Microbiology: A Systems Approach,

Drugs, Microbes, Host – The Elements of Chemotherapy

12.1 Principles of Antimicrobial Therapy

- Goal of antimicrobial chemotherapy: administer a drug to an infected person, which destroys the infective agent without harming the host's cells
- Rather difficult to achieve this goal
- Chemotherapeutic agents described with regard to their origin, range of effectiveness, and whether they are naturally produced or chemically synthesized

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

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
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

The Origins of Antimicrobial Drugs

- Antibioitics are common metabolic products of aerobic bacteria and fungi
  - Bacteria: *Streptomyces* and *Bacillus*
  - Molds: *Penicillium* and *Cephalosporium*
- Chemists have created new drugs by altering the structure of naturally occurring antibiotics
- Also Searching for metabolic compounds with antimicrobial effects in species other than bacteria and fungi

12.2 Interactions Between Drug and Microbe

- Goal of antimicrobial drugs
  - Disrupt the cell processes or structures of bacteria, fungi, and protozoa
  - Or inhibit virus replication
- Most interfere with the function of enzymes required to synthesize or assemble macromolecules or destroy structures already formed in the cell
- Drugs should be **selectively toxic**- they kill or inhibit microbial cells without damaging host tissues

Mechanisms of Drug Action

- Inhibition of cell wall synthesis
- Inhibition of nucleic acid structure and function
- Inhibition of protein synthesis
- Interference with cell membrane structure or function
- Inhibition of folic acid synthesis

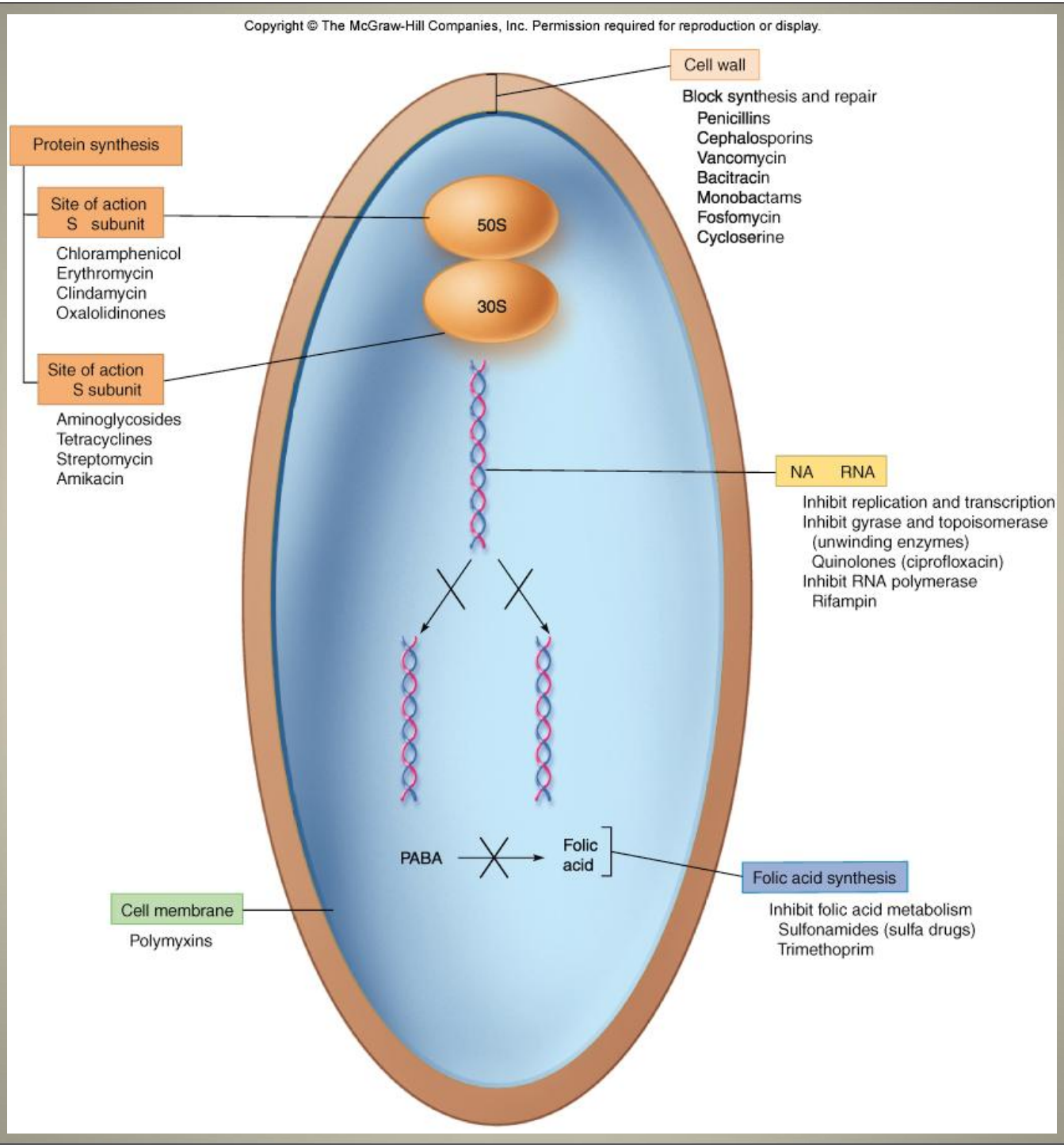

Figure 12.1

Antimicrobial Drugs that Affect the Bacterial Cell Wall

- Active cells must constantly synthesize new peptidoglycan and transport it to the proper place in the cell envelope
- Penicillins and cephalosporins react with one or more of the enzymes required to complete this process
- Bactericidal antibiotics

