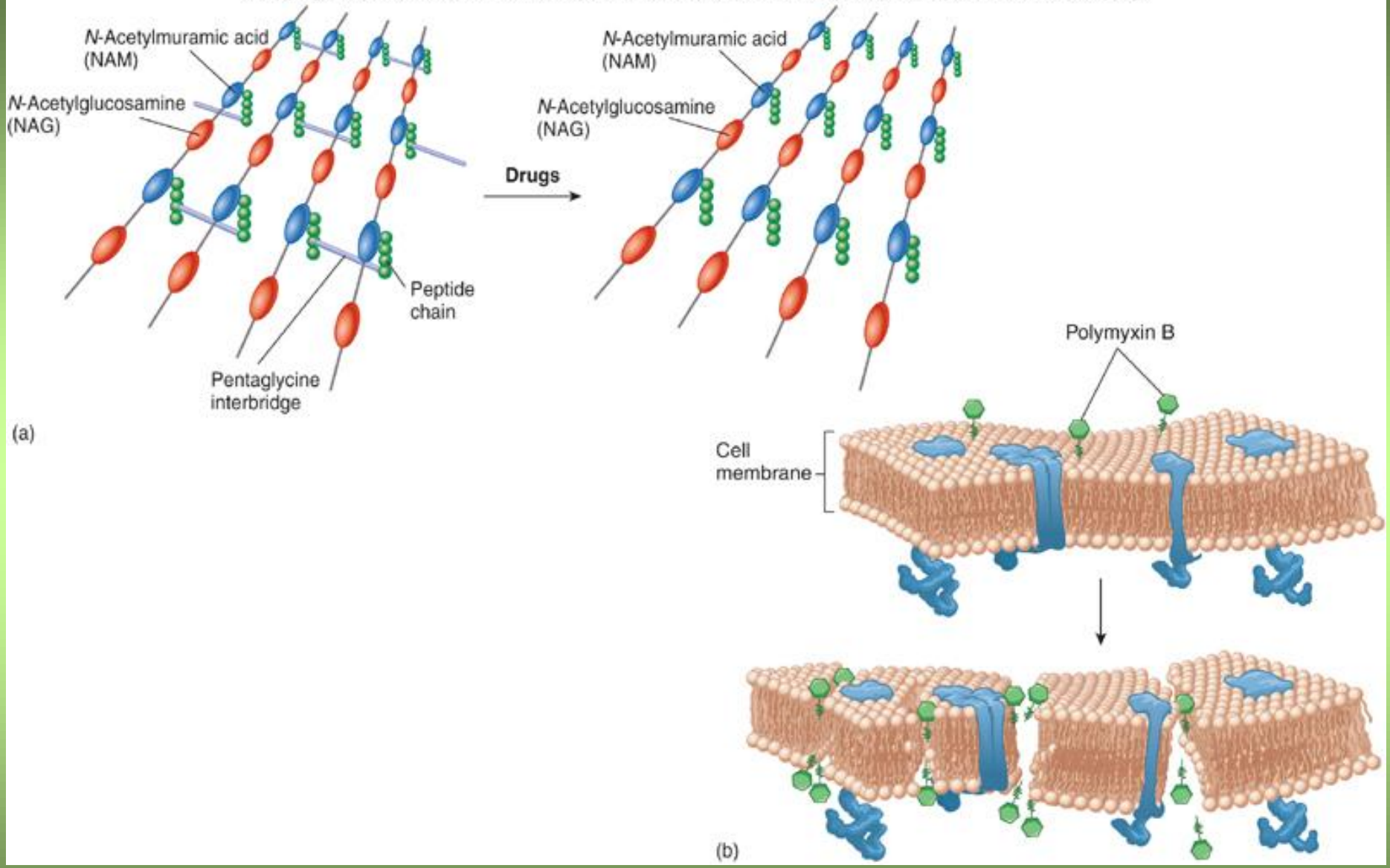
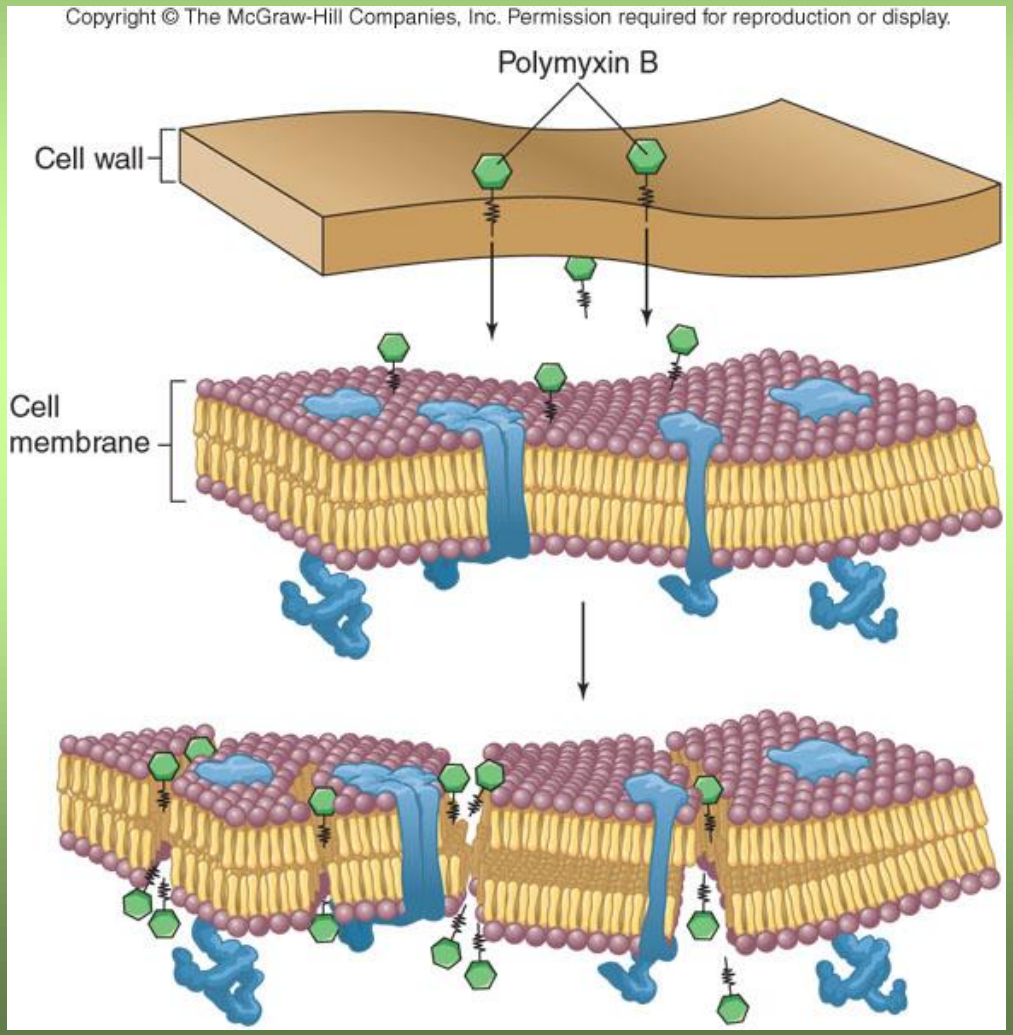


2. Drugs that disrupt cell membrane function

- 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.

2. Drugs that disrupt cell membrane function



3. Drugs That Inhibit Nucleic Acid Synthesis

- May block synthesis of nucleotides, inhibit replication, or stop transcription
- Chloroquine binds and cross-links the double helix; quinolones inhibit DNA helicases.
- Antiviral drugs that are analogs of purines and pyrimidines insert in viral nucleic acid, preventing replication.

