Antibiotics

What are antibiotics?
Who are the main producers?
Biological functions?
Resistance
New developments

First antimicrobial aproaches

Louis Pasteur (1822-1895):

"pasteurization"
Fermentation: wine
contamination
Germ theory: silkworn disease
Vaccine: anthrax, fowl cholera
Rabies

First antimicrobial drugs

Paul Ehrilch (1854-1915):

- Methylene blue: malaria
-Toxin and antitoxin

-Salvarsan: magic bullet against syphilis, *Treponema pallidum*

First antimicrobial drugs

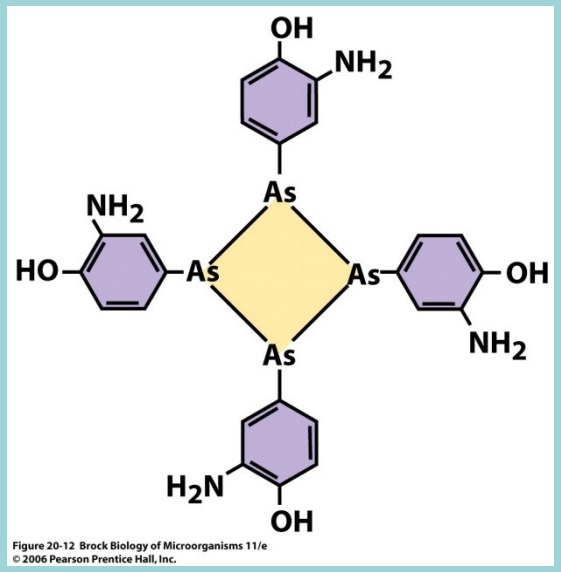

Figure 20-12 Brock Biology of Microorganisms 11/e
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- Gerhard Domagk (Nobel Prize 1939)

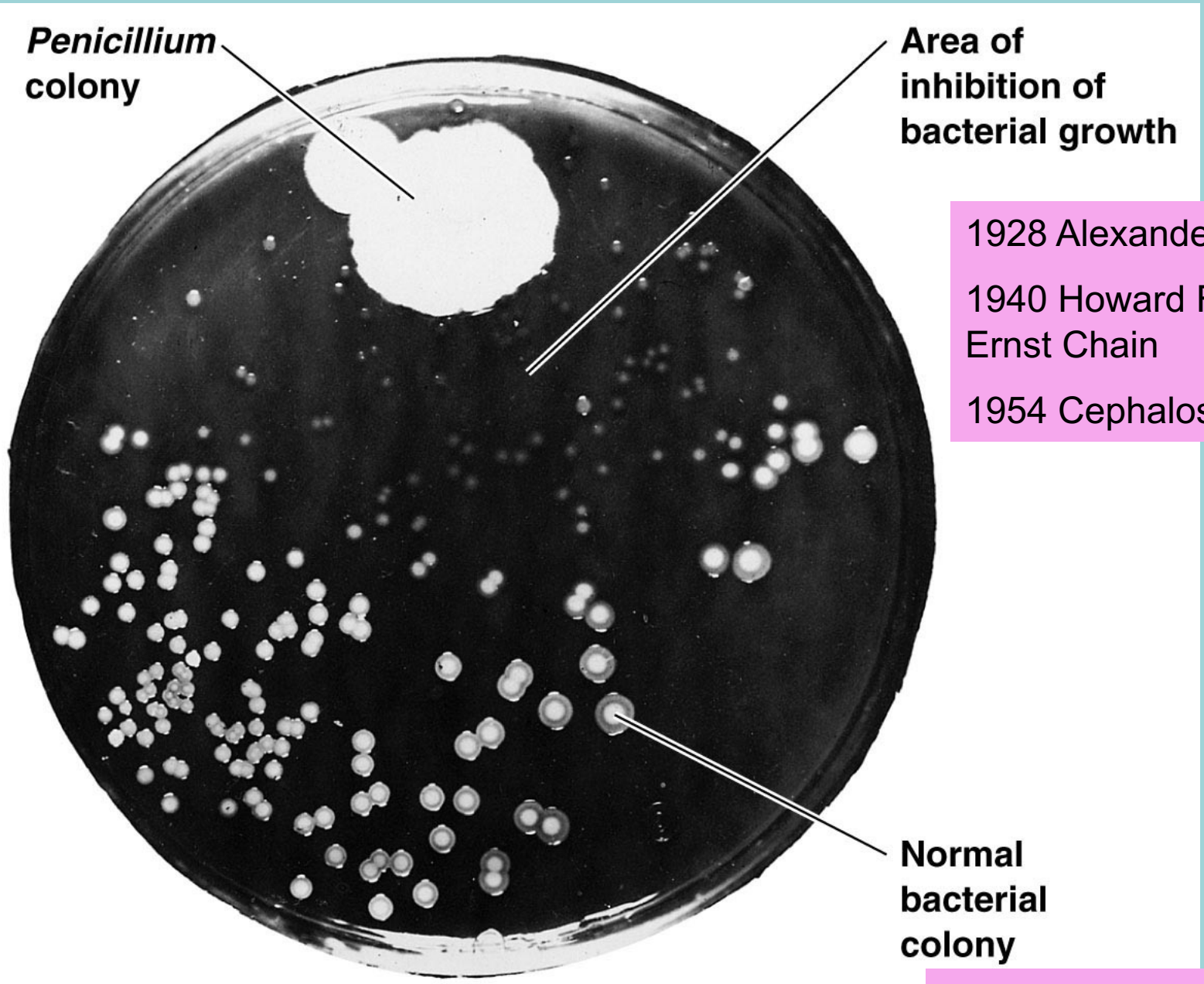
  Sulfa drugs

  Prontosil

  Sulfanilamide, analog of p-aminobenzoic acid

  (part of folic acid, precursor of nucleic acids)