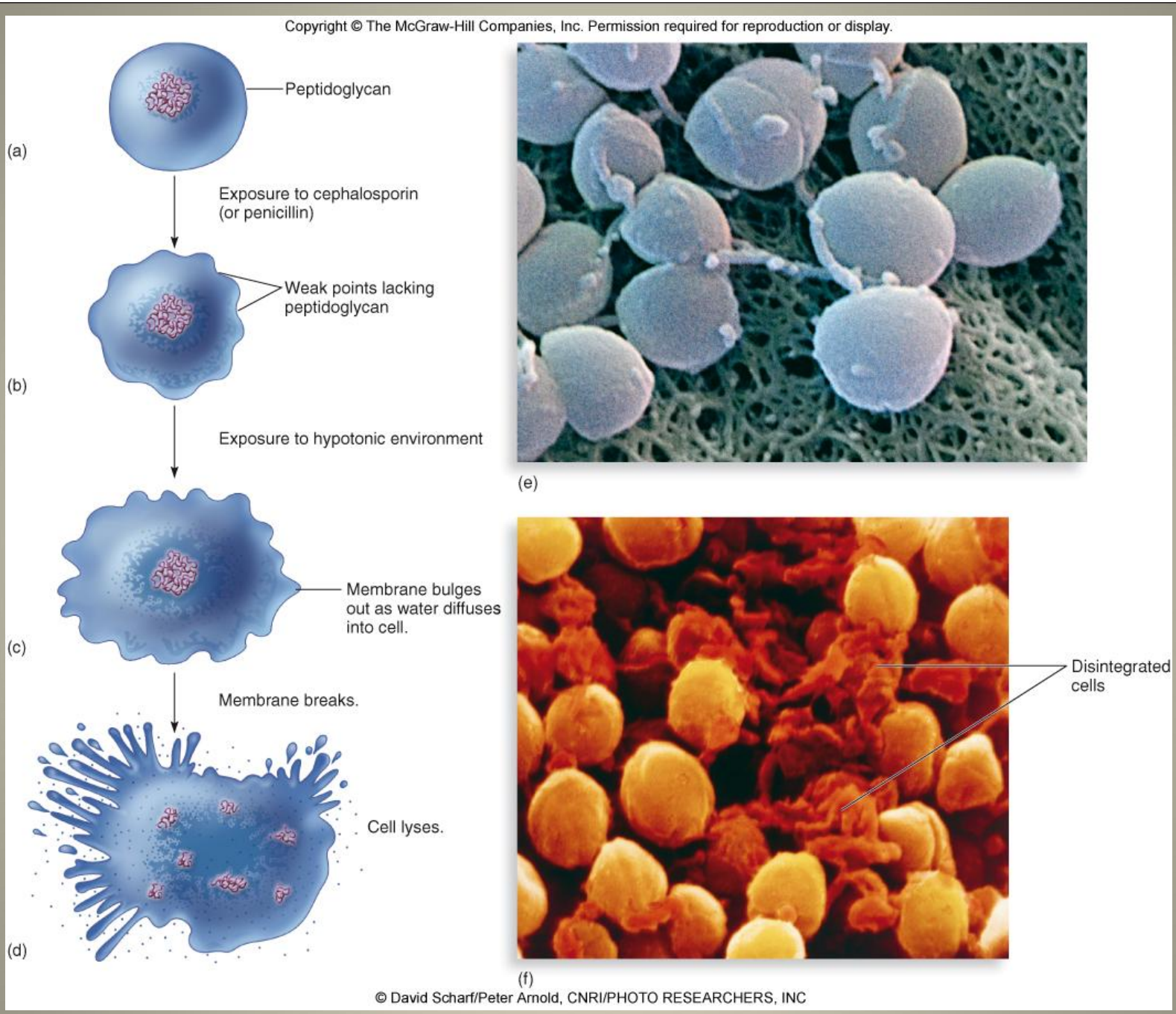

Figure 12.2

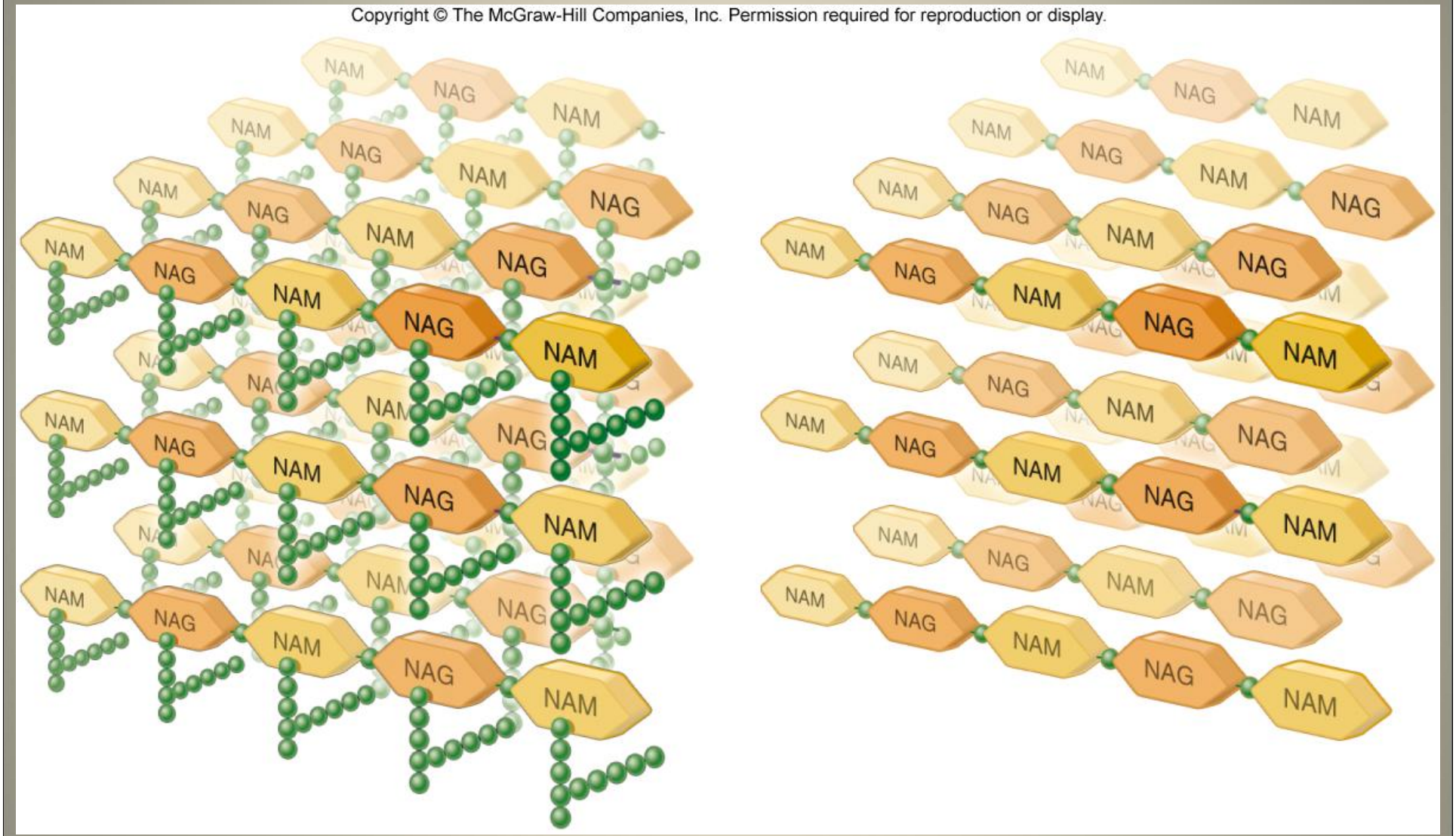

Figure 12.3

Antimicrobial Drugs that Affect Nucleic Acid Synthesis

- Block synthesis of nucleotides
- Inhibit replication
- Stop transcription
- Inhibit DNA synthesis

Antimicrobial Drugs that Block Protein Synthesis

- Inhibit translation by reacting with the ribosome-mRNA complex
- Prokaryotic ribosomes are different from eukaryotic ribosomes- selective

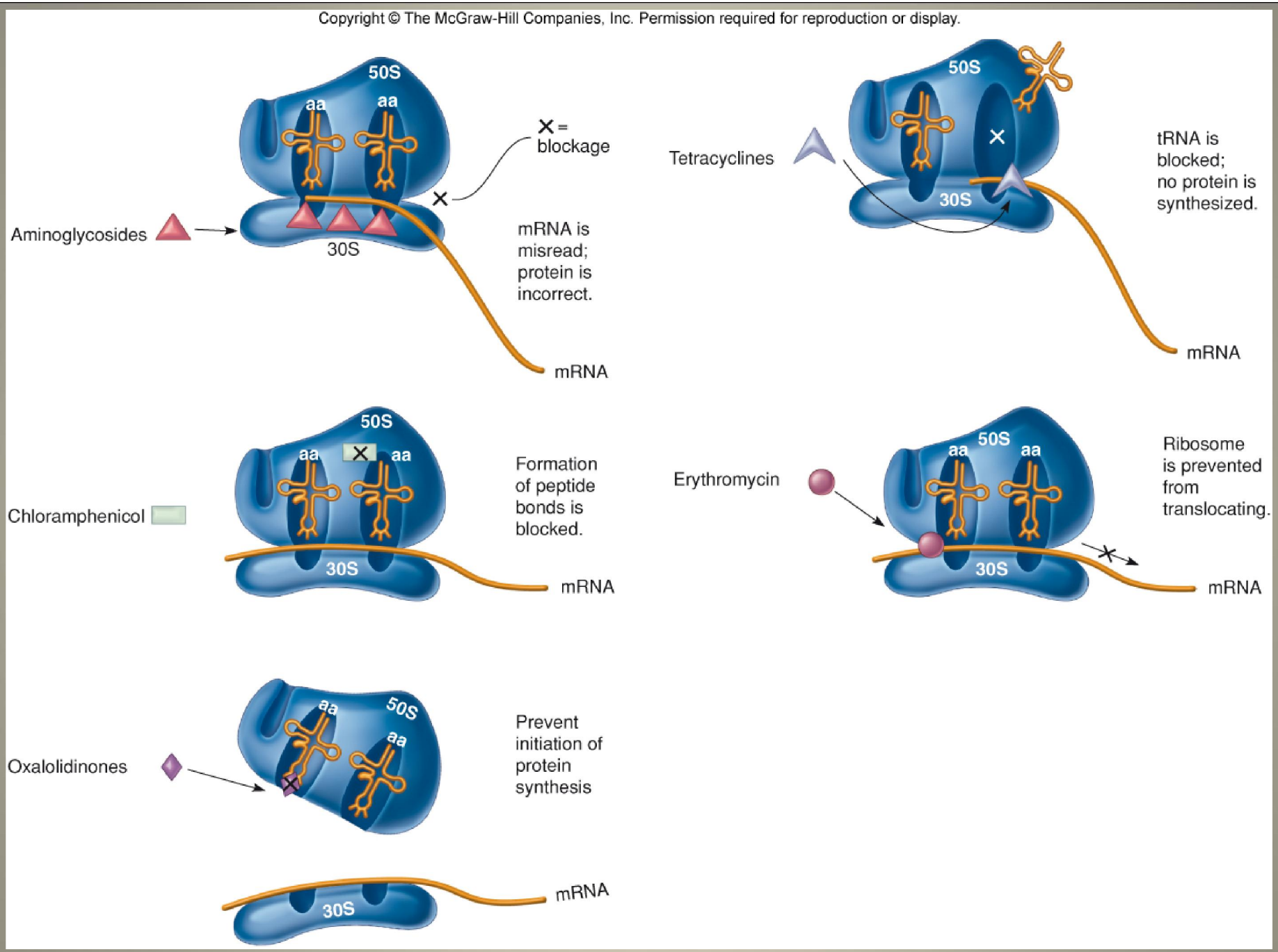

Figure 12.4

Antimicrobial Drugs that Disrupt Cell Membrane Function

- Damaged membrane invariably results in death from disruption in metabolism or lysis
- Specificity for particular microbial groups based on differences in the types of lipids in their cell membranes

Antimicrobial Drugs that Inhibit Folic Acid Synthesis

- Sulfonamides and trimethoprim- **competitive inhibition**
- Supplied to cells in high concentrations to make sure enzyme is constantly occupied with the **metabolic analog** rather than the true substrate

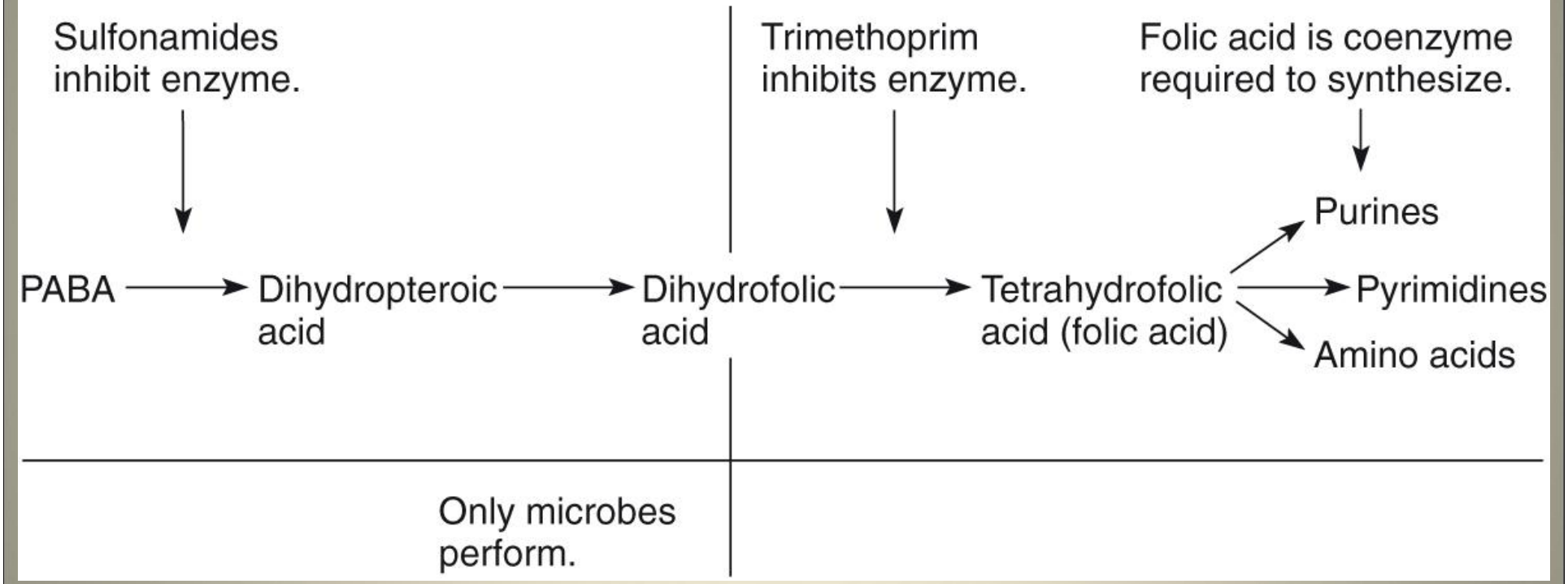

Figure 12.5

12.3 Survey of Major Antimicrobial Drug Groups

- About 260 different antimicrobial drugs
- Classified in 20 drug families
- Largest number of antimicrobial drugs are for bacterial infections

TABLE 12.3 Selected Survey of Chemotherapeutic Agents in Infectious Diseases

Infectious Agent	Typical Infection	Drugs of Choice*
Bacteria		
Gram-positive cocci		
Staphylococcus aureus	Abscess, skin infections, toxic shock	Penicillins, vancomycin, cephalosporin
Streptococcus pyogenes	Strep throat, erysipelas, rheumatic fever	Penicillin, cephalosporin, erythromycin
Gram-positive rods		
Bacillus	Anthrax	Ciprofloxacin, doxycycline
Acid-fast rods		
Mycobacterium tuberculosis	Tuberculosis	(Isoniazid, rifampin, pyrazinamide),* ethambutol streptomycin
Gram-negative cocci		
Neisseria gonorrhoeae	Gonorrhea	Ceftriaxone, ciprofloxacin
Neisseria meningitidis	Meningitis	Penicillin G, cefotaxime
Gram-negative rods		
Escherichia coli	Sepsis, diarrhea, urinary tract infection	Cephalosporin
Haemophilus influenzae	Meningitis	Cefotaxime, cephtriaxone
Pseudomonas	Opportunistic lung and burn infections	Ticarcillin, aminoglycoside
Vibrio cholerae	Cholera	Tetracyclines, sulfamethoxazole-trimethoprim
Spirochetes		
Borrelia	Lyme disease	Doxycycline, amoxicillin
Treponema pallidum	Syphilis	Penicillin, tetracyclines
Rickettsia	Rocky Mountain spotted fever	Doxycycline
Chlamydia	Urethritis, vaginitis	Azithromycin, doxycycline
Fungi		
Systemic mycoses		
Aspergillus	Aspergillosis	Amphotericin B, azoles, flucytosine
Candida albicans	Candidiasis	Itraconazole, fluconazole
Cryptococcus neoformans	Cryptococcosis	Amphotericin B, fluconazole
Pneumocystis (carinii) jiroveci	Pneumonia (PCP)	Sulfamethoxazole-trimethoprim
Protozoa		
Giardia lamblia	Giardiasis	Quinacrine, metronidazole
Plasmodium	Malaria	Chloroquine, mefloquine
Toxoplasma gondii	Toxoplasmosis	Pyrimethamine, sulfadiazine
Trichomonas vaginalis	Trichomoniasis	Metronidazole
Helminths		
Cestodes	Tapeworm	Niclosamide, praziquantel
Various roundworm infections		Alebendazole
Viruses		
Herpesvirus	Genital herpes, oral herpes, shingles	Acyclovir, valacyclovir
HIV	AIDS	(AZT, protease inhibitors), ddI, ddC, d4T
Orthomyxovirus	Type A influenza	Amantadine, rimantidine