4.Drugs That Block Protein Synthesis

- Ribosomes of eucaryotes differ in size and structure from procaryotes; antimicrobics usually have a selective action against procaryotes; can also damage the eucaryotic mitochondria
- Aminoglycosides (streptomycin, gentamycin) 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.

4. Drugs that block protein synthesis

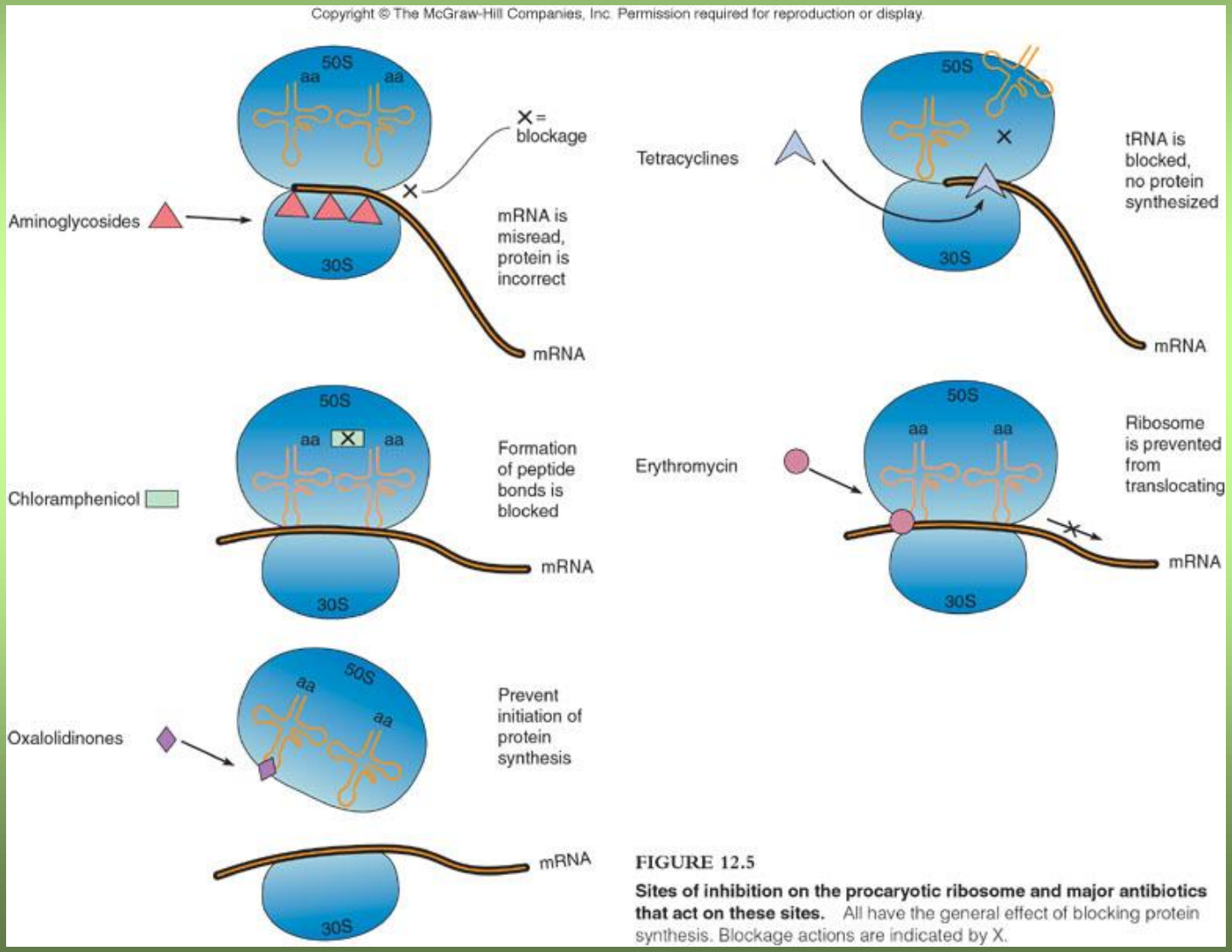


FIGURE 12.5

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.

5. Drugs that Affect Metabolic Pathways

- Sulfonamides and trimethoprim block enzymes required for tetrahydrofolate synthesis needed for DNA and 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

Survey of Major Antimicrobial Drug Groups

- Antibacterial drugs
  - antibiotics
  - synthetic drugs
- Antifungal drugs
- Antiprotozoan drugs
- Antiviral drugs

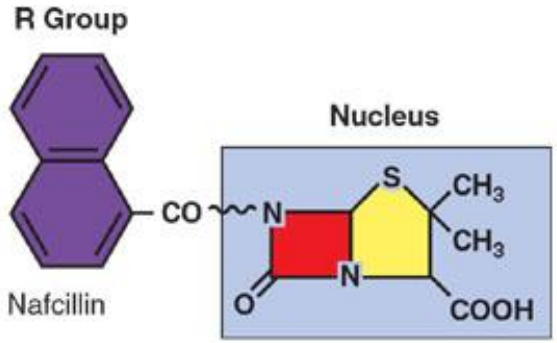
About 260 different antimicrobial drugs are classified in 20 drug families.

Antibacterial antibiotics

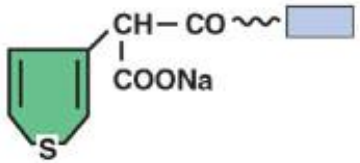
- Penicillins
- Cephalosporins
- Other beta-lactam antibiotics
- Aminoglycosides
- Tetracycline antibiotics
- Chloramphenicol
- Other *Streptomyces* antibiotics
- The *Bacillus* antibiotics
- New classes

- Beta-lactam antimicrobials - all contain a highly reactive 3 carbon, 1 nitrogen ring
- Primary mode of action is to interfere with cell wall synthesis.
- Greater than ½ of all antimicrobic drugs are beta-lactams.
- Penicillins and cephalosporins most prominent beta-lactams

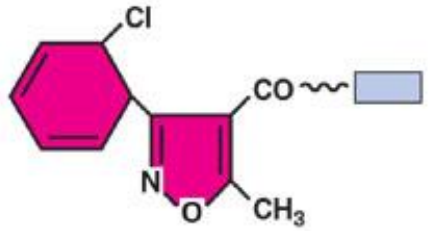
Penicillins



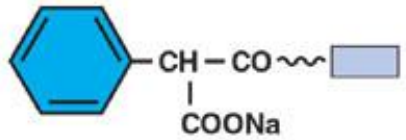
Nafcillin



Ticarcillin



Cloxacillin



Carbenicillin

TABLE 12.5

Characteristics of Selected Penicillin Drugs

Name	Spectrum of Action	Uses, Advantages	Disadvantages
Penicillin G	Narrow	Best drug of choice when bacteria are sensitive; low cost; low toxicity	Can be hydrolyzed by penicillinase; allergies occur; requires injection
Penicillin V	Narrow	Good absorption from intestine; otherwise, similar to penicillin G	Hydrolysis by penicillinase; allergies
Oxacillin, dicloxacillin	Narrow	Not susceptible to penicillinase; good absorption	Allergies; expensive
Methicillin, nafcillin	Narrow	Not usually susceptible to penicillinase	Poor absorption; allergies; growing resistance
Ampicillin	Broad	Works on gram-negative bacilli	Can be hydrolyzed by penicillinase; allergies; only fair absorption
Amoxicillin	Broad	Gram-negative infections; good absorption	Hydrolysis by penicillinase; allergies
Carbenicillin	Broad	Same as ampicillin	Poor absorption; used only parenterally
Azlocillin, mezlocillin ticarcillin	Very broad	Effective against *Pseudomonas* species; low toxicity compared with aminoglycosides	Allergies, susceptible to many beta-lactamases