  Development of antituberculosis compounds thiosemiccarbasone and isoniazid



1928 Alexander Fleming

1940 Howard Florey
Ernst Chain

1954 Cephalosporin C

Staphylococcus aureus

Figure 20.1

Salman Waksman, Albert Schatz

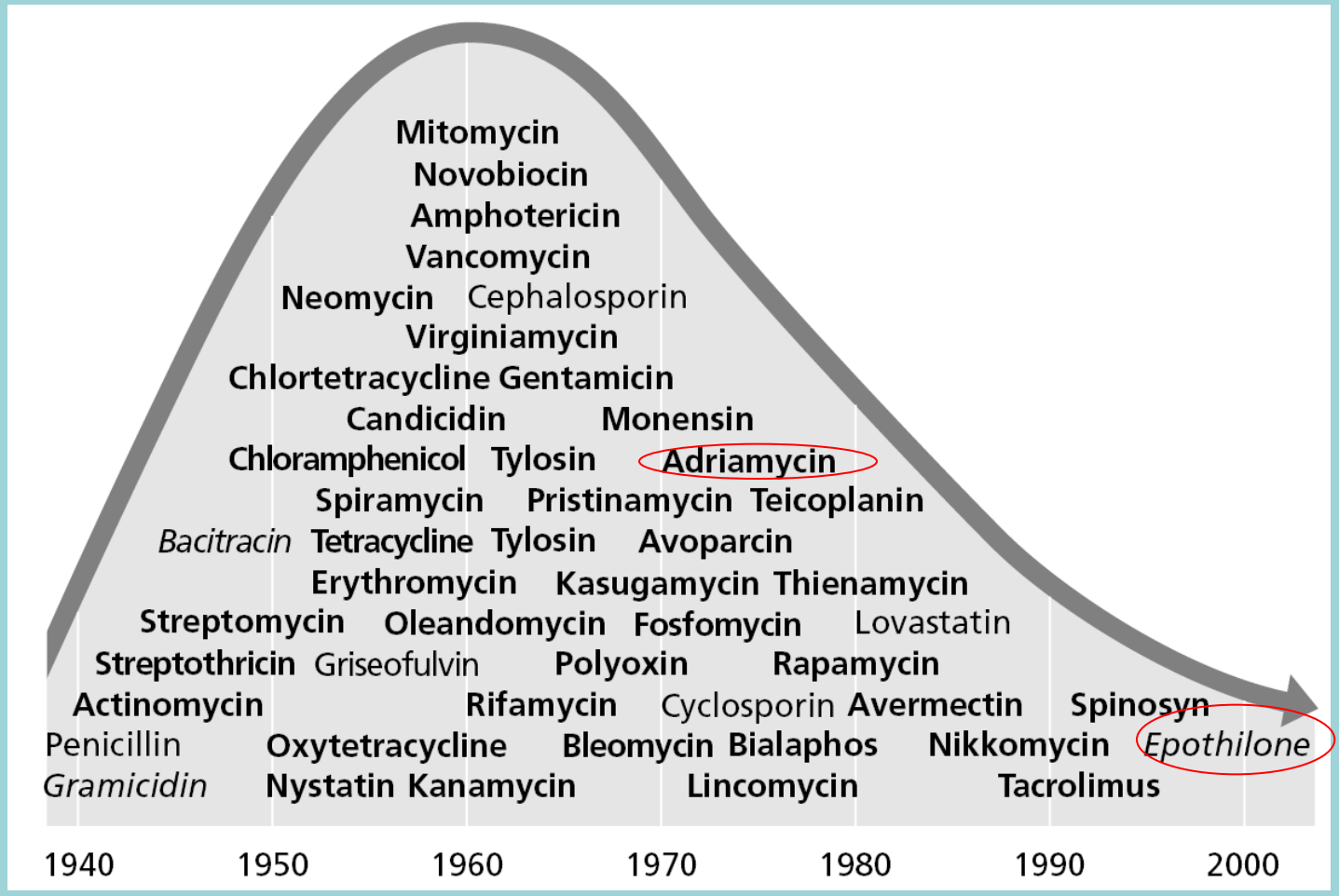
Antibiotics produced by *Streptomyces* filamentous bacteria

1943. Streptomyces griseus

Actinomycin

Streptomycin

Diminishing returns in finding natural products: Genetics to the rescue?