Antibacterial Drugs Targeting the Cell Wall

- Penicillin group
  - Most end in the suffix *–cillin*
  - Can obtain natural penicillin through microbial fermentation
  - All consist of three parts: a thiazolidine ring, a beta-lactam ring, and a variable side chain

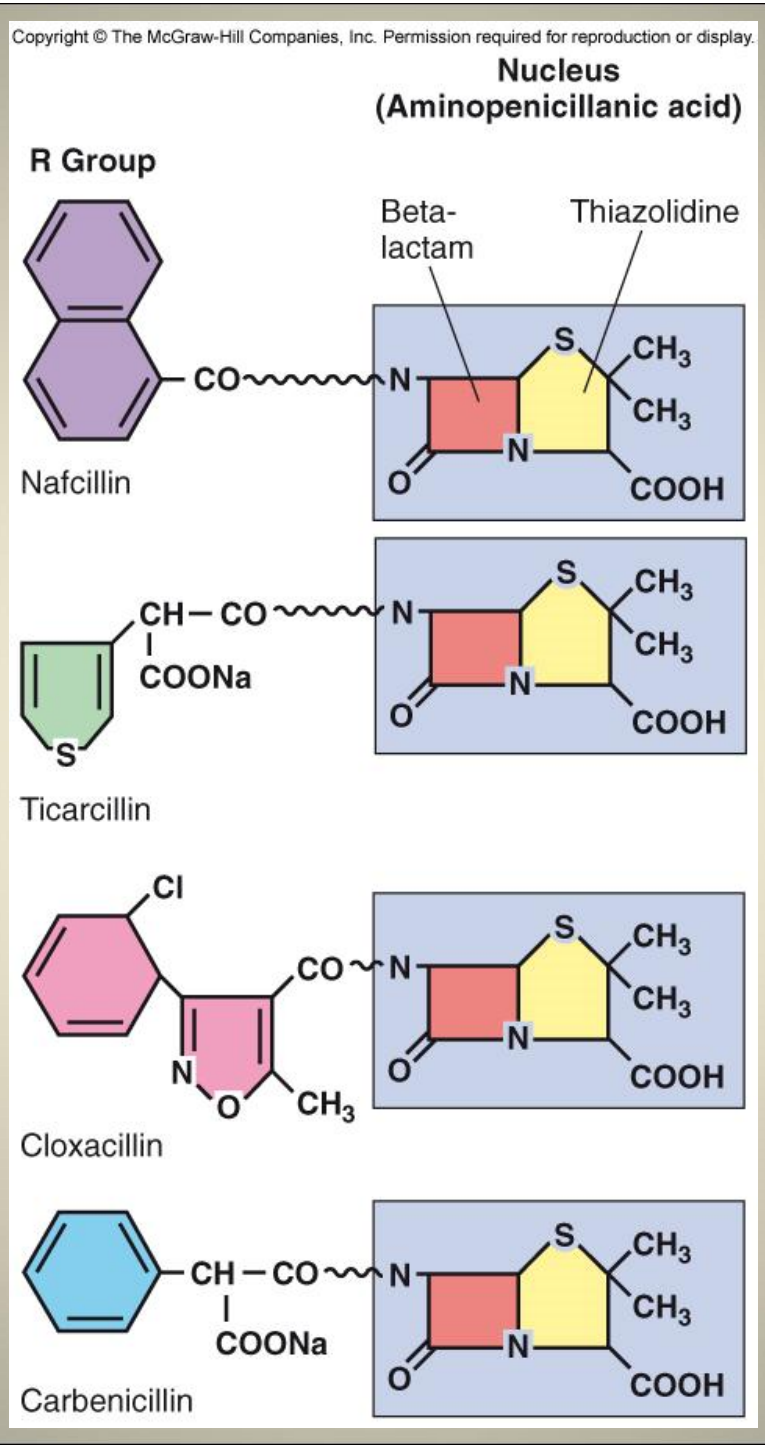

Figure 12.6

Subgroups and Uses of Penicillins

TABLE 12.4 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

The Cephalosporin Group of Drugs

- Newer group
- Currently account for a majority of all antibiotics administered

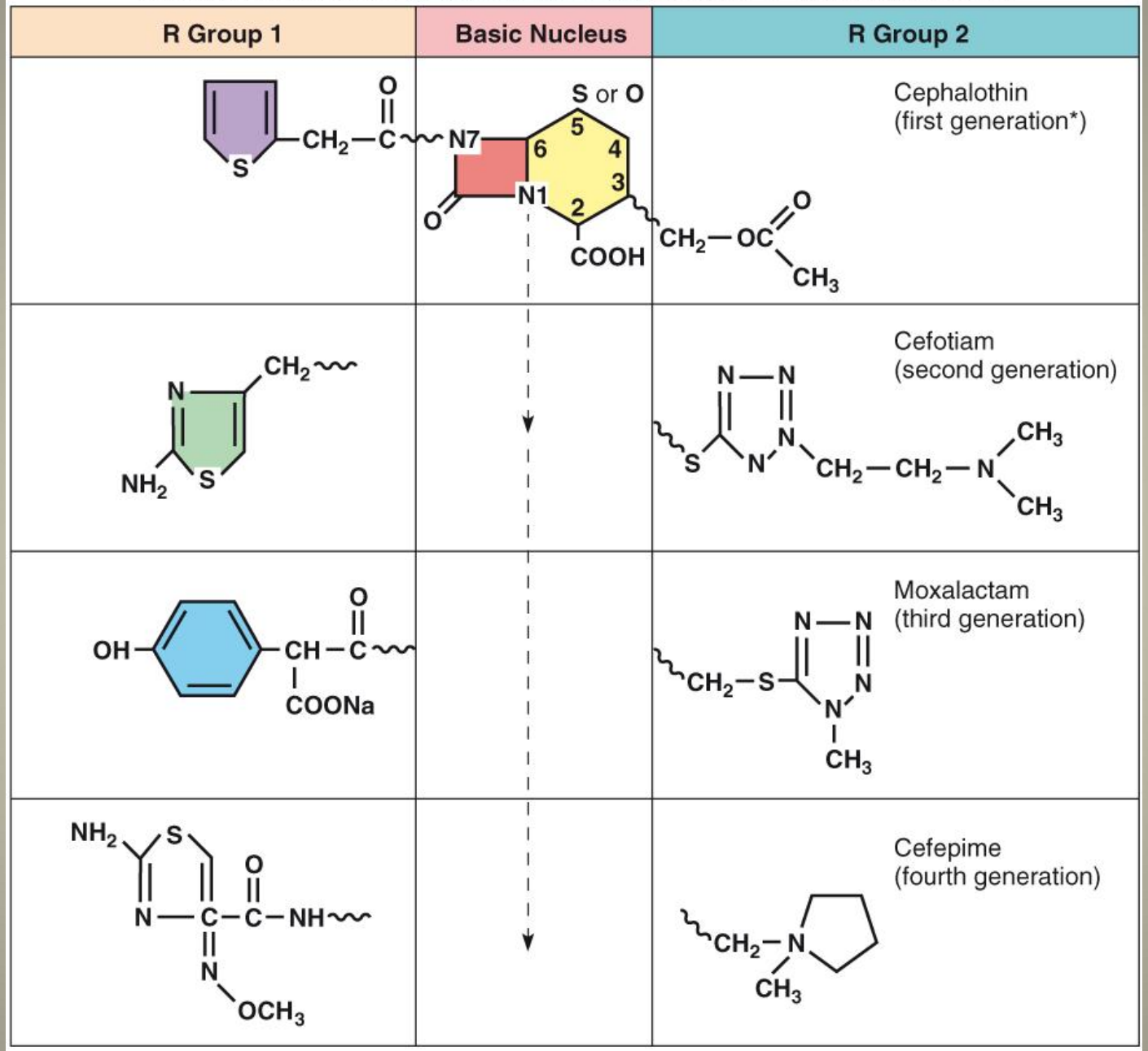

Figure 12.7

Subgroups and Uses of Cephalosporins

- Broad-spectrum
- Resistant to mot penicillinases
- Cause fewer allergic reactions than penicillins
- Four generations of cephalosporins exist based on their antibacterial activity

Other Beta-Lactam Antibiotics

- Imipenem
- Aztreonam

Other Drugs Targeting the Cell Wall

- Bacitracin
- Isoniazid
- Vancomycin
- Fosfomycin trimethamine

Antibacterial Drugs Targeting Protein Synthesis

- Aminoglycoside Drugs
  - Products of various species of soil actinomycetes in the genera *Streptomyces* and *Micromonospora*
  - Relatively broad spectrum because they inhibit protein synthesis
  - Subgroups and uses
    - Aerobic gram-negative rods and certain gram-positive bacteria
    - Streptomycin: Bubonic plague and tularemia and good antituberculosis agent
    - Gentamicin: Less toxic and used for gram-negative rods