Penicillins Video

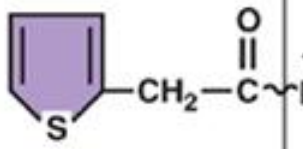
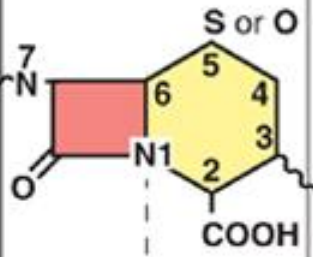
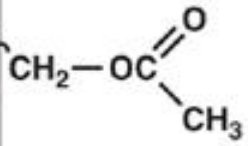
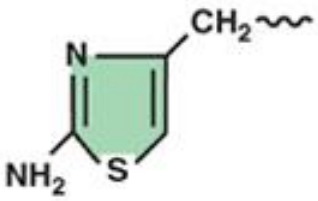
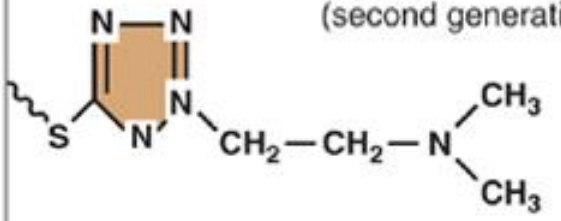
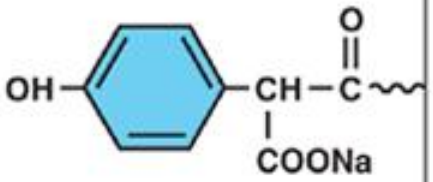
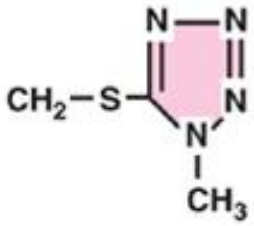
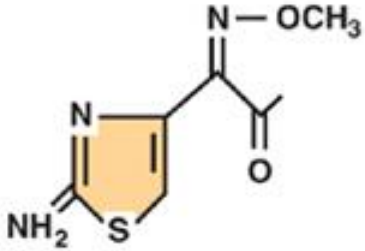
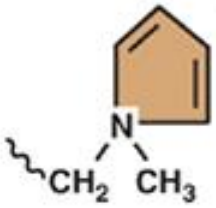
- Penicillins G and V most important natural forms
- Penicillin is the drug of choice for gram-positive cocci (streptococci) and some gram-negative bacteria (meningococci and syphilis spirochete)
- Semisynthetic penicillins – **ampicillin**, carbenicillin & amoxicillin have broader spectra – gram negative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

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
- Generic names have root – *cef*, *ceph*, or *kef*.

Cephalosporins

- 4 generations exist: each group more effective against Gram-negatives than the one before with improved dosing schedule and fewer side effects
  - **first generation** – cephalothin, cefazolin – most effective against Gram-positive cocci and few Gram-negative
  - **second generation** – cefaclor, cefonacid – more effective against Gram-negative bacteria
  - **third generation** – cephalexin, ceftriaxone – broad-spectrum activity against enteric bacteria with beta-lactamases
  - **fourth generation** – cefepime – widest range; both Gram-negative and Gram-positive

R Group 1	Basic Nucleus	R Group 2
		Cephalothin (first generation*) 
	2nd	Cefotiam (second generation) 
	3rd	Moxalactam (third generation) 
	4th	Cefepime (fourth generation) 

*New improved versions of drugs are referred to as new "generations."

Additional Beta-lactam Drugs

- Carbapenems
  - **imipenem** – broad-spectrum drug for infections with aerobic and anaerobic pathogens; low dose, administered orally with few side effects
- Monobactams
  - aztreonam –newer narrow-spectrum drug for infections by Gram-negative aerobic bacilli; may be used by people allergic to penicillin

Non Beta-lactam Cell Wall Inhibitors

- **vancomycin** – narrow-spectrum, most effective in treatment of Staphylococcal infections in cases of penicillin and methicillin resistance or if patient is allergic to penicillin; toxic and hard to administer; restricted use
- bacitracin – narrow-spectrum produced by a strain of *Bacillus subtilis*; used topically in ointment
- **isoniazid** (INH) – works by interfering with mycolic acid synthesis; used to treat infections with *Mycobacterium tuberculosis;* oral doses in combination with other antimicrobials such as rifampin, ethambutol

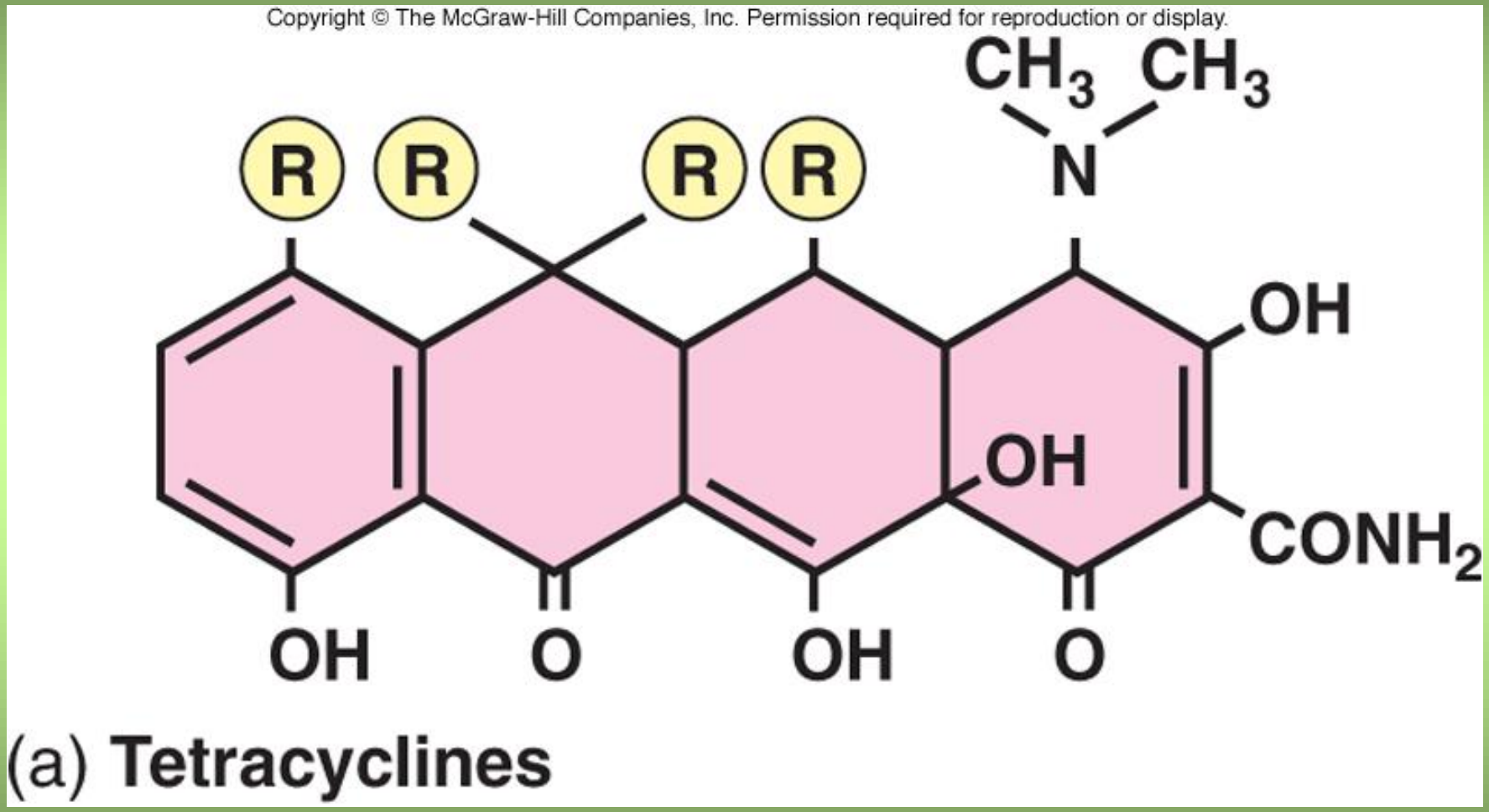
Drugs That Interfere with Protein Synthesis