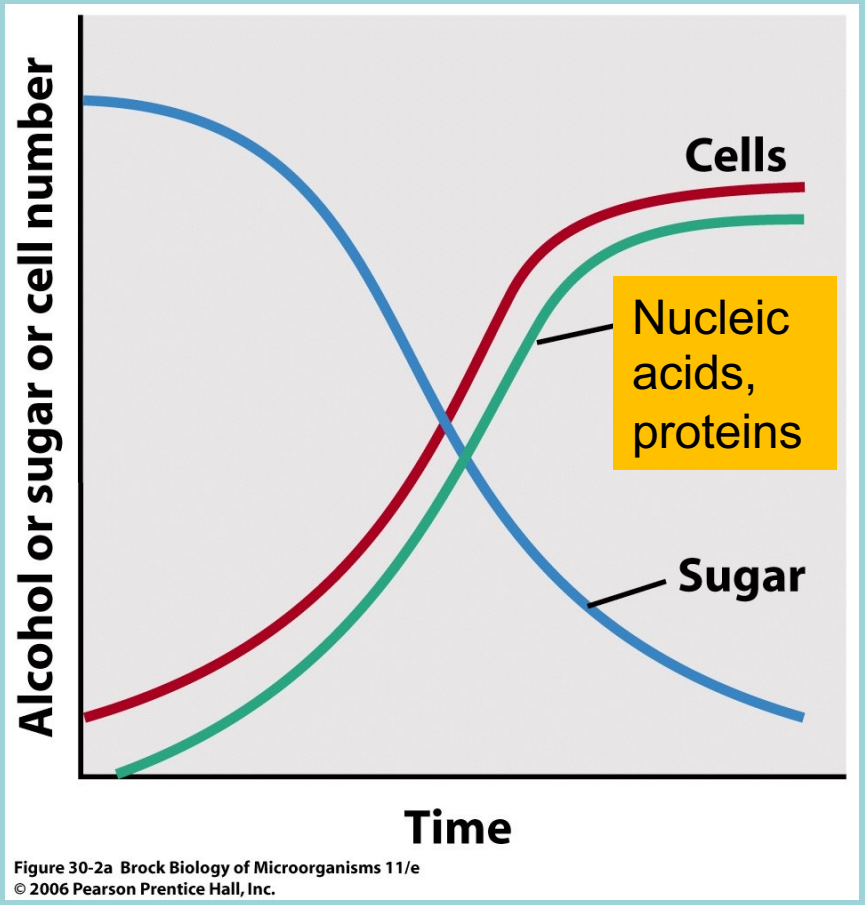


Figure 30-2a Brock Biology of Microorganisms 11/e

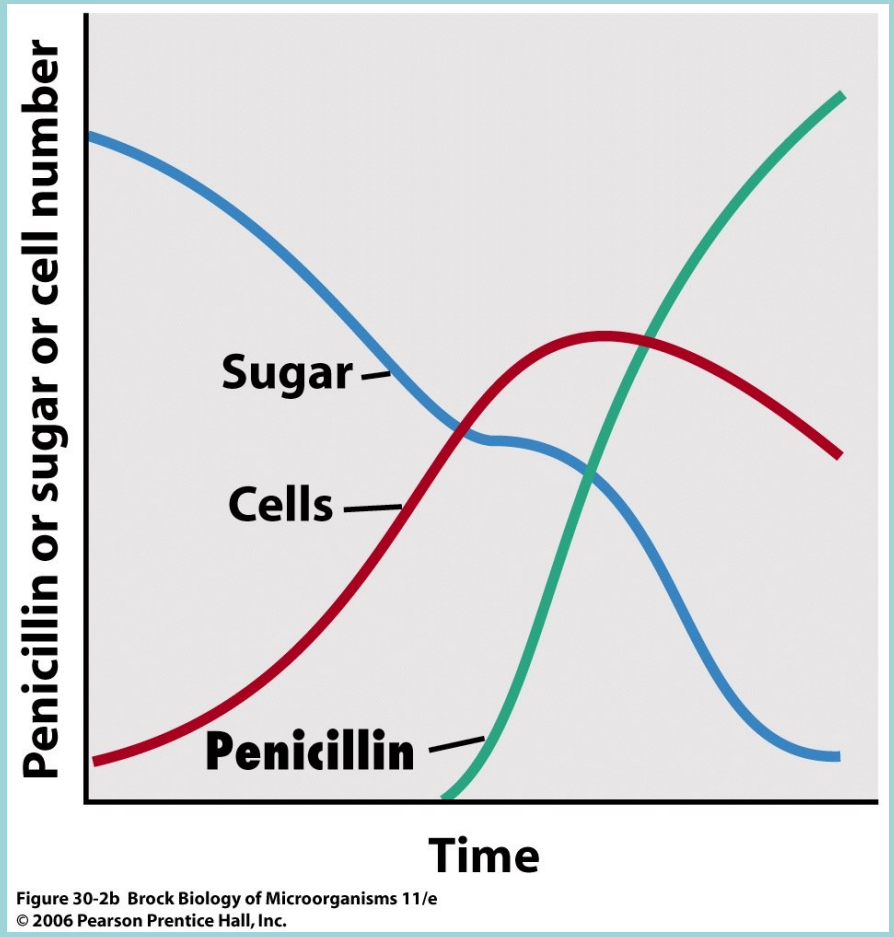


Figure 30-2b Brock Biology of Microorganisms 11/e

Primary and secondary metabolism

What are antibiotics?

- Secondary metabolites synthesized by some microorganisms

Who are the main producers

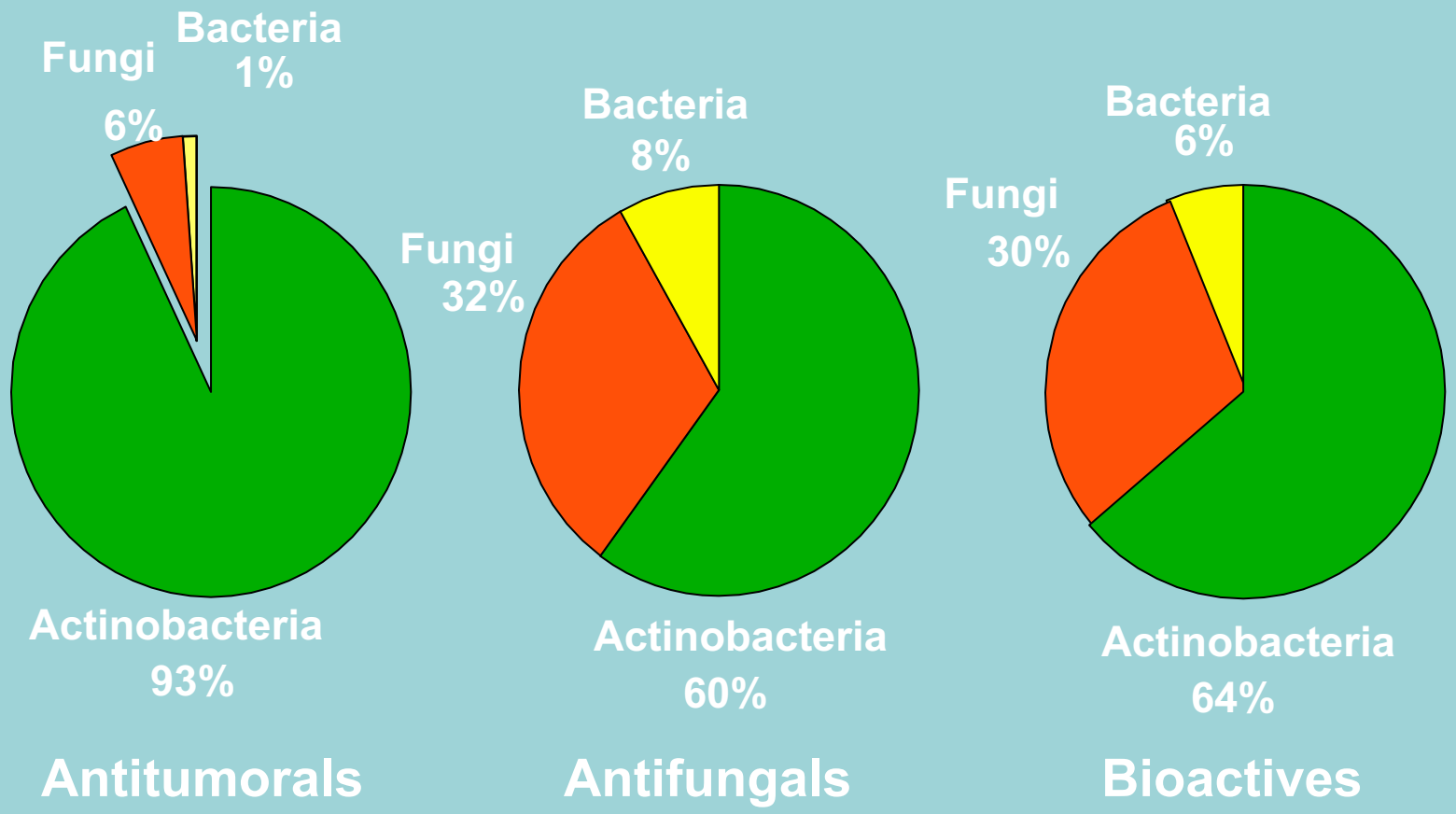
- Bacteria

  Gram positive *Streptomyces*
- Fungi
- Other bacteria

TABLE 20.1 Representative Sources of Antibiotics

Microorganism	Antibiotic
Gram-Positive Rods	
Bacillus subtilis	Bacitracin
Paenibacillus polymyxa	Polymyxin
Actinomycetes	
Streptomyces nodosus	Amphotericin B
Streptomyces 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