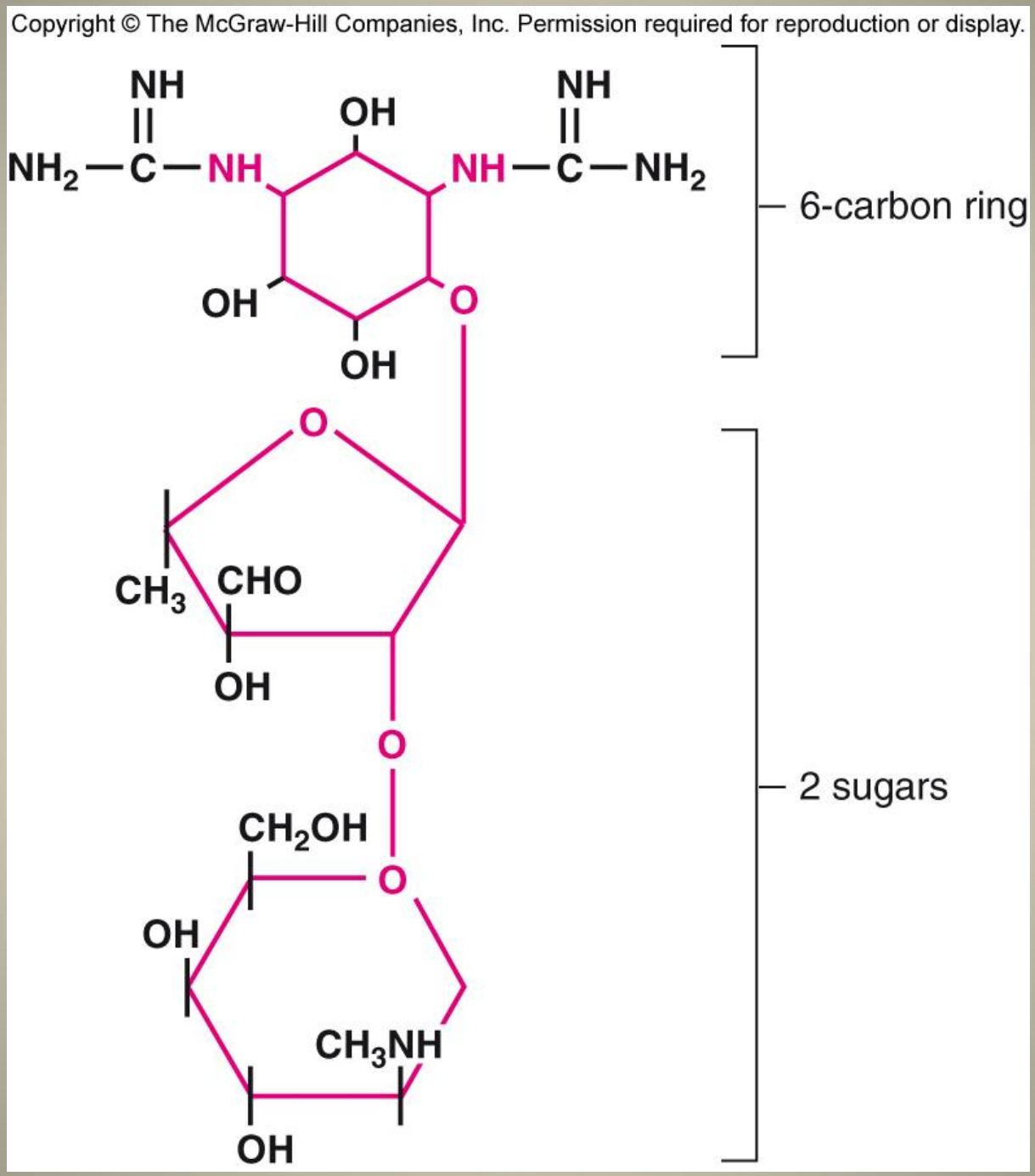

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Figure 12.9

Tetracycline Antibiotics

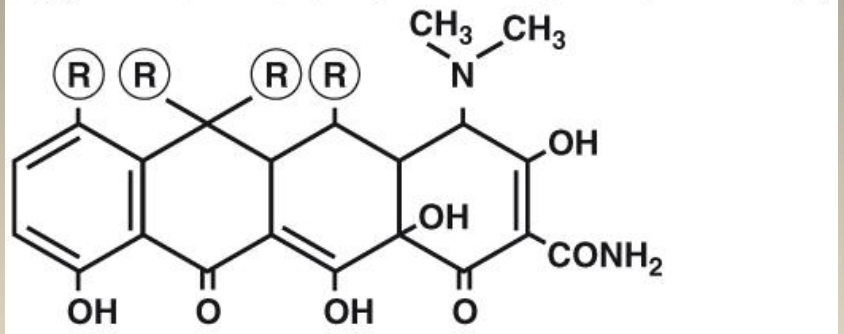
- Bind to ribosomes and block protein synthesis
- Broad-spectrum
- Subgroups and uses
  - Gram –positive and gram-negative rods and cocci
  - Aerobic and anerobic bacteria
  - Mycoplasmas, rickettsias, and spirochetes
  - Doxycycline and minocycline for sexually transmitted diseases, Rocky Mountain spotted fever, Lyme disease, typhus, *Mycoplasma* pneumonia, cholera, leptospirosis, acne, even some protozoan

Chloramphenicol

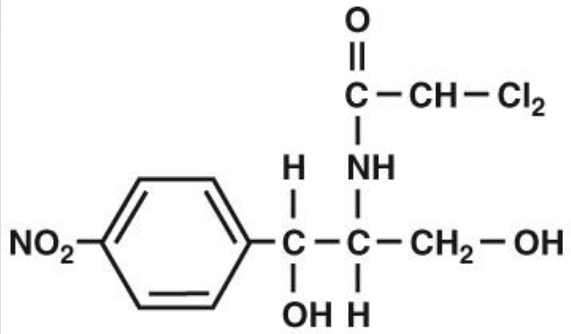
- Broad-spectrum
- Unique nitrobenzene structure
- Blocks peptide bond formation and protein synthesis
- Entirely synthesized through chemical processes
- Very toxic to human cells so its uses are restricted

Erythromycin and Clindamycin

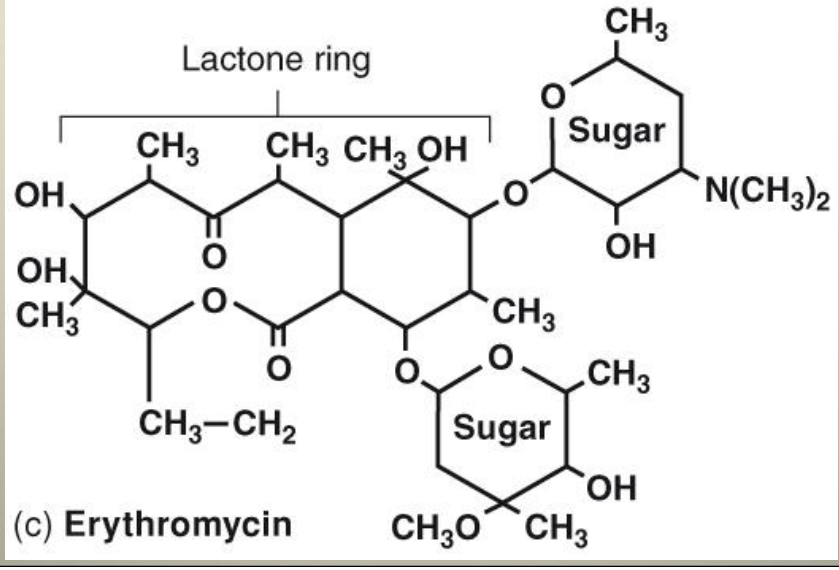
- Erythromycin
  - Large lactone rinig with sugars attached
  - Relatively broad-spectrum
  - Fairly low toxicity
  - Blocks protein synthesis by attaching to the ribosome
  - *Mycoplasma* pneumonia, legionellosis, *Chlamydia* infections, pertussis, diphtheria
- Clindamycin
  - Broad-spectrum
  - Derived from lincomycin
  - Causes adverse reactions in the gastrointestinal tract, so applications are limited



(a) **Tetracyclines**



(b) **Chloramphenicol**



(c) **Erythromycin**

Figure 12.10

Synercid and Oxazolidones

- Synercid
  - Combined antibiotic from the streptogramin group
  - Effective against *Staphylococcus* and *Enterococcus* species and against resistant strains of *Streptococcus*
  - Binds to sites on the 50S ribosome, inhibiting translation
- Oxazolidones
  - Inhibit the initiation of protein synthesis
  - Not found in nature
  - Hoping that drug resistance among bacteria will be slow to develop
  - Used to treat infections caused by two of the most difficult clinical pathogens: methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE)

Antibacterial Drugs Targeting Folic Acid Synthesis

- Sulfonamides, Trimethoprim, and Sulfones
  - Sulfonamides
    - Sulfa drugs
    - Very first modern antimicrobial drug
    - Synthetic
    - Shigellosis, acute urinary tract infections, certain protozoan infections
  - Trimethoprim
    - Inhibits the enzymatic step immediately following the step inhibited by solfonamides in the synthesis of folic acid
    - Often given in combination with sulfamethoxazole
    - One of the primary treatments for *Pneumocystis (carinii) jiroveci* pneumonia (PCP) in AIDS patients
  - Sulfones
    - Chemically related to sulfonamides
    - Lack their broad-spectrum effects
    - Key drugs in treating Hansen's disease (leprosy)

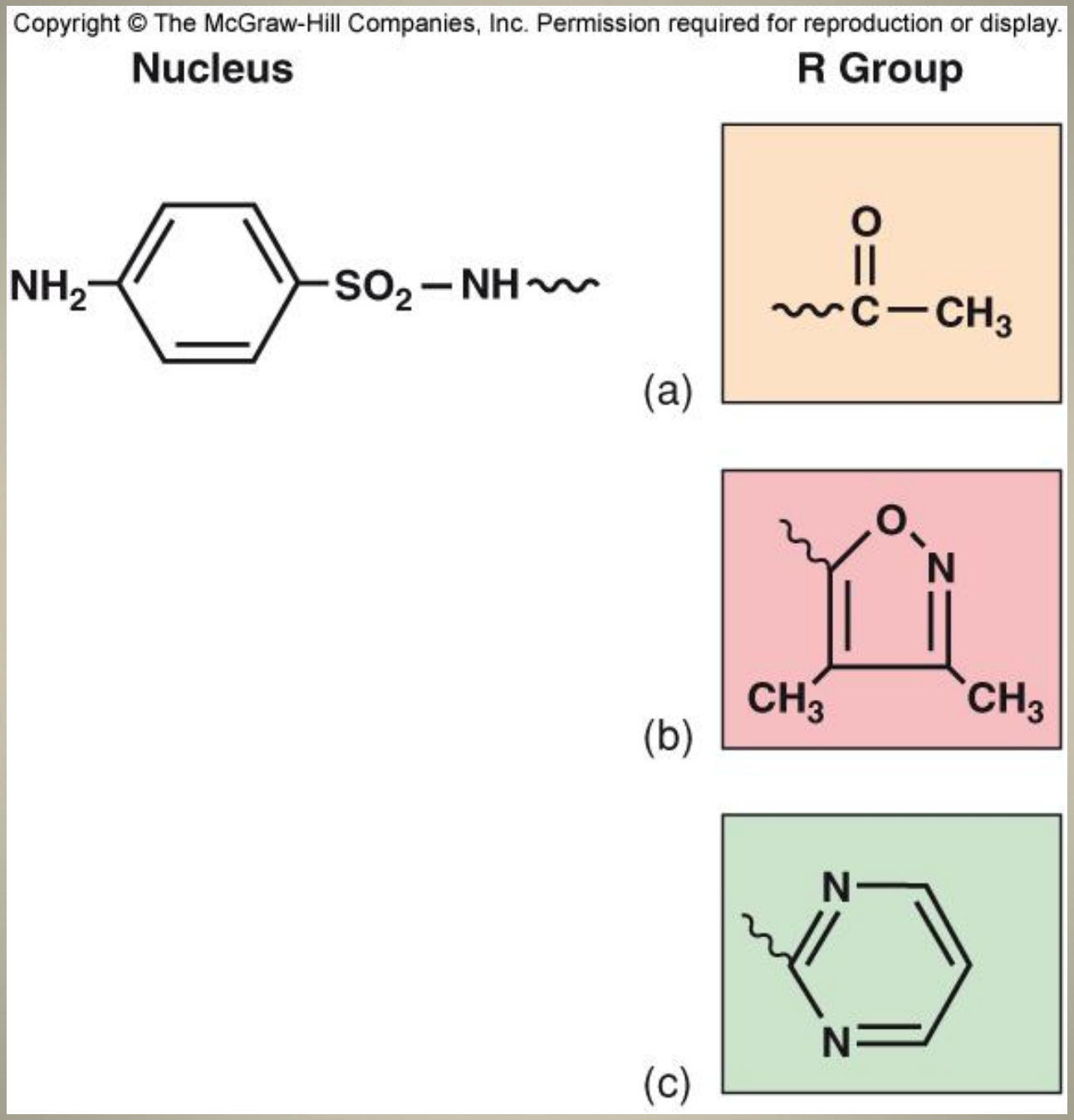


Figure 12.11

Antibacterial Drugs Targeting DNA or RNA

- **Fluoroquinolones**
- High potency
- Broad spectrum
- Inhibit a wide variety of gram-positive and gram-negative bacterial species even in minimal concentrations