- **Aminoglycosides** – composed of 2 or more amino sugars and an aminocyclitol (6C) ring; binds ribosomal subunit
- Products of various species of soil actinomycetes in genera *Streptomyces* and *Micromonospora*
- Broad-spectrum, inhibit protein synthesis, especially useful against aerobic Gram-negative rods and certain gram-positive bacteria
  - **streptomycin** – bubonic plague, tularemia, TB
  - **gentamicin** – less toxic, used against Gram-negative rods
  - newer – **tobramycin** and **amikacin** Gram-negative bacteria

Tetracycline Antibiotics

- Broad-spectrum, block protein synthesis by binding ribosomes
- Aureomycin, terramycin, tetracycline, doxycycline and minocycline – low cost oral drugs; side effects are a concern
- Treatment for STDs, Rocky Mountain spotted fever, Lyme disease, typhus, acne and protozoa

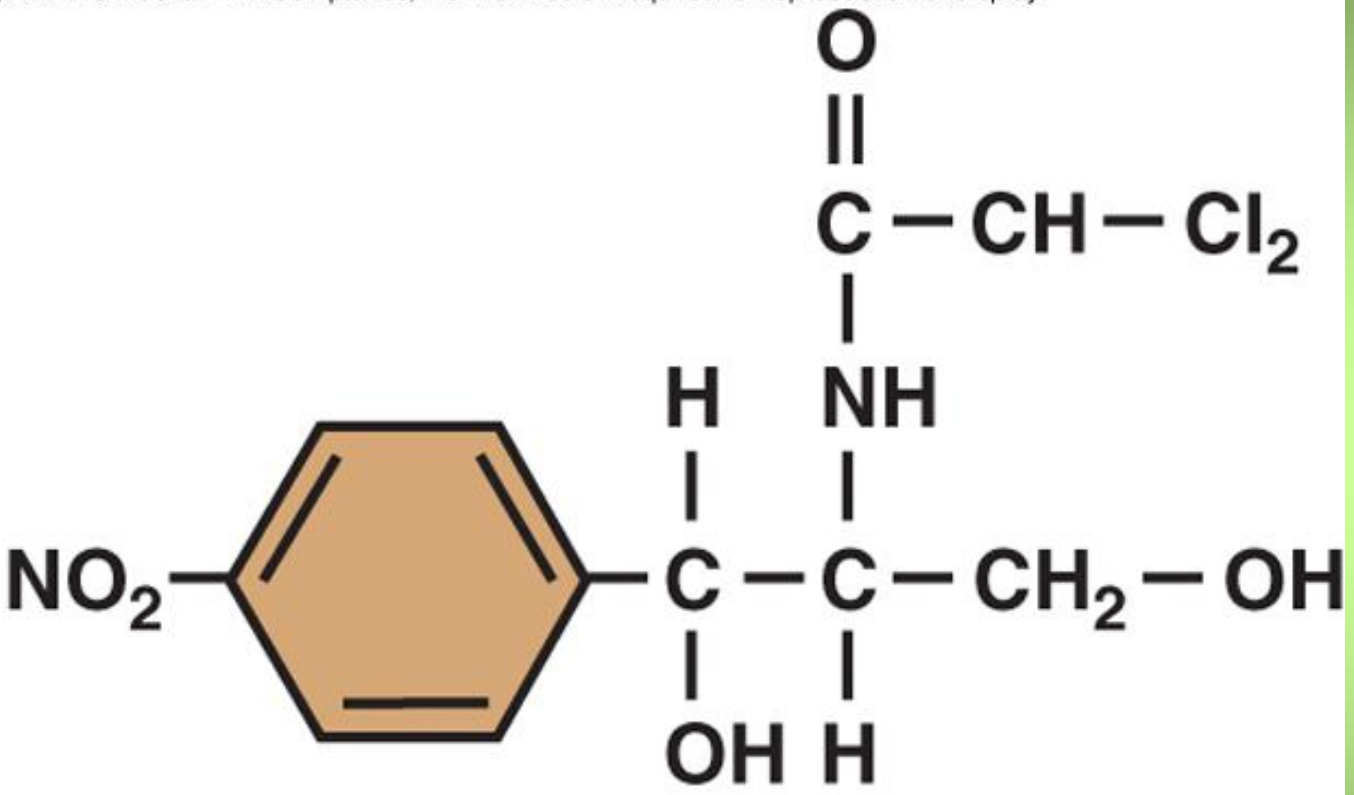
Figure 12.10 (a)



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

Figure 12.10 (b)