MICROORGANISMS and BIOACTIVE COMPOUNDS



BIOACTIVE COMPOUNDS SYNTHESIZED BY ACTINOBACTERIA

ANTIBACTERIALS

Erythromycin
Tetracycline
Gentamicin

ANTIFUNGALS

Amphotericin B
Nystatin

ANTIPARASITICS

Avermectins

ANTITUMORALS

Doxorubicin
Mitramycin
Bleomycin

IMUNOSUPRESSANTS

Rapamycin
FK506

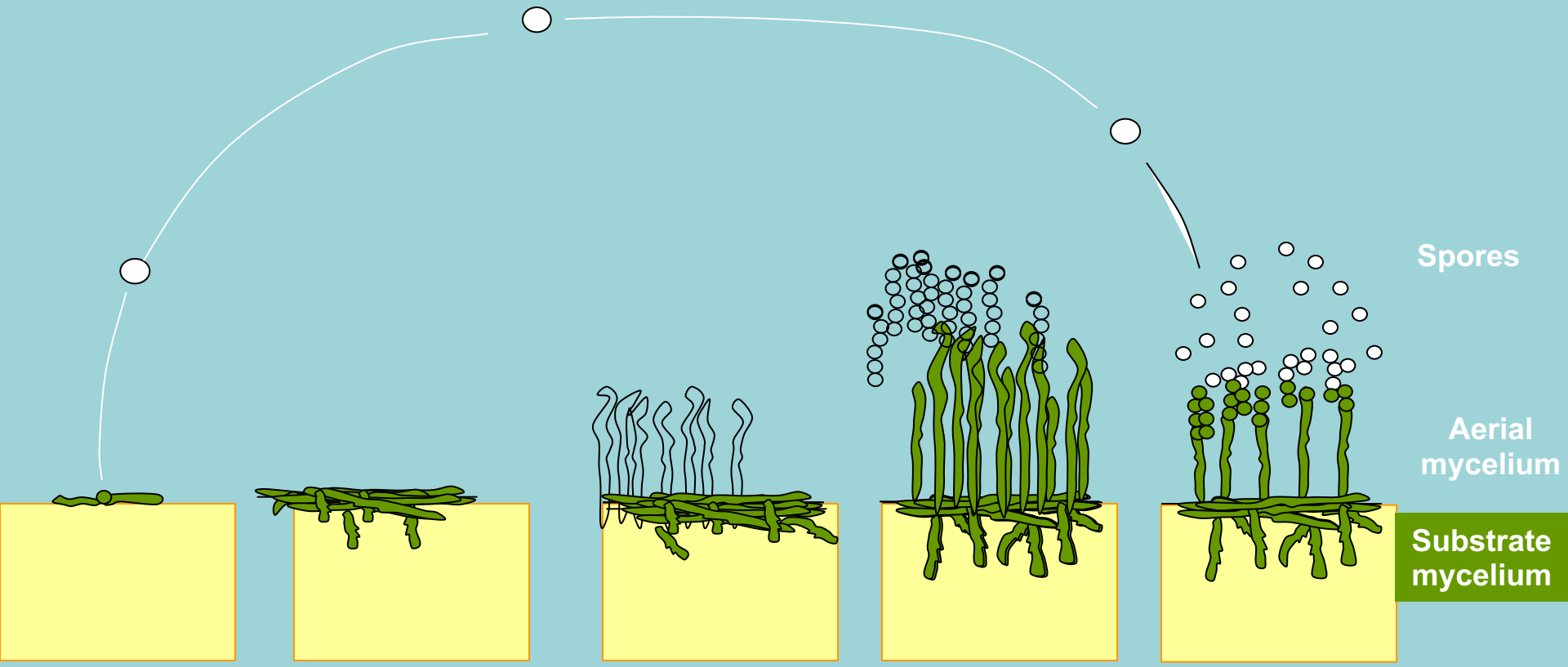
INSETICIDES

Espinosin

HERBICIDES

Bialaphos

LIFE CYCLE OF *Streptomyces*



Production of secondary metabolites

(antibiotics, fungicides, antitumorals,..)

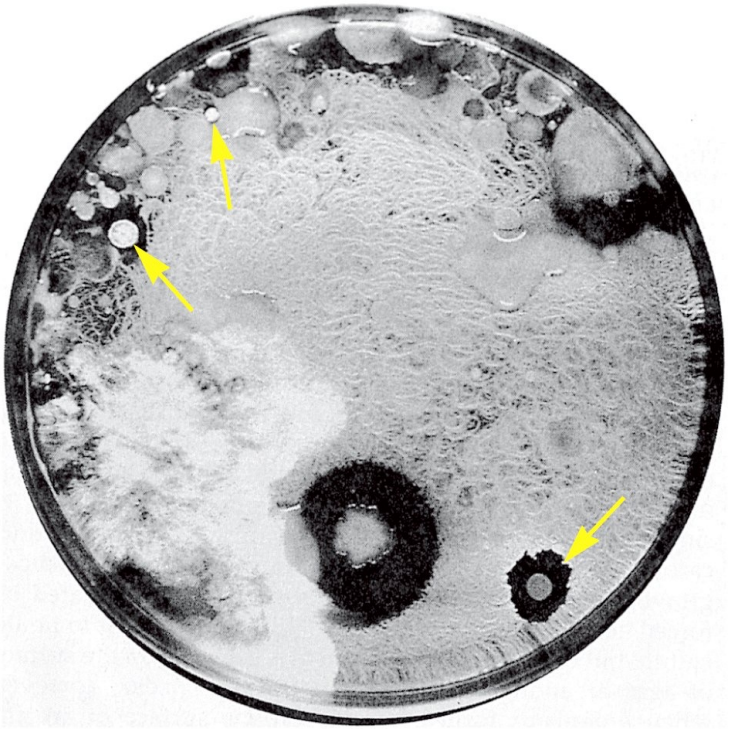


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Figure 12-77a Brock Biology of Microorganisms 11/e
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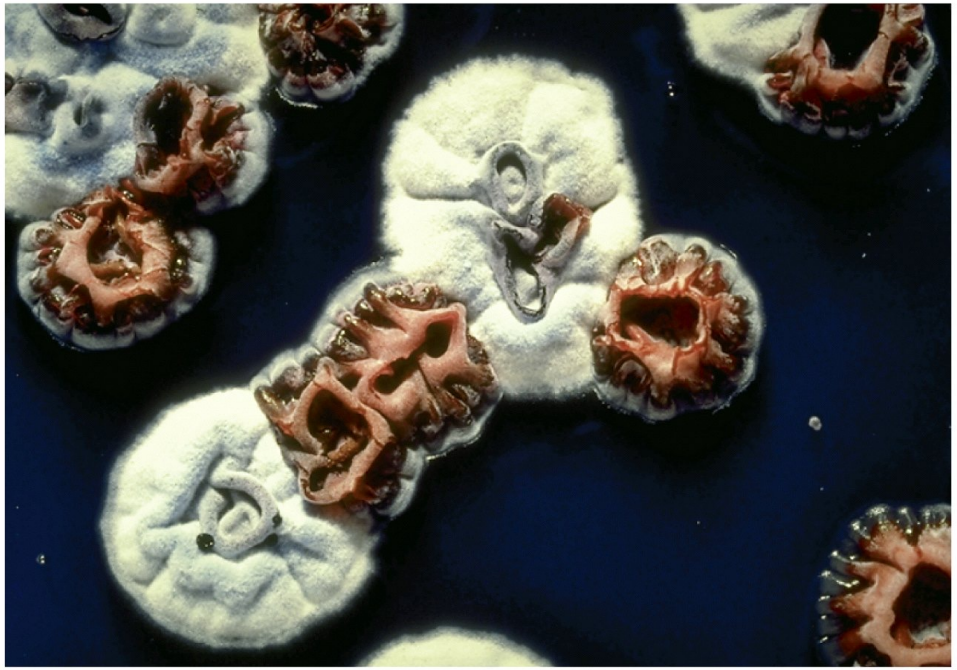