Norfloxacin and Ciprofloxacin

- Urinary tract infections, STDs, gastrointestinal infections, osteomyelitis, respiratory infections, soft tissue infections

Sparfloxacin and Levofloxacin

- Newer drugs
- Pneumonia, bronchitis sinusitis

Rifampin

- Product of the genus *Streptomyces*
- Limited in spectrum
- Mainly for infections by several gram-positive rods and cocci and a few gram-negative bacteria
- Mycobacterial infections such as tuberculosis and leprosy
- Usually given in combination with other drugs

Antibacterial Drugs Targeting Cell Membranes

- **Polymyxins**: narrow-spectrum peptide antibiotics
  - From *Bacillus polymyxa*
  - Limited by their toxicity to the kidney
  - B and E can be used to treat drug-resistant *Pseudomonas aeruginosa*
- **Daptomycin**
  - Lipopeptide made by *Streptomyces*
  - Most active against gram-positive bacteria

Agents to Treat Fungal Infections

- Fungal cells are eukaryotic, so present special problems
  - Majority of chemotherapeutic drugs are designed to act on bacteria and are ineffective for fungal infections
  - Similarities between fungal and human cells- toxicity to humans
- Four main groups
  - Macrolide polyene antibiotics, Griseofulvin, Synthetic azoles, Flucystosine

Macrolide Polyene Antibiotics

- Bind to fungal membranes and cause loss of selective permeability
- Specific for fungal membranes because fungal membranes contain ergosterol
- Examples: amphotericin B and nystatin
- Mimics lipids in some cell membranes

Griseofulvin

- Especially active in certain dermatophyte infections such as athlete's foot
- Requires several months and is relatively nephrotoxic, so only given for most stubborn cases

Synthetic **Azoles**

- Broad-spectrum antifungal agents
- Ketoconazole, fluconazole, clotrimazole, and miconazole
- Ketoconazole: orally and topically for cutaneous mycoses, vaginal and oral candidiasis, and some systemic mycoses
- Fluconazole: used in selected patients for AIDS-related mycoses
- Clotrimazole and miconazole: mainly topical ointments for infections in the skin, mouth, and vagina

Flucystosine

- Analog of the nucleotide cytosine
- Can be used to treat certain cutaneous mycoses
- Usually combined with amphotericin B for systemic mycoses

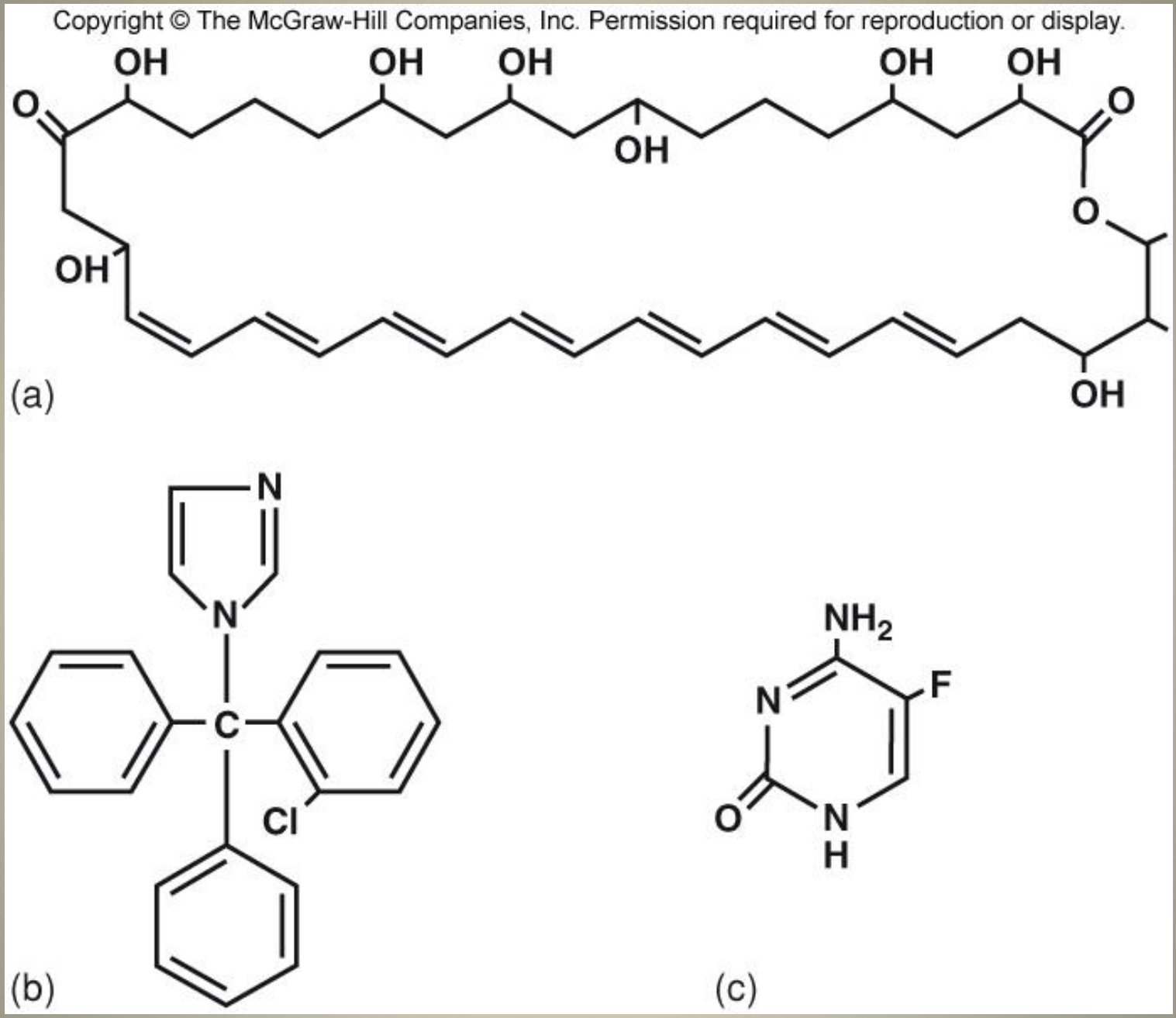


Figure 12.12

Antiparasitic Chemotherapy

- Antimalarial Drugs: Quinine and Its Relatives
  - Quinine: extracted from the bark of the cinchona tree
  - Replaced by synthesized quinolines (chloroquine and primaquine) which have less toxicity to humans
- Chemotherapy for Other Protozoan Infections
  - Metronidazole (Flagyl)
    - Amoebicide
    - Treating mild and severe intestinal infections by *Entamoeba histolytica*
    - Orally can also apply to infections by *Giardia lamblia* and *Trichomonas vaginalis*
  - Quinicrine, sulfonamides, tetracyclines

Antihelminthic Drug Therapy

- Flukes, tapeworms, and roundworms have greater similarities to human physiology
- Using drugs to block their reproduction is usually not successful in eradicating adult worms
- Most effective drugs immobilize, disintegrate, or inhibit the metabolism of all stages of the life cycle

Mebendazole and Thiabendazole

- Broad-spectrum
- Used in several roundworm intestinal infestations
- Inhibit the function of microtubules of worms, eggs, and larvae

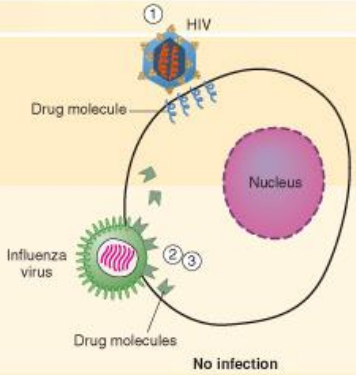
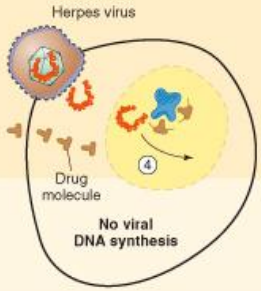
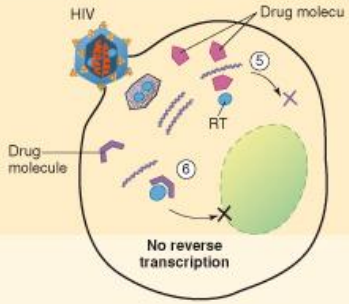
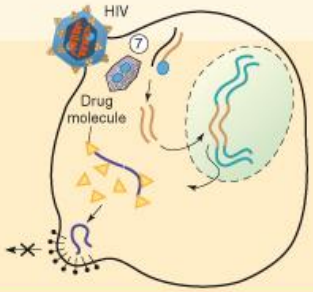
Pyrantel and Piperazine; Praziquantel; Ivermectin

- Pyrantel and piperazine
  - Paralyze the muscles of intestinal roundworms
- Praziquantel
  - Tapeworm and fluke infections
- Ivermectin
  - Veterinary drug now used for strongyloidiasis and oncocercosis in humans

Antiviral Chemotherapeutic Agents

- Selective toxicity is almost impossible to achieve because a single metabolic system is responsible for the well-being of both virus and host
- Several antiviral drugs have been developed that target specific points in the infectious cycle of viruses
- Three major modes of action:
  - Barring penetration of the virus into the host cell
  - Blocking the transcription and translation of viral molecules
  - Preventing the maturation of viral particles

TABLE 12.5 Actions of Antiviral Drugs

Mode of Action	Examples	Effects of Drug	
Inhibition of Virus Entry: Receptor/Fusion/ Uncoating Inhibitors	Enfuvirtide (Fuzeon)	Blocks **HIV** infection by preventing the binding of viral GP-41 receptors to cell receptor ①, thereby preventing fusion of virus with cell	
	Amantidine and its relatives, zanamivir (Relenza), oseltamivir (Tamiflu)	Block entry of **influenza virus** by interfering with fusion of virus with cell membrane (also release); stop the action of influenza neuraminidase, required for entry of virus into cell (also assembly) ②③	
Inhibition of Nucleic Acid Synthesis	Acyclovir (Zovirax), other "cyclovirs," vidarabine	Purine analogs that terminate DNA replication in **herpesviruses** ④	
	Ribavirin	Purine analog, used for **respiratory syncytial virus (RSV)** and some **hemorrhagic fever viruses**	
	Zidovudine (AZT), abacavir, lamivudine (3T3), didanosine (ddI), zalcitabine (ddC), and stavudine (d4T)	Nucleotide analog reverse transcriptase (RT) inhibitors; stop the action of RT in **HIV,** blocking viral DNA production ⑤	
	Nevirapine, efavirenz, delaviridine	Nonnucleotide analog reverse transcriptase inhibitors; attach to **HIV** RT binding site, stopping its action ⑥	
Inhibition of Viral Assembly/Release	Indinavir, saquinavir, nelfinavir, crixivan	Protease inhibitors; insert into **HIV** protease, stopping its action and resulting in inactive noninfectious viruses ⑦	