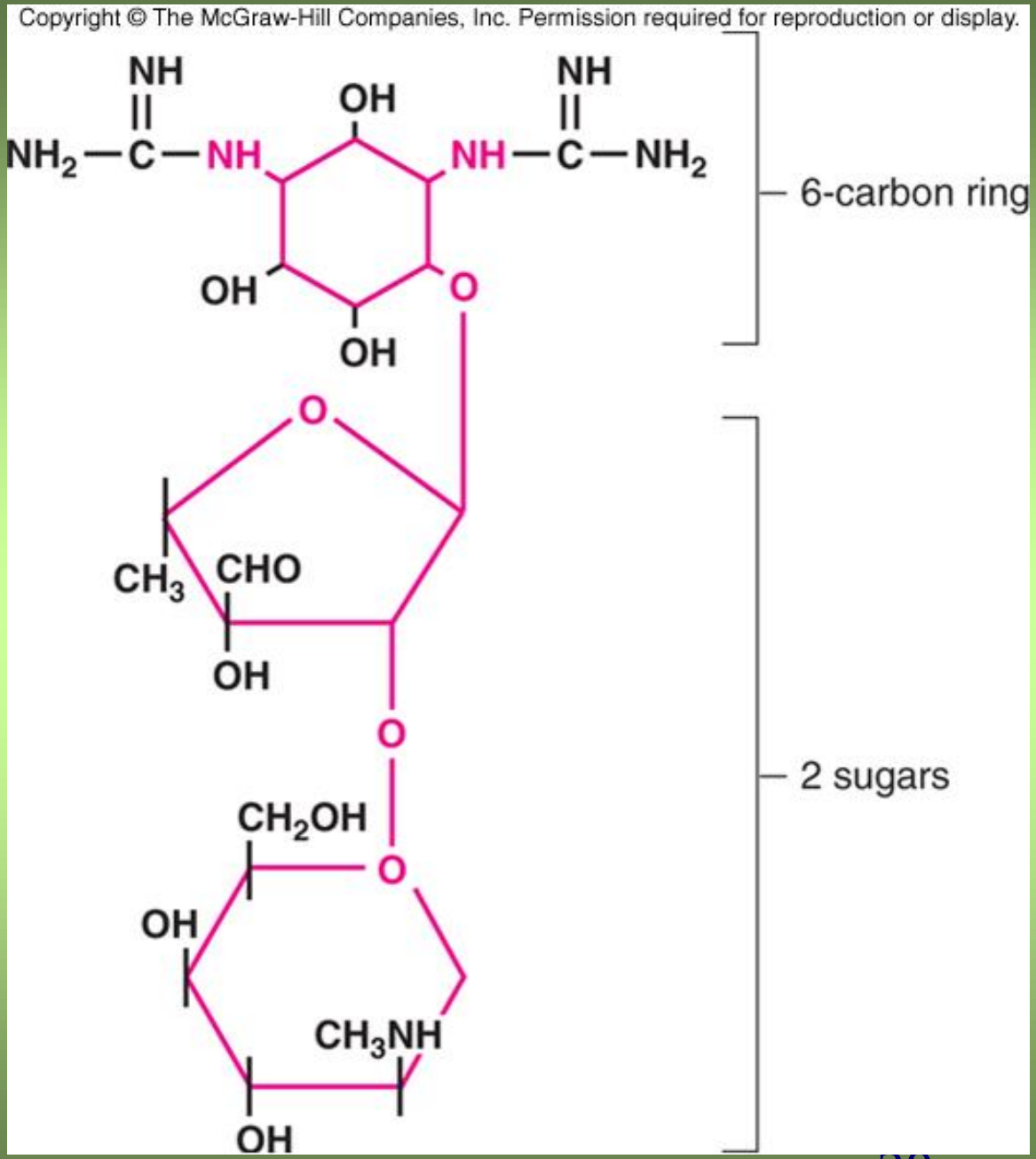


(b) **Chloramphenicol**

Drugs that Act on DNA or RNA

- Fluoroquinolones – work by binding to DNA gyrase and topoisomerase IV
  - Broad spectrum effectiveness
- Concerns have arisen regarding the overuse of quinoline drugs
  - CDC is recommending careful monitoring of their use to prevent ciprofloxacin-resistant bacteria

Figure 12.9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NH
NH2 — C — NH
OH
NH
NH — C — NH2
OH
OH
O
6-carbon ring
O
CH3
CHO
OH
O
CH2OH
O
OH
CH3NH
OH
2 sugars

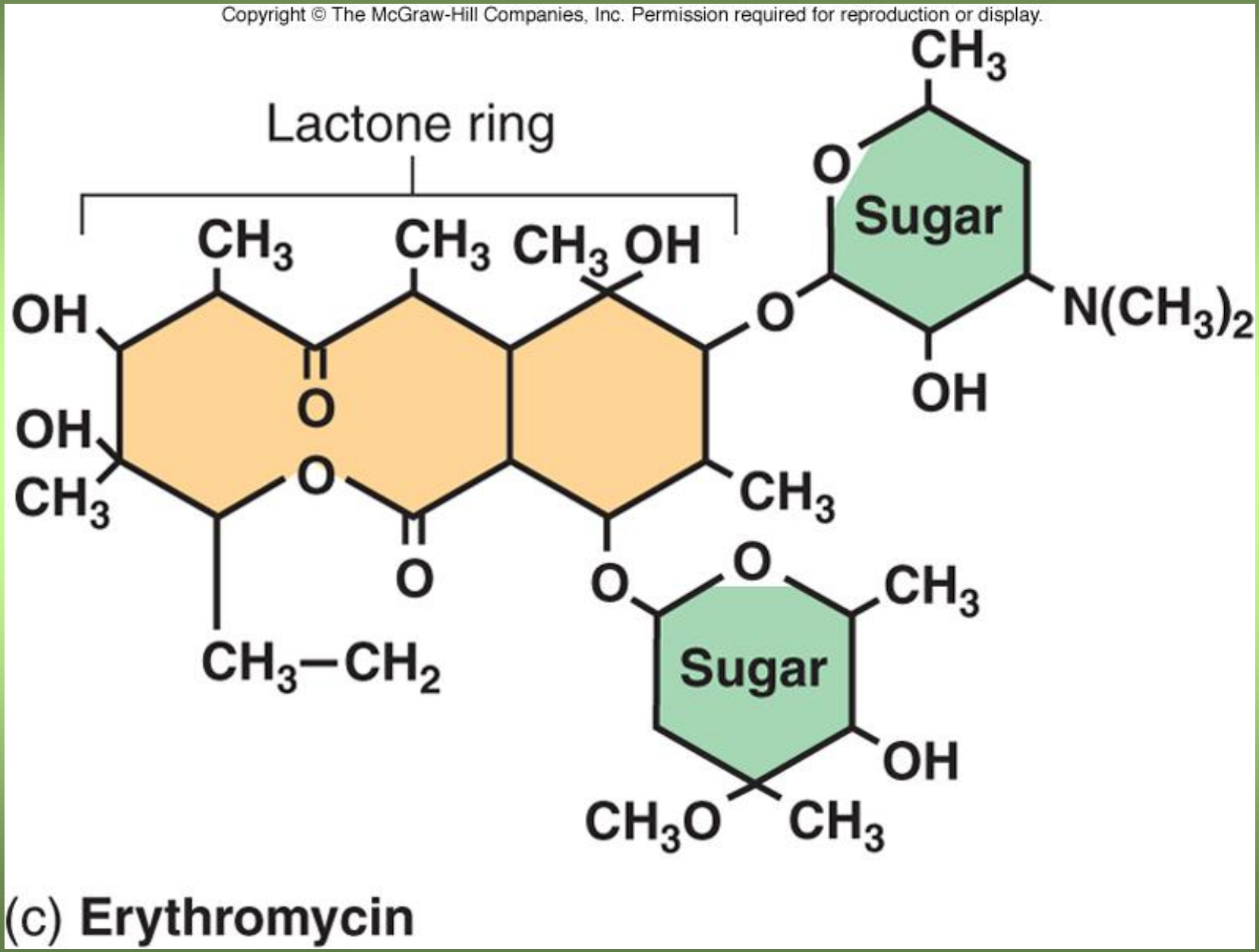
Drugs That Interfere with Protein Synthesis

- Aminoglycosides – composed of one or more amino sugars and an aminocyclitol (6C) ring; binds ribosomal subunit
- Products of various species of soil actinomycetes in genera *Streptomyces* and *Micromonospora*
- Broad-spectrum, inhibit protein synthesis, especially useful against aerobic gram-negative rods and certain gram-positive bacteria
  - Streptomycin – bubonic plague, tularemia, TB
  - Gentamicin – less toxic, used against gram-negative rods
  - Newer – tobramycin and amikacin gram-negative bacteria

Macrolides and Related Antibiotics

- Erythromycin –large lactone ring with sugars; attaches to ribosomal 50s subunit
- Broad-spectrum, fairly low toxicity
- Taken orally for Mycoplasma pneumonia, legionellosis, Chlamydia, pertussis, diphtheria and as a prophylactic prior to intestinal surgery
- For penicillin-resistant – gonococci, syphilis, acne
- Newer semi-synthetic macrolides – clarithomycin, azithromycin

Figure 12.10 (c)