David A. Hopwood

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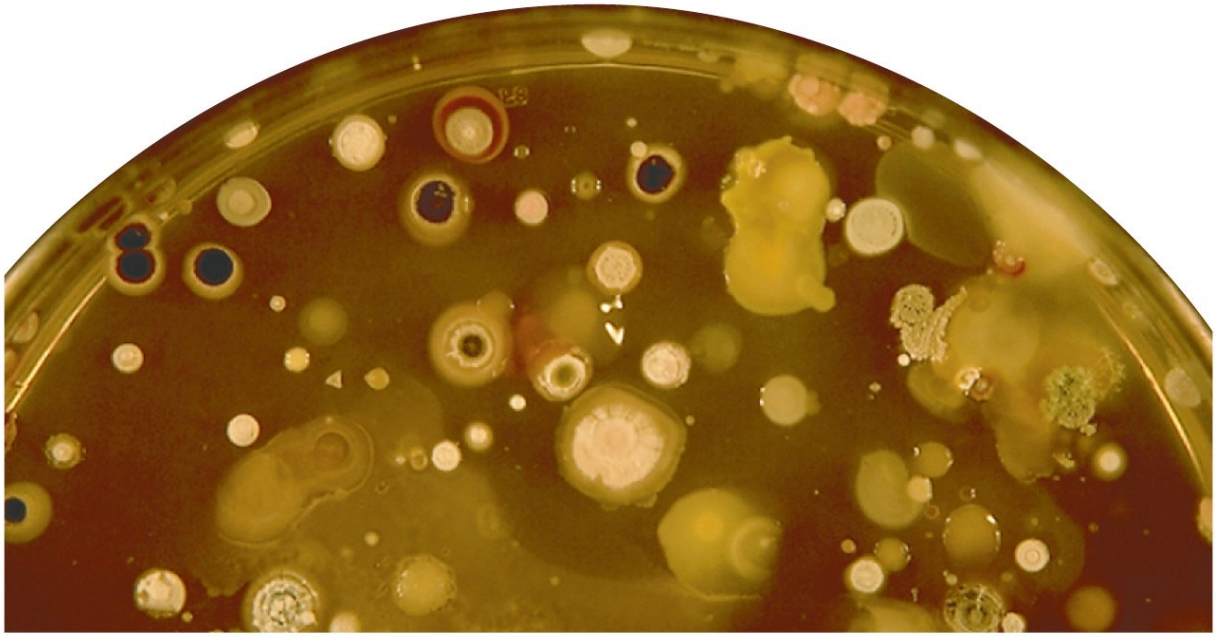


Figure 12-76a Brock Biology of Microorganisms 11/e

Figure 12-76b Brock Biology of Microorganisms 11/e

Biological functions of antibiotics?

- In the producer:

  Activators of morphological differentiation, UV protector, communication

- In the target microorganism:

  Toxicity

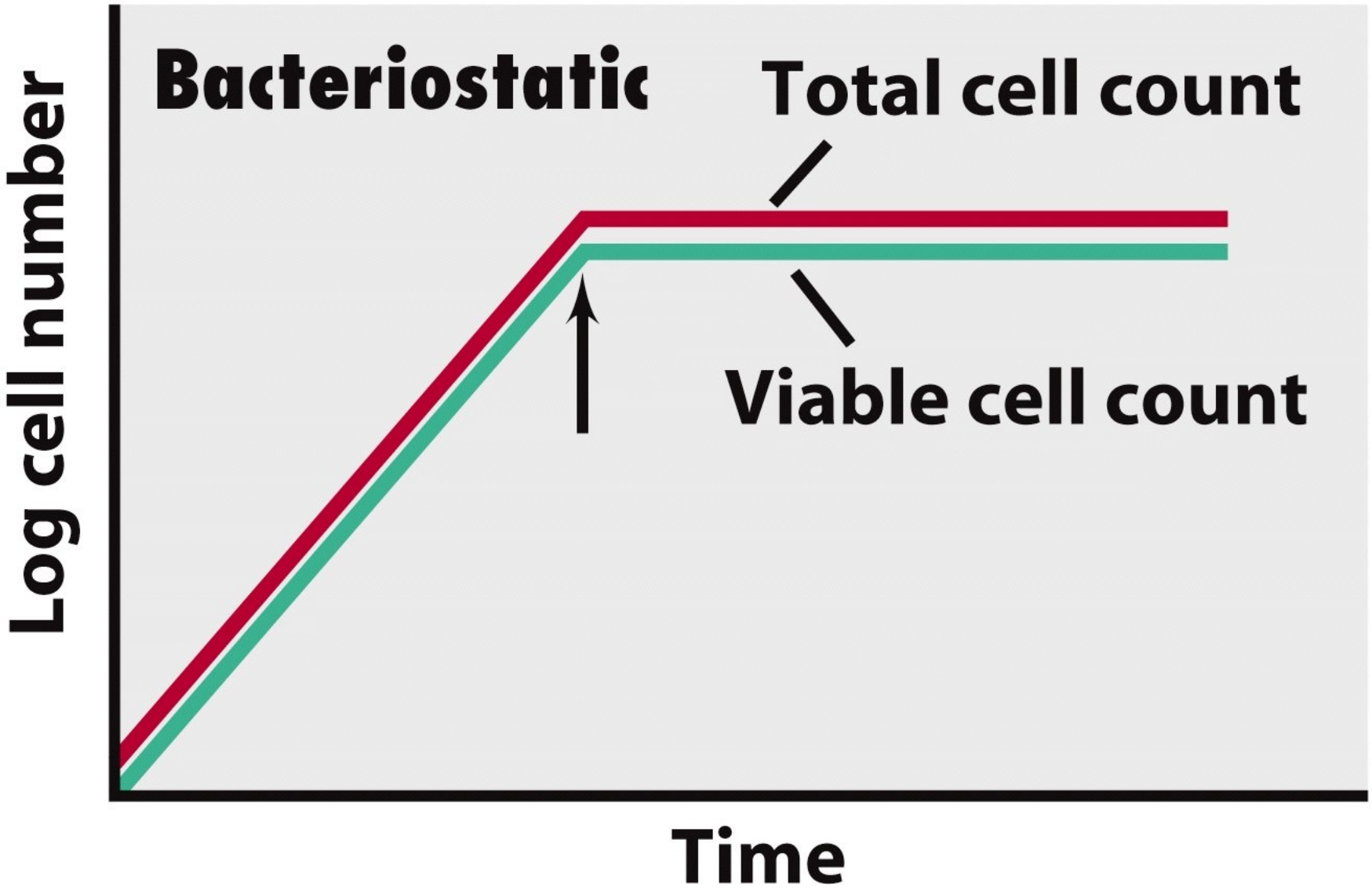


Figure 20-9a Brock Biology of Microorganisms 11/e

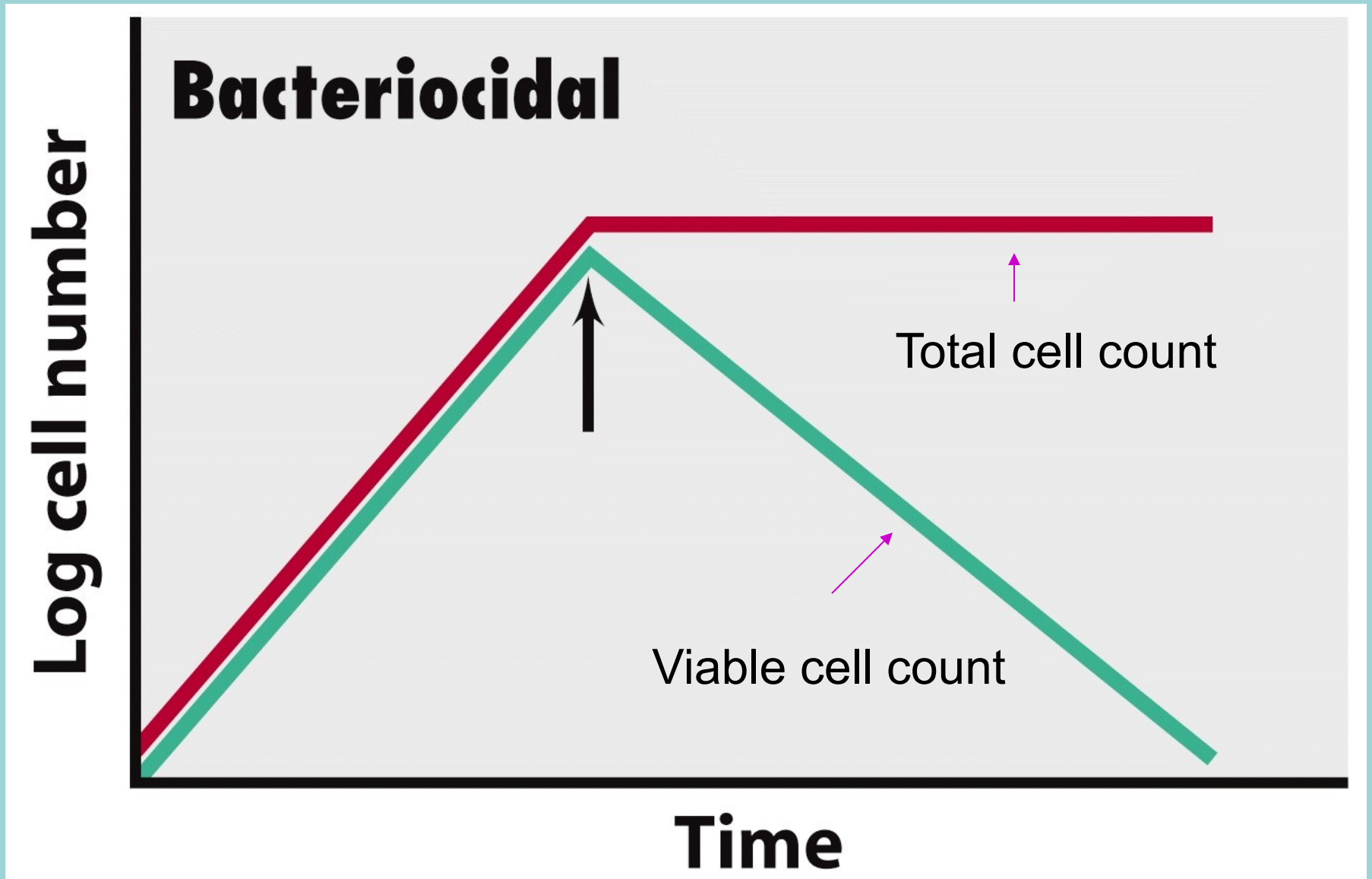


Figure 20-9b Brock Biology of Microorganisms 11/e

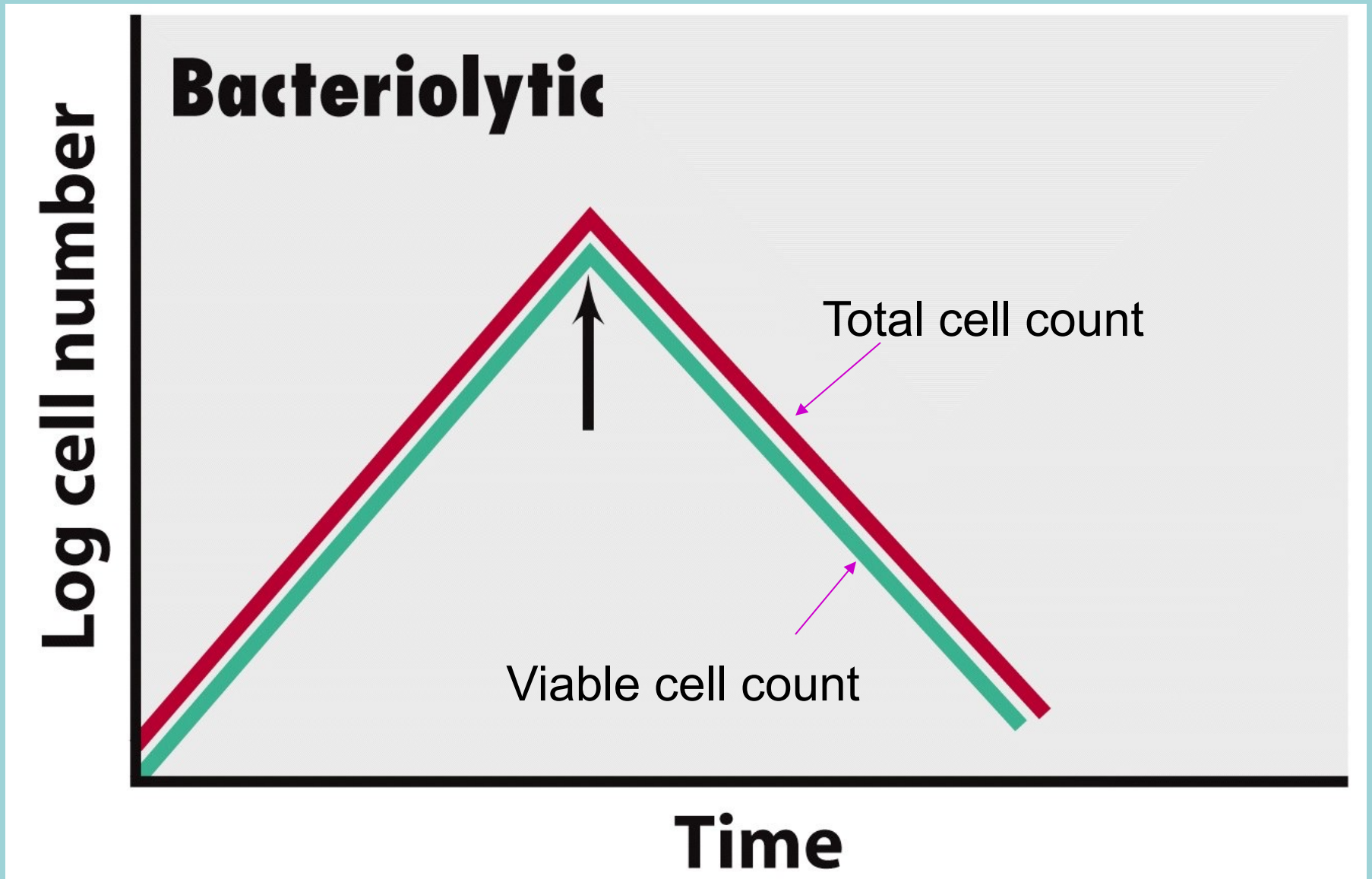
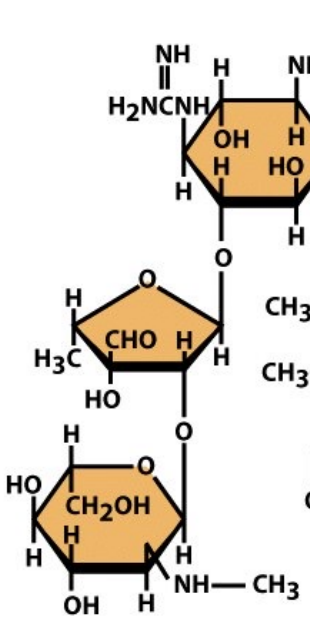