Interferon (IFN): An Alternative to Artificial Drugs

- Glycoprotein produced by fibroblasts and leukocytes in response to various immune stimuli
- Produced by recombinant DNA technologies
- Known therapeutic benefits:
  - Reducing the time of healing and some of the complications in certain infections
  - Preventing or reducing some symptoms of cold and papillomaviruses
  - Slowing the progress of certain cancers
  - Treating a rare cancer called hairy-cell leukemia, hepatitis C, genital warts, and Kaposi's sarcoma in AIDS patients
- Often results in serious side effects

Interactions Between Microbes and Drugs: The Acquisition of Drug Resistance

- **Drug resistance**: an adaptive response in which microorganisms begin to tolerate an amount of drug that would ordinarily be inhibitory
- Can be intrinsic or acquired
- Microbes become newly resistant to a drug after
  - Spontaneous mutations in critical chromosomal genes
  - Acquisition of entire new genes or sets of genes via transfer from another species (plasmids called **resistance (R) factors**)
- Specific Mechanisms of Drug Resistance

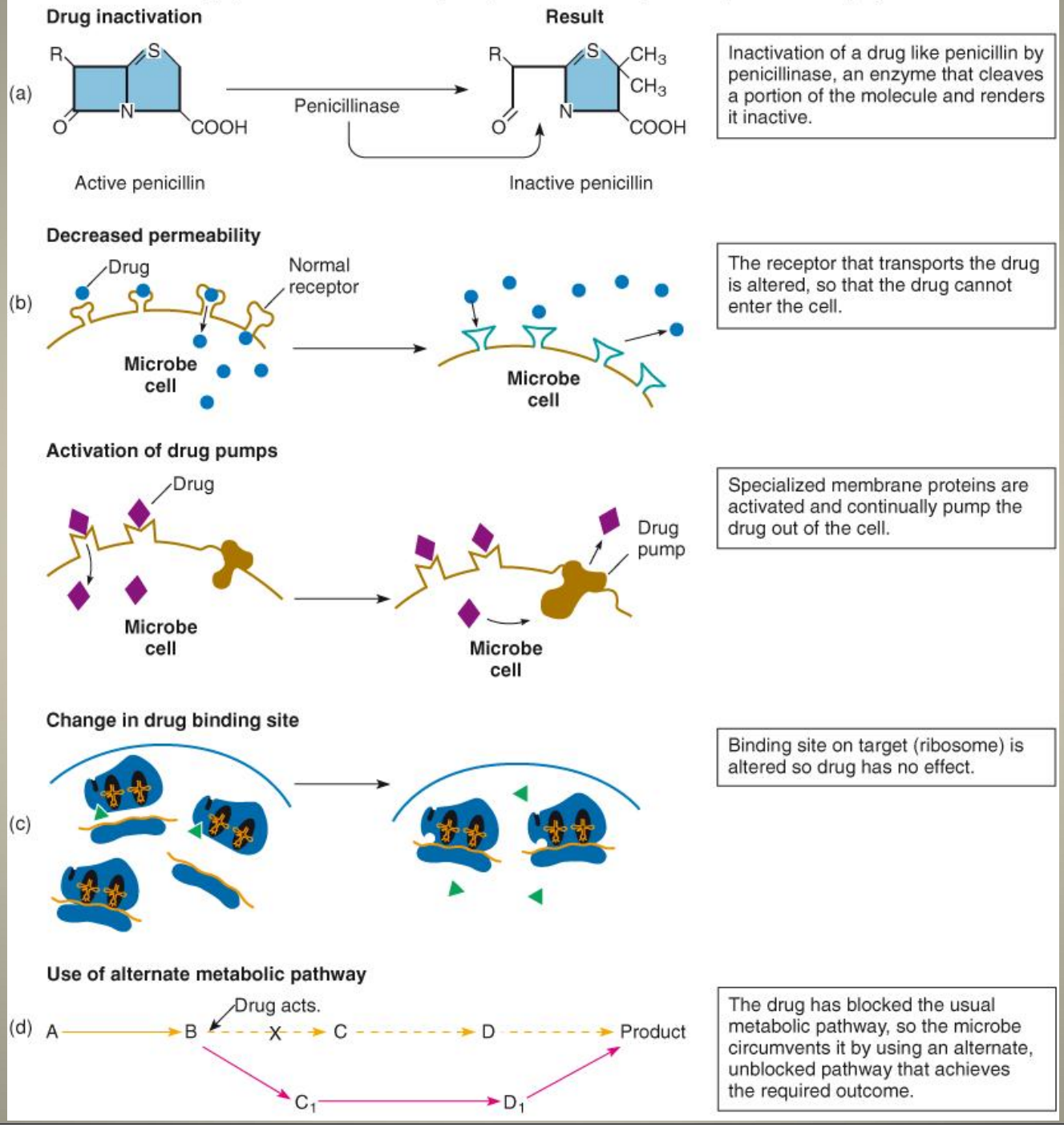


Figure 12.13

Natural Selection and Drug Resistance

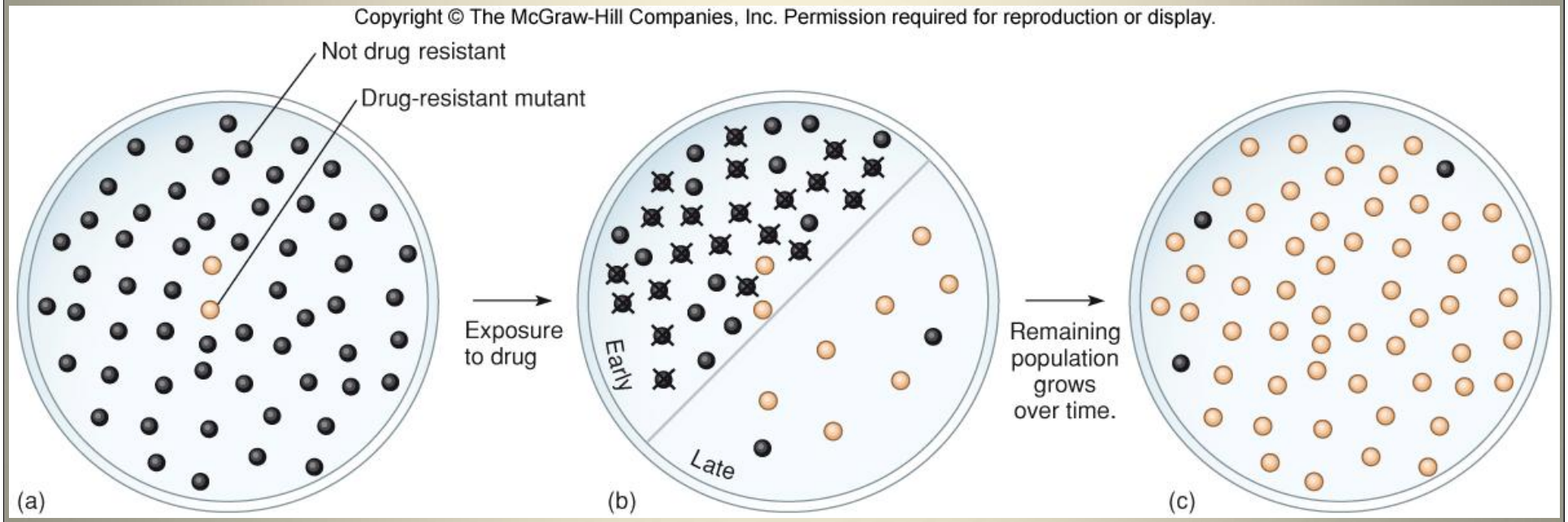


Figure 12.14

New Approaches to Antimicrobial Therapy

- Often researchers try to find new targets in the bacterial cell and custom-design drugs that aim for them
  - Targeting iron-scavenging capabilities of bacteria
  - Targeting a genetic control mechanism in bacteria referred to as riboswitches
- **Probiotics** and **prebiotics**
- **Lantibiotics**

12.4 Interaction Between Drug and Host

TABLE 12.6 Major Adverse Toxic Reactions to Common Drug Groups

Antimicrobial Drug	Primary Damage or Abnormality Produced
Antibacterials	
Penicillin G	Skin
Carbenicillin	Abnormal bleeding
Ampicillin	Diarrhea and enterocolitis
Cephalosporins	Inhibition of platelet function
	Decreased circulation of white blood cells
	Nephritis
Tetracyclines	Diarrhea and enterocolitis
	Discoloration of tooth enamel
	Reactions to sunlight (photosensitization)
Chloramphenicol	Injury to red and white blood cell precursors
Aminoglycosides (streptomycin, gentamicin, amikacin)	Diarrhea and enterocolitis; malabsorption; loss of hearing, dizziness, kidney damage
Isoniazid	Hepatitis
	Seizures
	Dermatitis
Sulfonamides	Formation of crystals in kidney; blockage of urine flow
	Hemolysis
	Reduction in number of red blood cells
Polymyxin	Kidney damage
	Weakened muscular responses
Quinolones (ciprofloxacin, norfloxacin)	Headache, dizziness, tremors, GI distress
Rifampin	Damage to hepatic cells
	Dermatitis
Antifungals	
Amphotericin B	Disruption of kidney function
Flucytosine	Decreased number of white blood cells
Antiprotozoan drugs	
Metronidazole	Nausea, vomiting
Chloroquine	Vomiting
	Headache
	Itching
Antihelminthics	
Niclosamide	Nausea, abdominal pain
Pyrantel	Irritation
	Headache, dizziness
Antivirals	
Acyclovir	Seizures, confusion
	Rash
Amantadine	Nervousness, light-headedness
	Nausea
AZT	Immunosuppression, anemia

Toxicity to Organs

- Liver, kidneys, gastrointestinal tract, cardiovascular system and blood-forming tissue, nervous system, respiratory tract, skin, bones, and teeth