(c) **Erythromycin**

Drugs that Affect Metabolic Pathways

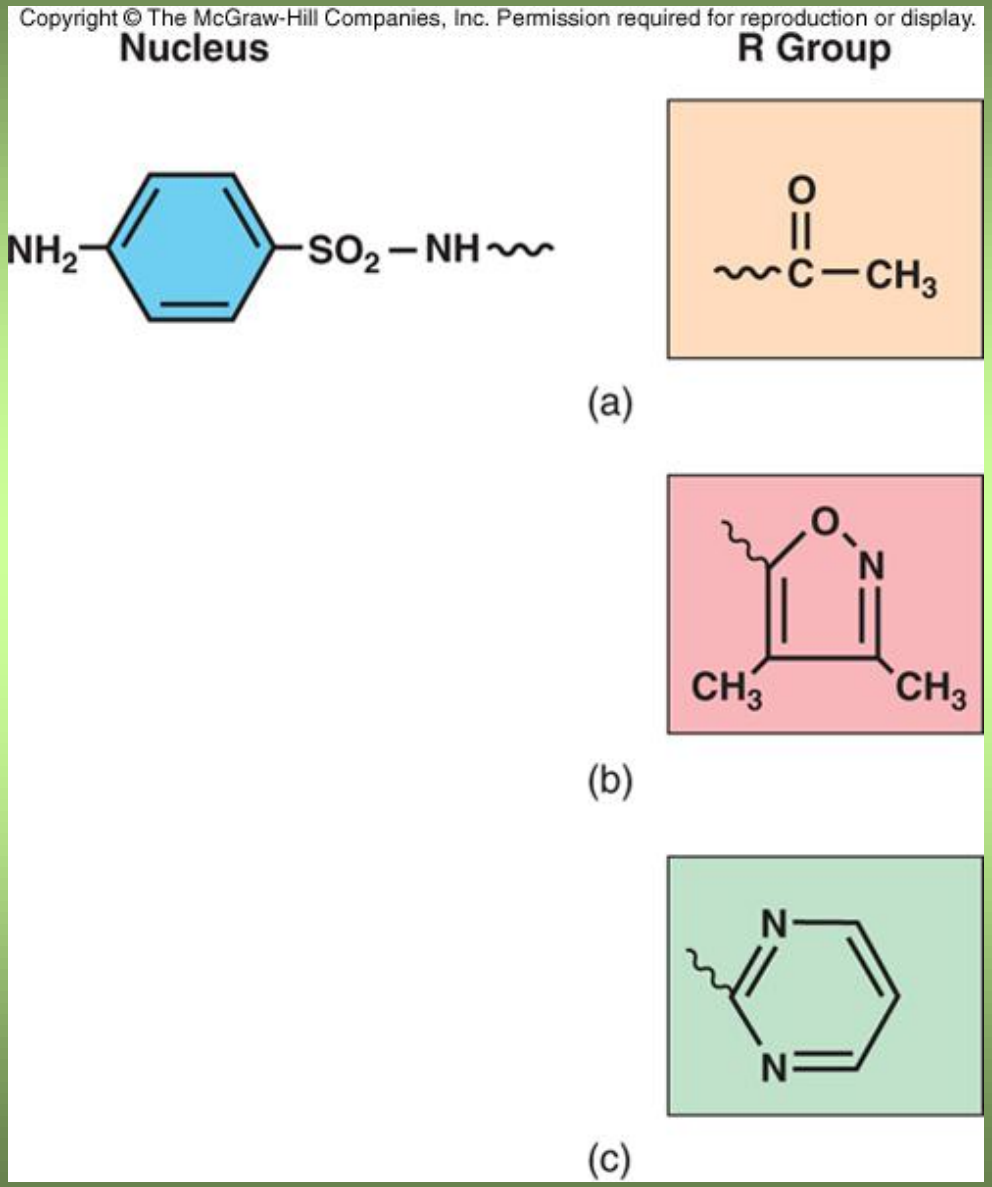
- Sulfonamides and trimethoprim block enzymes required for tetrahydrofolate synthesis needed for DNA and RNA synthesis.

- **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

Drugs That Block Metabolic Pathways

- Most are synthetic; most important are sulfonamides, or sulfa drugs - first antimicrobic drugs
- Narrow-spectrum; block the synthesis of folic acid by bacteria
  - sulfisoxazole – shigellosis, UTI, protozoan infections
  - silver sulfadiazine –burns, eye infections
  - trimethoprim – given in combination with sulfamethoxazole – UTI, PCP

Figure 12.11 Structure of sulfonamides



Newly Developed Classes of Antimicrobials

- Formulated from pre-existing drug classes
- Three new drug types:
  - Fosfomycin trimethamine – a phosphoric acid effective as alternate treatment for UTIs; inhibits cell wall synthesis
  - Synercid – effective against *Staphylococcus* and *Enterococcus* that cause endocarditis and surgical infections; used when bacteria is resistant to other drugs; inhibits protein synthesis
  - Daptomycin – directed mainly against gram-positive; disrupts membrane function

Newly Developed Classes of Antimicrobials

- Ketolides – telitromycin (Ketek), new drug with different ring structure from Erythromycin; used for infection when resistant to macrolides
- Oxazolidinones – linezolid (Zyvox); synthetic antimicrobial that blocks the interaction of mRNA and ribosome
  - Used to treat methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant *Enterococcus* (VRE)

Agents to Treat Fungal Infections

- Fungal cells are eukaryotic; a drug that is toxic to fungal cells also toxic to human cells
- Five antifungal drug groups:
  - Macrolide polyene
    - Amphotericin B – mimic lipids, most versatile and effective, topical and 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
  - Echinocandins – damage cell walls; capsofungin

Antiparasitic Chemotherapy

- 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, interferes with glucose utilization and disables them
  - Pyrantel, piperazine – paralyze muscles
  - Niclosamide – destroys scolex

Antiviral Chemotherapeutic Agents

- Selective toxicity is almost impossible due to obligate intracellular parasitic nature of viruses
- Block penetration into host cell
- Block replication, transcription, or translation of viral genetic material
  - Nucleotide analogs
    - Acyclovir – herpesviruses
    - Ribavirin – a guanine analog – RSV, hemorrhagic fevers
    - AZT – thymine analog – HIV
- Prevent maturation of viral particles
  - Protease inhibitors – HIV

TABLE 12.6 Actions of Selected Antiviral Drugs*

I. Inhibition of Virus Entry or Release

① **Fuzeon**

Polypeptide of 36 amino acids (trade secret)

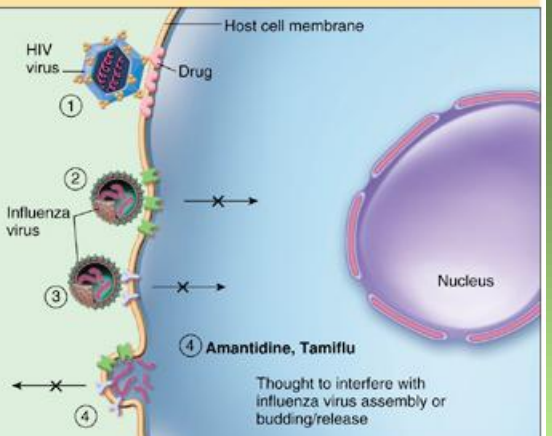
Blocks HIV infection by preventing binding of viral GP-41 receptors to cell receptor, thereby preventing fusion of virus with cell

② **Amantidine** and relatives

Block entry of influenza virus by interfering with fusion of virus with cell membrane (also release)

③ **Tamiflu, Relenza**

Stop the actions of influenza neuraminidase, required for entry of virus into cell



II. Inhibition of Nucleic Acid Synthesis

⑤ **Acyclovir,** other "cyclovirs"