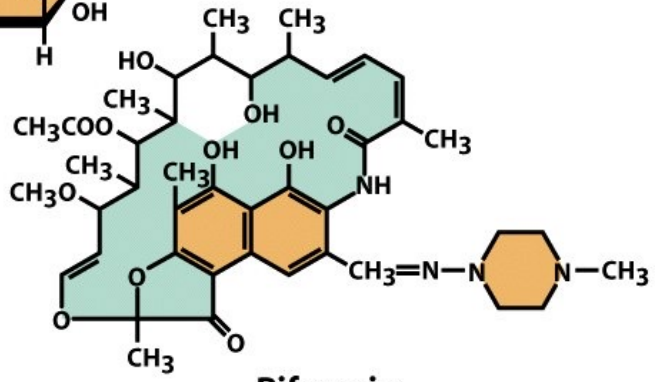
Figure 20-9c Brock Biology of Microorganisms 11/e

Antibiotic classification		Subclassification	Example
I.	Carbohydrate-containing compounds	Pure sugars	Nojirimycin
		Aminoglycosides	Streptomycin
		Orthosomycins	Everninomicin
		N-Glycosides	Streptothricin
		C-Glycosides	Vancomycin
		Glycolipids	Moenomycin
II.	Macrocyclic lactones	Macrolide antibiotics	Erythromycin
		Polyene antibiotics	Candicidin
		Ansamycins	Rifampin
		Macrotetrolides	Tetranactin
III.	Quinones and related compounds	Tetracyclines	Tetracycline
		Anthracyclines	Adriamycin
		Naphthoquinones	Actinorhodin
		Benzoquinones	Mitomycin

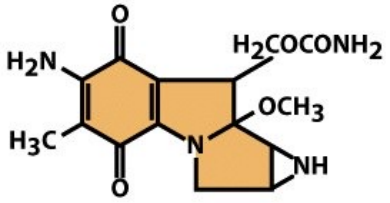
Representative structure



Streptomycin



Rifampin



Mitomycin C

Figure 20-13 part 1 Brock Biology of Microorganisms 11/e

Antibiotic classification		Subclassification	Example
IV.	Amino acid and peptide analogs	Amino acid derivatives	Cycloserine
		β-Lactam antibiotics	Penicillin, ceftriaxone
		Peptide antibiotics	Bacitracin
		Chromopeptides	Actinomycin
		Depsipeptides	Valinomycin
		Chelate-forming peptides	Bleomycin
V.	Heterocyclic compounds containing nitrogen	Nucleoside antibiotics	Polyoxins
VI.	Heterocyclic compounds containing oxygen	Polyether antibiotics	Monensin

Representative structure

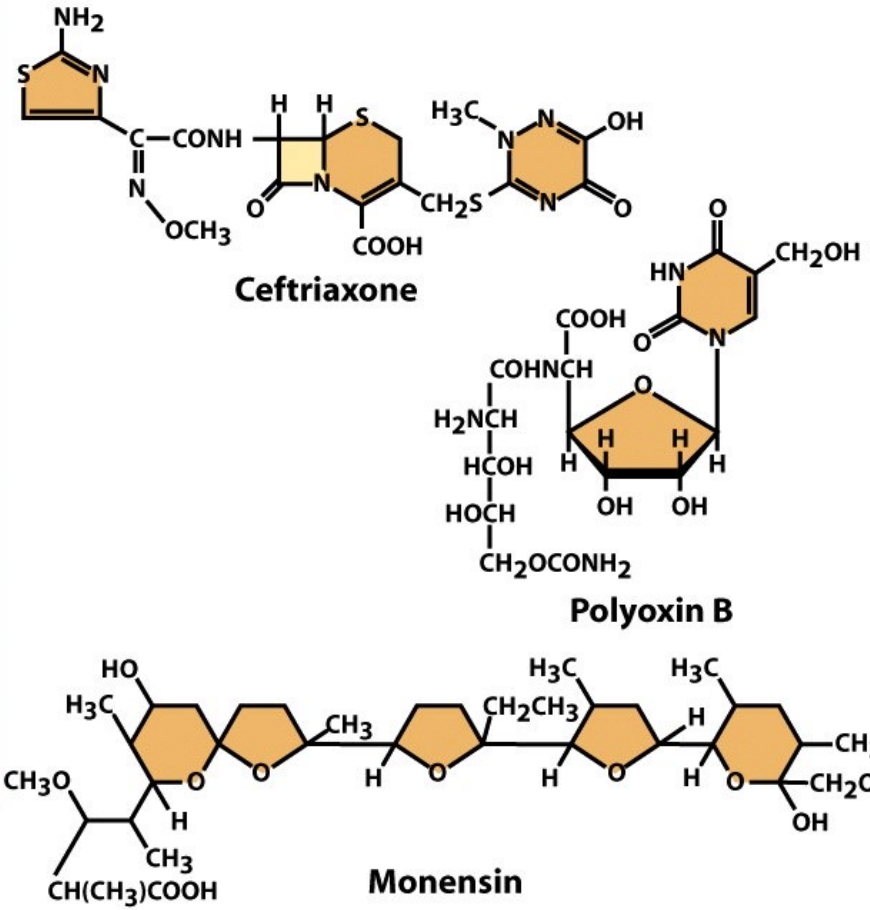


Figure 20-13 part 2 Brock Biology of Microorganisms 11/e

Antibiotic classification	Subclassification	Example
VII. Alicyclic derivatives	Cycloalkane derivatives	Cycloheximide
	Steroid antibiotics	Fusidic acid
VIII. Aromatic compounds	Benzene derivatives	Chloramphenicol
	Condensed aromatics	Griseofulvin
	Aromatic ether	Novobiocin
IX. Aliphatic compounds	Compounds containing phosphorus	Fosfomycin