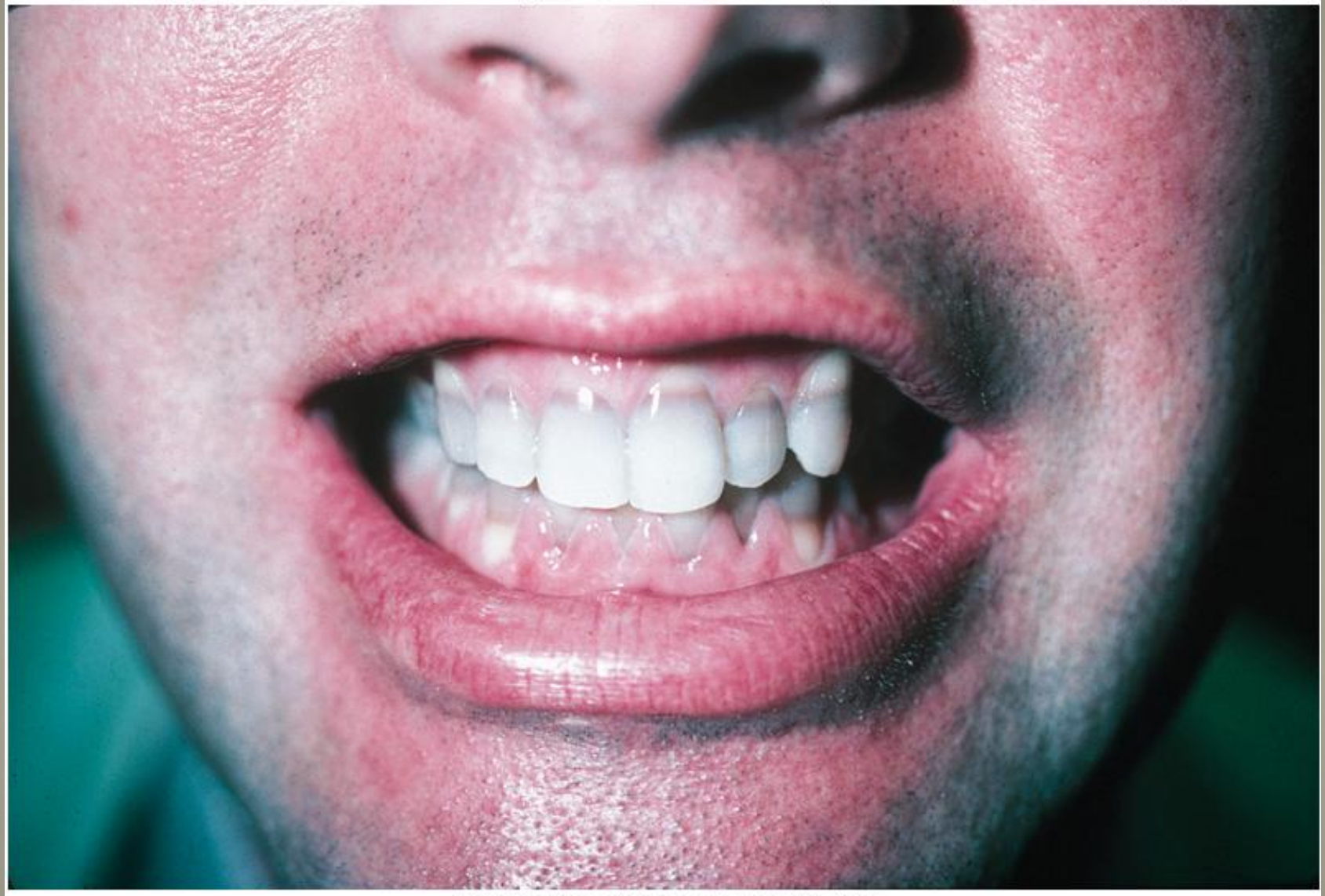


Figure 12.15

Allergic Responses to Drugs

- **Allergy**: heightened sensitivity
- The drug acts as an antigen and stimulates an allergic response
- Reactions such as skin rash, respiratory inflammation, and rarely anaphylaxis

Suppression and Alteration of the Microbiota by Antimicrobials

- **Biota**: normal colonists or residents of healthy body surfaces
  - Usually harmless or beneficial bacteria
  - Small number can be pathogens
- If a broad-spectrum antimicrobial is used, it will destroy both infectious agents but also some beneficial species

Superinfection

- When beneficial species are destroyed, microbes that were once kept in small numbers can begin to overgrow and cause disease- a **superinfection**
  - Using a broad-spectrum cephalosporin for a urinary tract infection; destroys lactobacilli in the vagina; without the lactobacilli *Candida albicans* can proliferate and cause a yeast infection
  - Oral therapy with tetracyclines, clindamycin, and broad-spectrum penicillins and cephalosporins is associated with antibiotic-associated colitis

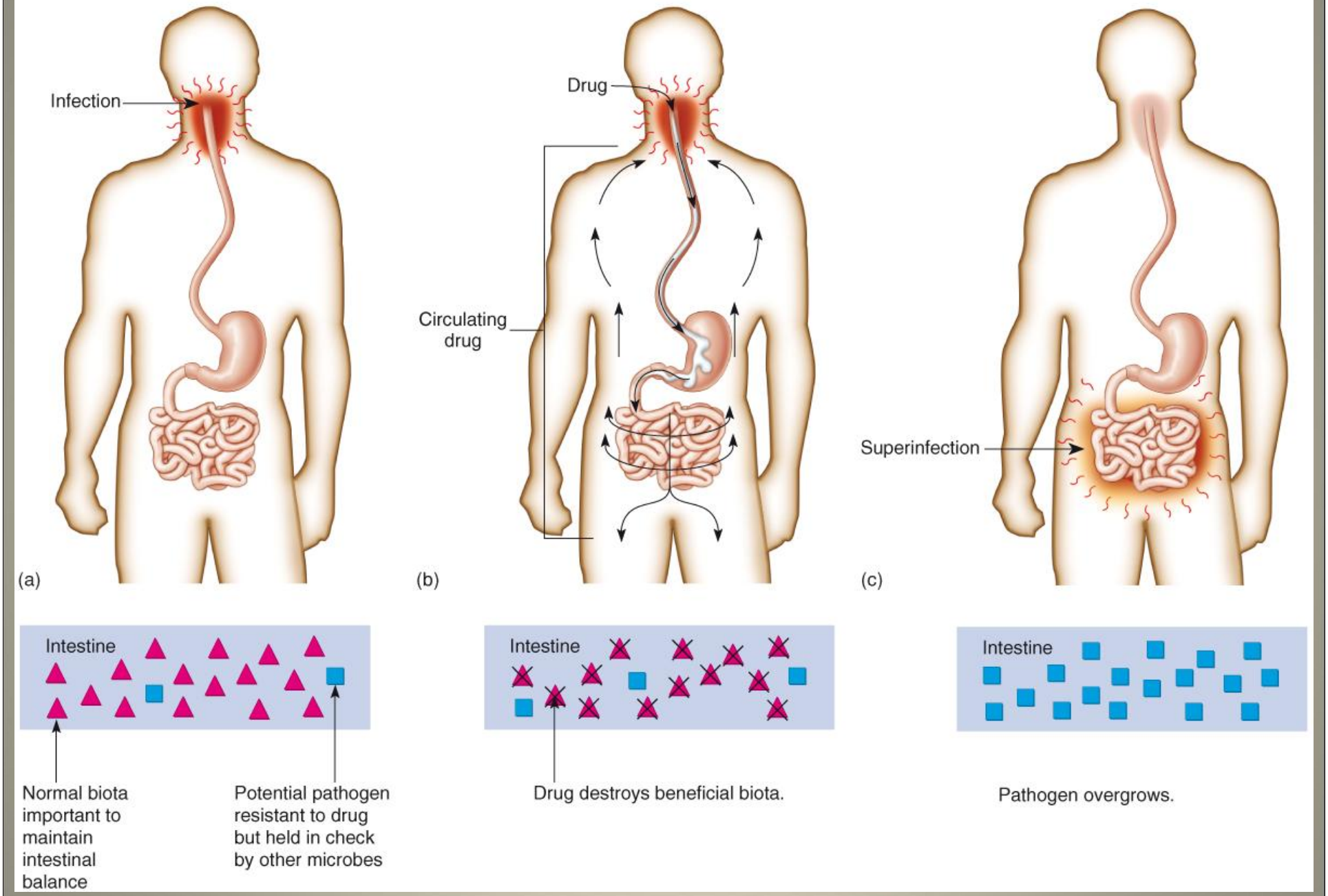
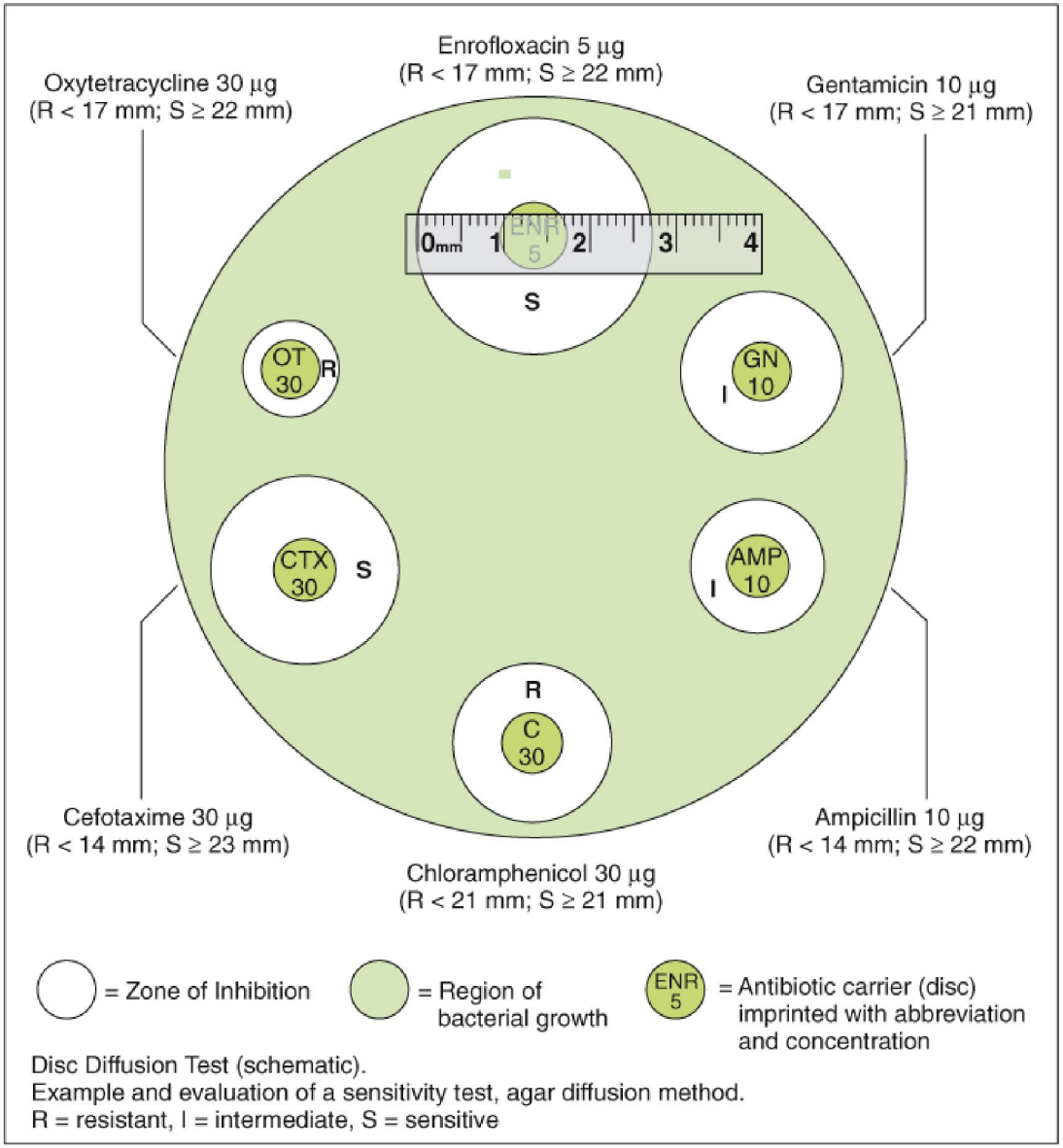