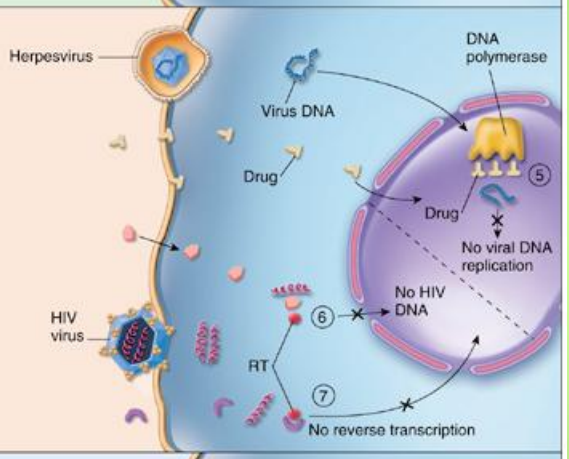
Terminates DNA replication in herpesviruses

⑥ **Nucleotide analog reverse transcriptase (RT) inhibitors (zidovudine–AZT) see 8 for comparison**

Stop the action of reverse transcriptase in HIV, blocking viral DNA production

⑦ **Non-nucleoside reverse transcriptase inhibitors (nevirapine) see 8 for comparison**

Attach to HIV RT binding site, stopping its action

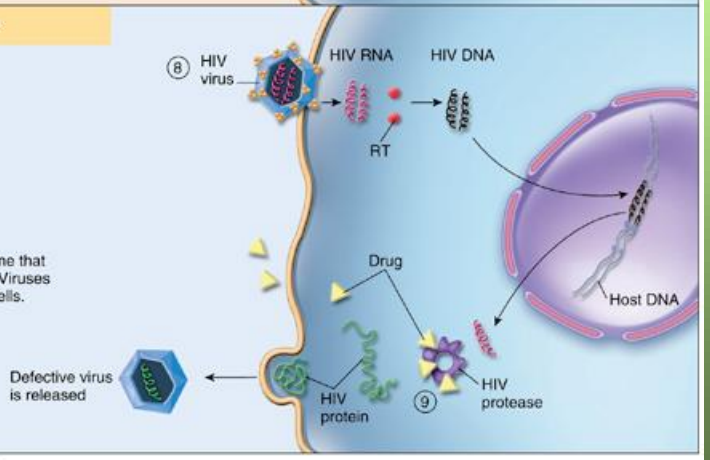


III. Inhibition of Effective Viral Assembly/Release

⑧ **Normal HIV binding and replication for comparison with 6, 7, and 9.**

⑨ **Protease inhibitors**
Saquinavir (Fortovase)
Ritonavir (Norvir)

These insert onto HIV protease, an enzyme that clips viral proteins into functional pieces. Viruses are defective and unable to infect other cells.



*Details of viral cycles are omitted for ease in observing drug effects.

Drugs for Treating Influenza

- Amantadine, rimantidine – restricted almost exclusively to influenza A viral infections; prevent fusion of virus with cell membrane
- Relenza and tamiflu – slightly broader spectrum; blocks neuraminidase in influenza A and B

Antiherpes Drugs

- Many antiviral agents mimic the structure of nucleotides and compete for sites on replicating DNA
  - Acyclovir – Zovirax
  - Valacyclovir – Valtrex
  - Famiciclovir – Famvir
  - Peniciclovir – Denavir
- Oral and topical treatments for oral and genital herpes, chickenpox, and shingles

Drugs for Treating HIV Infections and AIDS

- Retrovirus offers 2 targets for chemotherapy:
  - Interference with viral DNA synthesis from viral RNA using nucleoside reverse transcriptase inhibitors (nucleotide analogs)
  - Interference with synthesis of DNA using nonnucleoside reverse transcriptase inhibitors

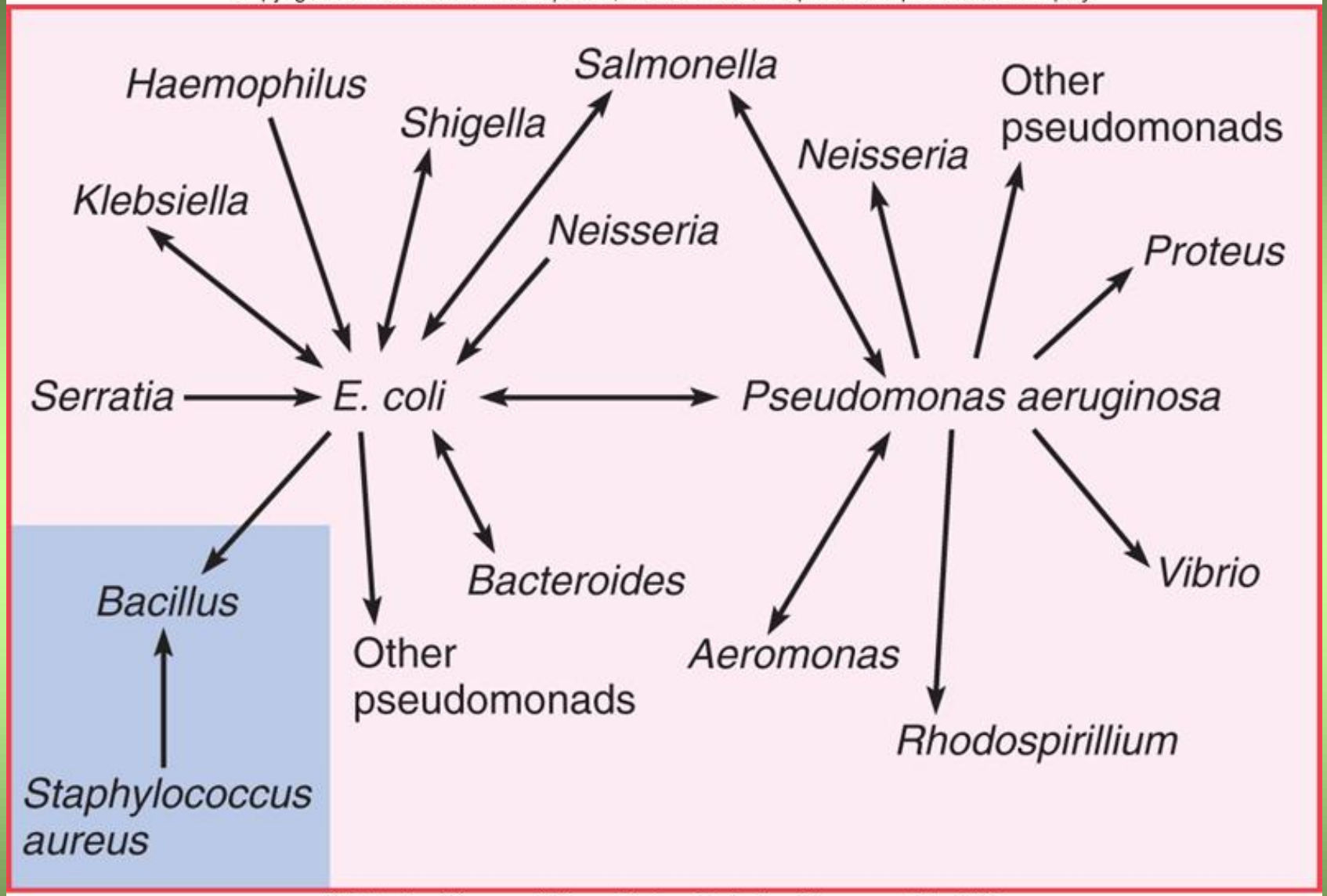
Azidothymidine (AZT) – first drug aimed at treating AIDS, thymine analog

Interferons (INF)

- Human-based glycoprotein produced primarily by fibroblasts and leukocytes
- Therapeutic benefits include:
  - Reduces healing time and some complications of infections
  - Prevents or reduces symptoms of cold and papillomavirus
  - Slows the progress of certain cancers, leukemias, and lymphomas
  - Treatment of hepatitis C, genital warts, Kaposi's sarcoma

12.4 The Acquisition of Drug Resistance

- Adaptive response in which microorganisms begin to tolerate an amount of drug that would ordinarily be inhibitory; due to genetic versatility or variation; intrinsic and acquired
- Acquired resistance:
  - Spontaneous mutations in critical chromosomal genes
  - Acquisition of new genes or sets of genes via transfer from another species
    - Originates from resistance factors (plasmids) encoded with drug resistance, transposons

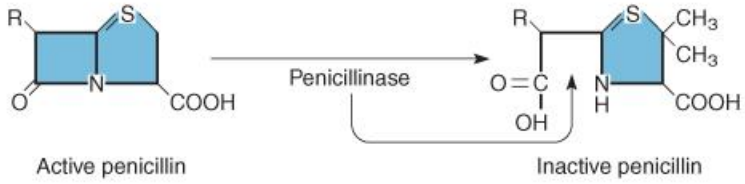


© Data from Young and Mayer, Review of Infectious Diseases, 1:55, 1979.

Mechanisms of Drug Resistance

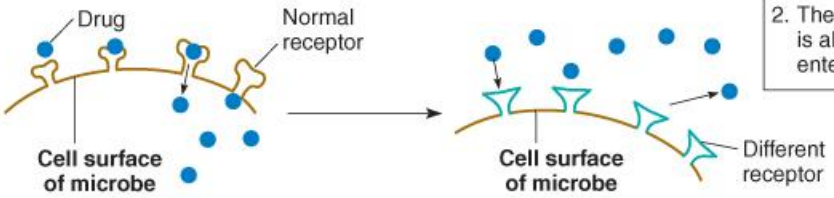
- Drug inactivation by acquired enzymatic activity – penicillinases
- Decreased permeability to drug or increased elimination of drug from cell – acquired or mutation
- Change in drug receptors – mutation or acquisition
- Change in metabolic patterns – mutation of original enzyme

1. Drug inactivation



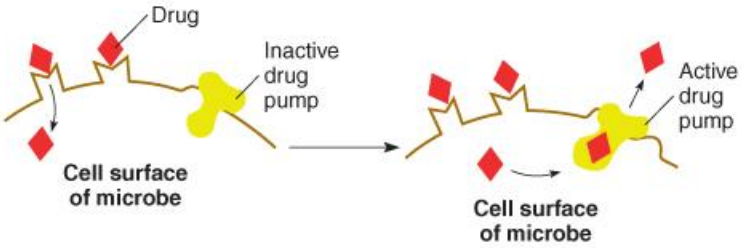
1. Inactivation of a drug like penicillin by penicillinase, an enzyme that cleaves a portion of the molecule and renders it inactive.

2. Decreased permeability



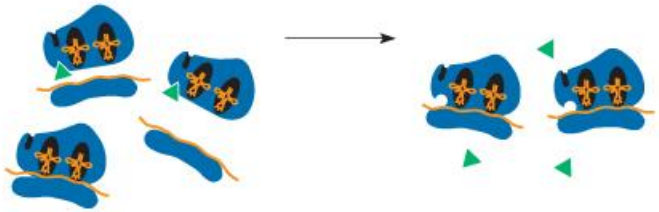
2. The receptor that transports the drug is altered, so that the drug cannot enter the cell.

3. Activation of drug pumps



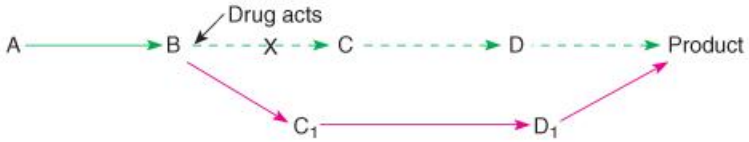
3. Specialized membrane proteins are activated and continually pump the drug out of the cell.

4. Change in drug binding site



4. Binding site on target (ribosome) is altered so drug has no effect.

5. Use of alternate metabolic pathway

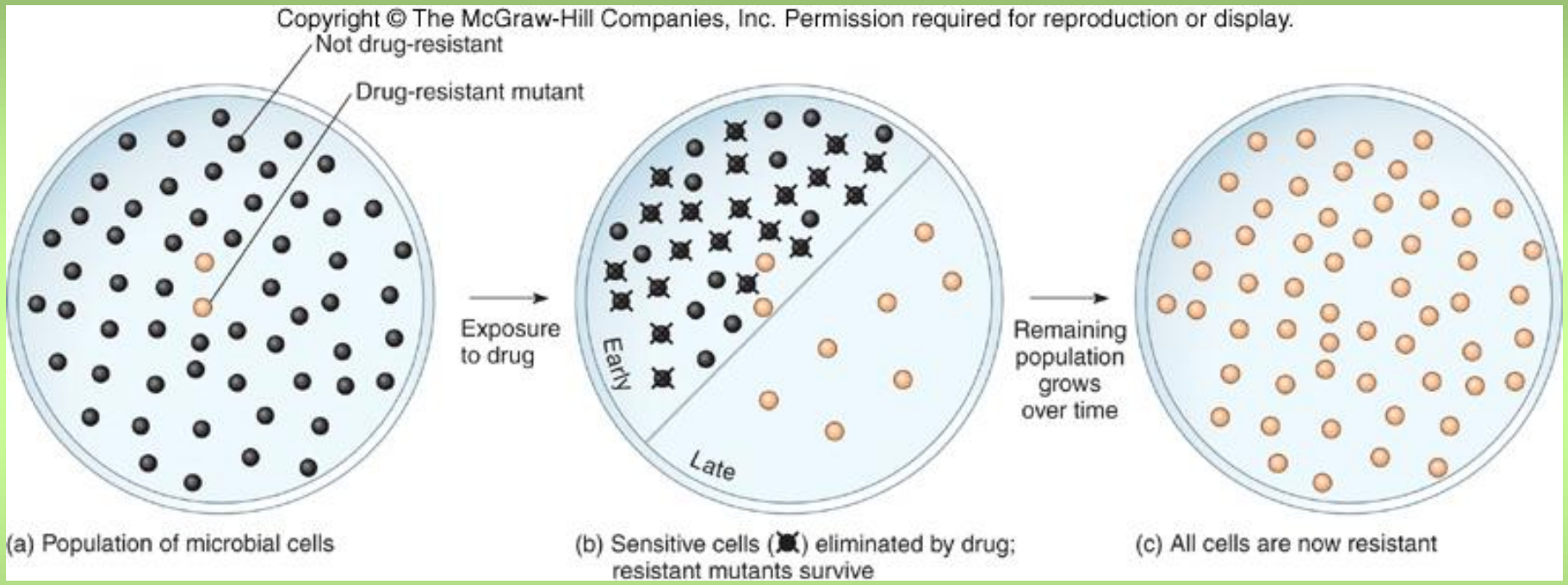


5. The drug has blocked the usual metabolic pathway (green), so the microbe circumvents it by using an alternate, unblocked pathway that achieves the required outcome (red).

Natural Selection and Drug Resistance

- Large populations of microbes likely to include drug resistant cells due to prior mutations or transfer of plasmids – no growth advantage until exposed to drug
- If exposed, sensitive cells are inhibited or destroyed while resistance cells will survive and proliferate.
- Eventually population will be resistant – selective pressure **- natural selection.**
- Worldwide indiscriminate use of antimicrobials has led to explosion of drug resistant microorganisms.

Selection for drug resistance



Side effects of drugs

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