Figure 12.16

12.5 Considerations in Selecting an Antimicrobial Drug

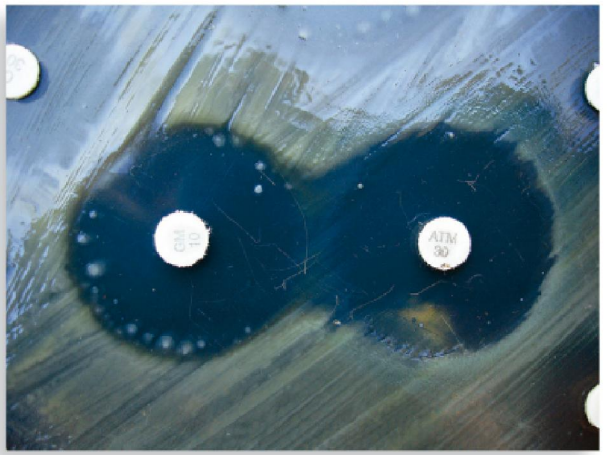
- Three factors must be known
  - The nature of the microorganism causing the infection
  - The degree of the microorganism's susceptibility to various drugs
  - The overall medical condition of the patient
- Identifying the Agent
  - Direct examination of body fluids, sputum, or stool is a rapid initial method
  - The choice of drug will be based on experience with drugs that are known to be effective against the microbe: the "informed best guess"
- Testing for the Drug Susceptibility of Microorganisms

Kirby-Bauer Disc Diffusion Test*



Disc Diffusion Test (schematic).
Example and evaluation of a sensitivity test, agar diffusion method.
R = resistant, I = intermediate, S = sensitive

(a) *R and S values differ from table 12.7 due to differing concentrations of the antimicrobials.



(c)

Figure 12.17

TABLE 12.7 Results of a Sample Kirby-Bauer Test

Drug	Zone Sites (mm) Required For: Susceptibility (S)	Resistance (R)	Actual Result (mm) for *Staphylococcus aureus*	Evaluation
Bacitracin	>13	<8	15	S
Chloramphenicol	>18	<12	20	S
Erythromycin	>18	<13	15	I
Gentamicin	>13	<12	16	S
Kanamycin	>18	<13	20	S
Neomycin	>17	<12	12	R
Penicillin G	>29	<20	10	R
Polymyxin B	>12	<8	10	R
Streptomycin	>15	<11	11	R
Vancomycin	>12	<9	15	S
Tetracycline	>19	<14	25	S

R = resistant, I = intermediate, S = sensitive

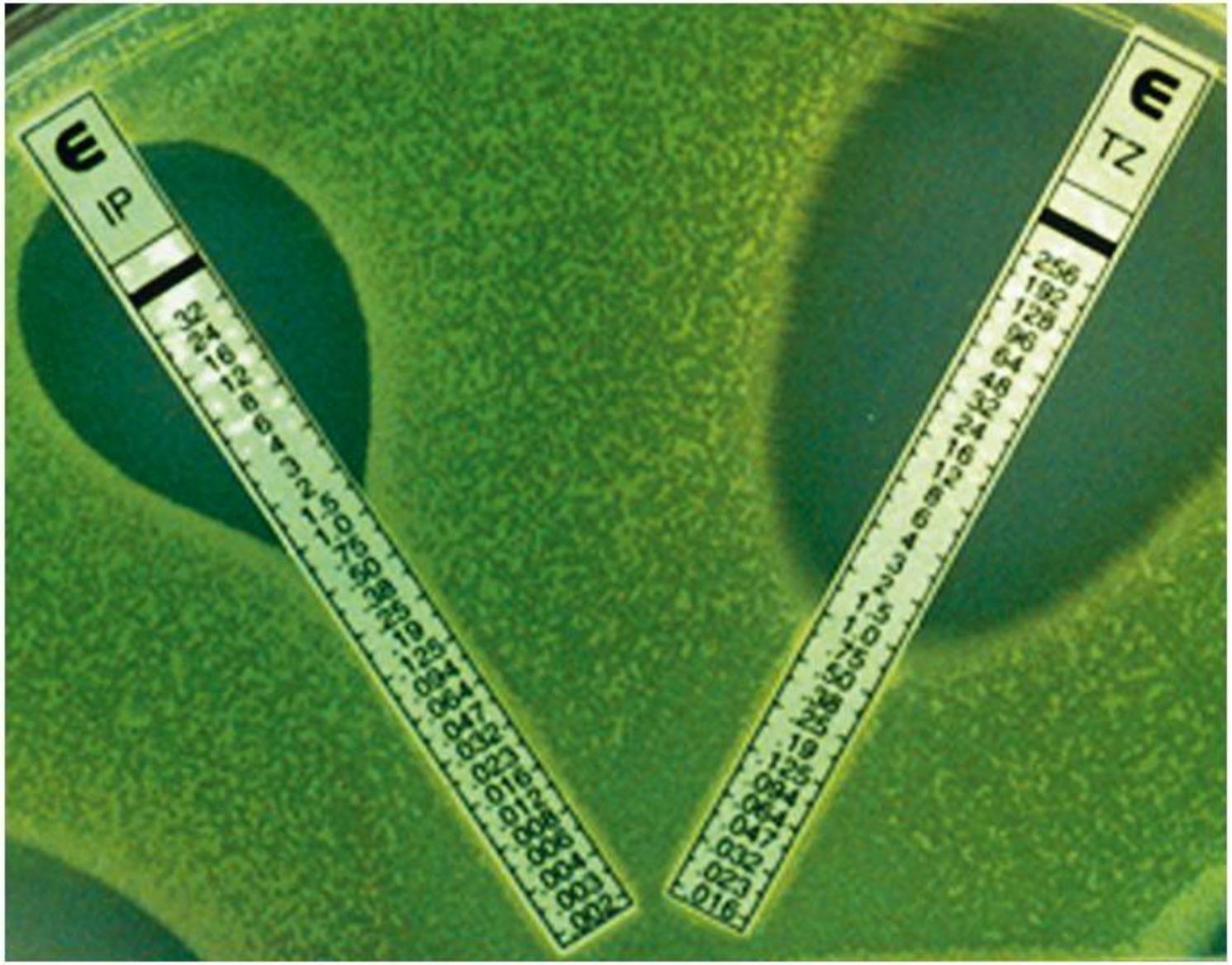


Figure 12.18

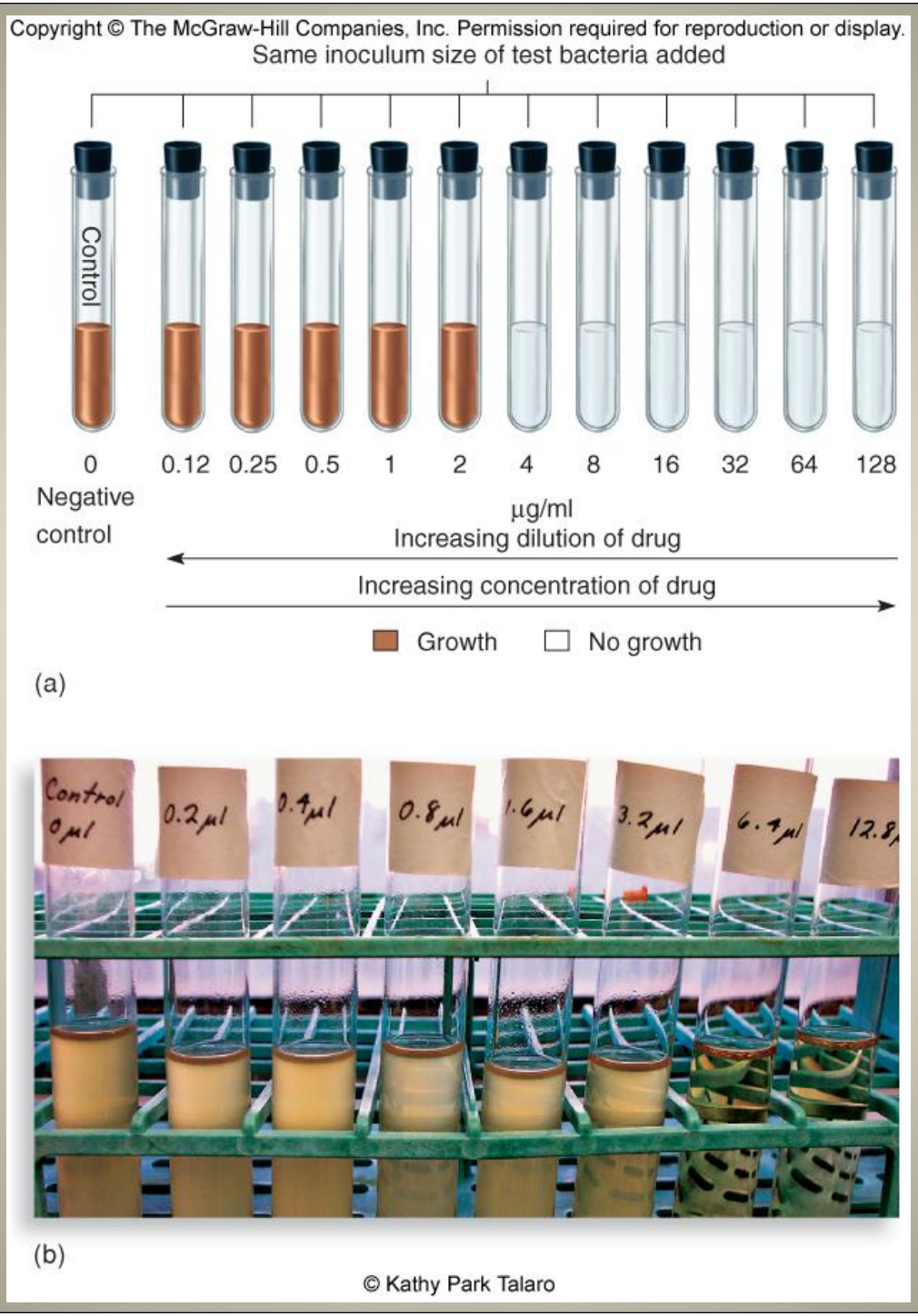


Figure 12.19

The MIC and Therapeutic Index

- **MIC- minimum inhibitory concentration**: the smallest concentration (highest dilution) of drug that visibly inhibits growth
- Once therapy has begun, it is important to observe the patient's clinical response

If Antimicrobial Treatment Fails

- If antimicrobial treatment fails, the failure is due to
  - The inability of the drug to diffuse into that body compartment
  - A few resistant cells in the culture that did not appear in the sensitivity test
  - An infection caused by more than one pathogen, some of which are resistant to the drug

Best Choice of Drug

- Best to choose the drug with high selective toxicity for the infectious agent and low human toxicity
  - **Therapeutic index (TI)**: the ratio of the dose of the drug that is toxic to humans as compared to its minimum effective dose
  - The smaller the ratio, the greater the potential for toxic drug reactions