Representative structure

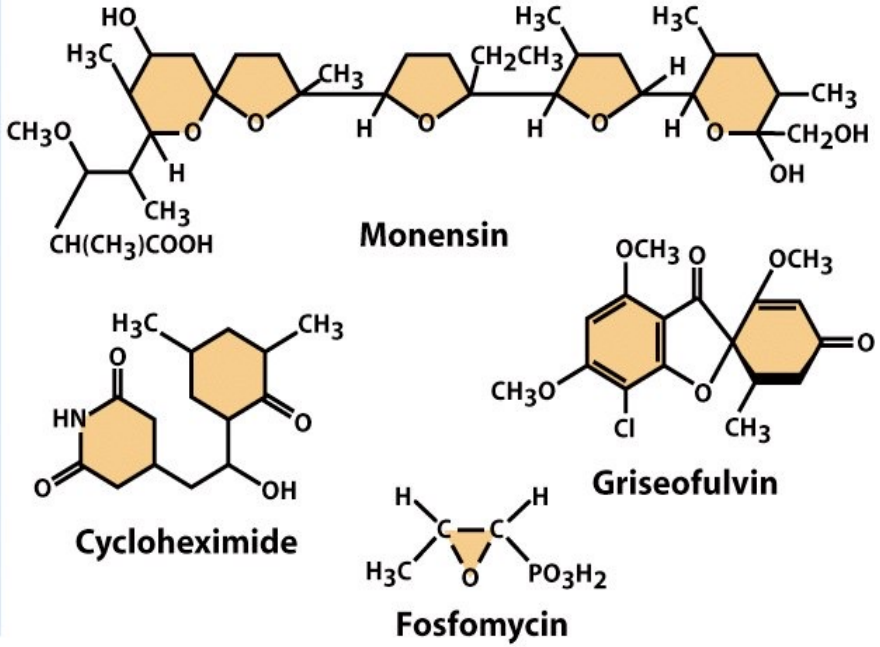
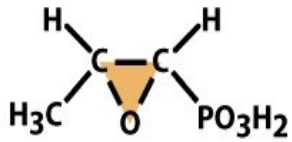
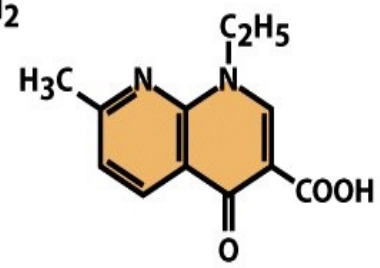


Figure 20-13 part 3 Brock Biology of Microorganisms 11/e

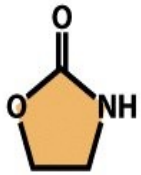
Antibiotic classification		Subclassification	Example	Representative structure
X.	Quinolone compounds	4-Quinolone Fluoro-4-quinolones	Nalidixic acid Ciprofloxacin	
XI.	Oxazolidinone	Cyclic lactone	2-Oxazolidinone	



Fosfomycin



Nalidixic acid



2-Oxazolidinone

Figure 20-13 part 4 Brock Biology of Microorganisms 11/e

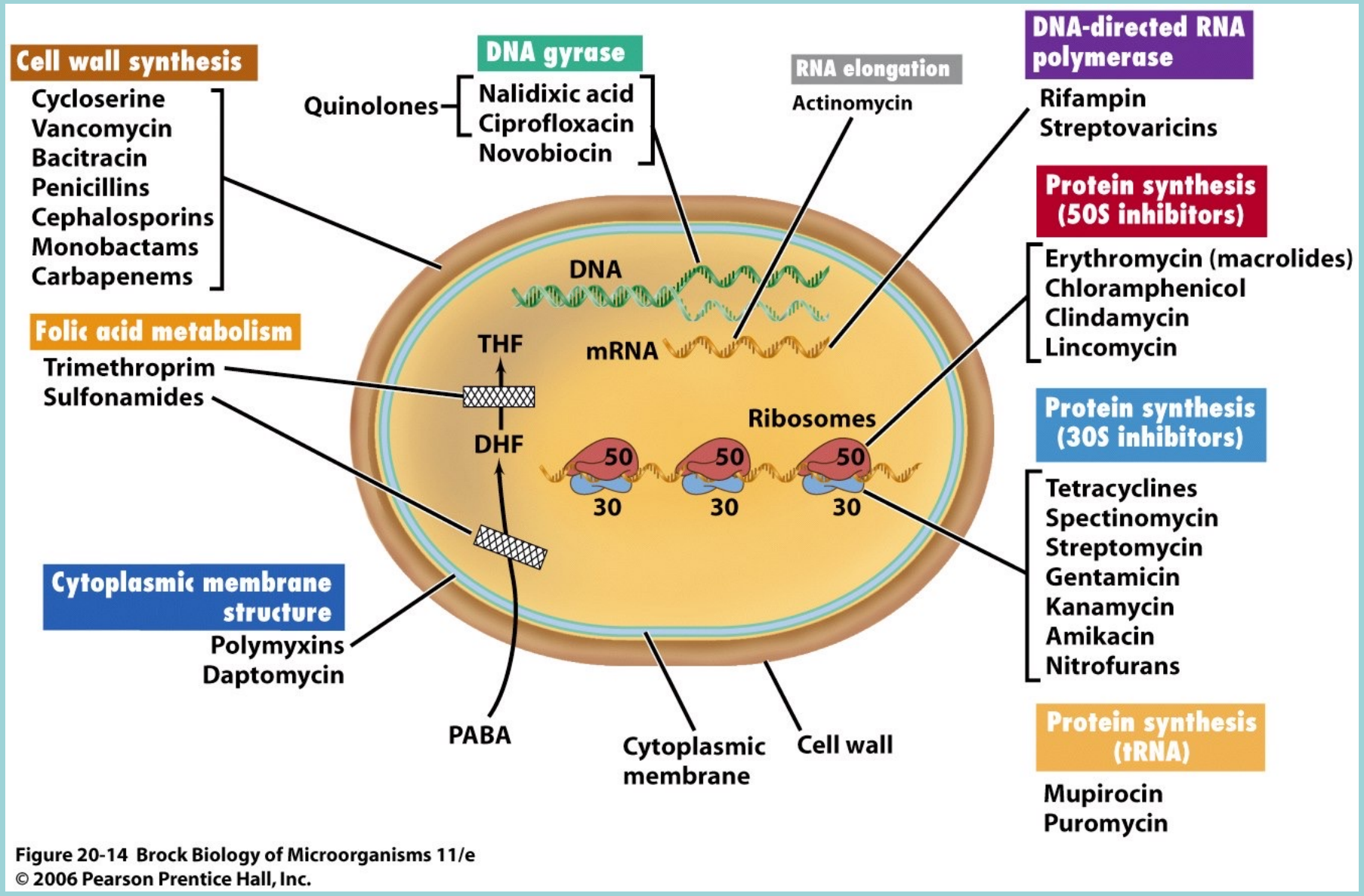


Figure 20-14 Brock Biology of Microorganisms 11/e

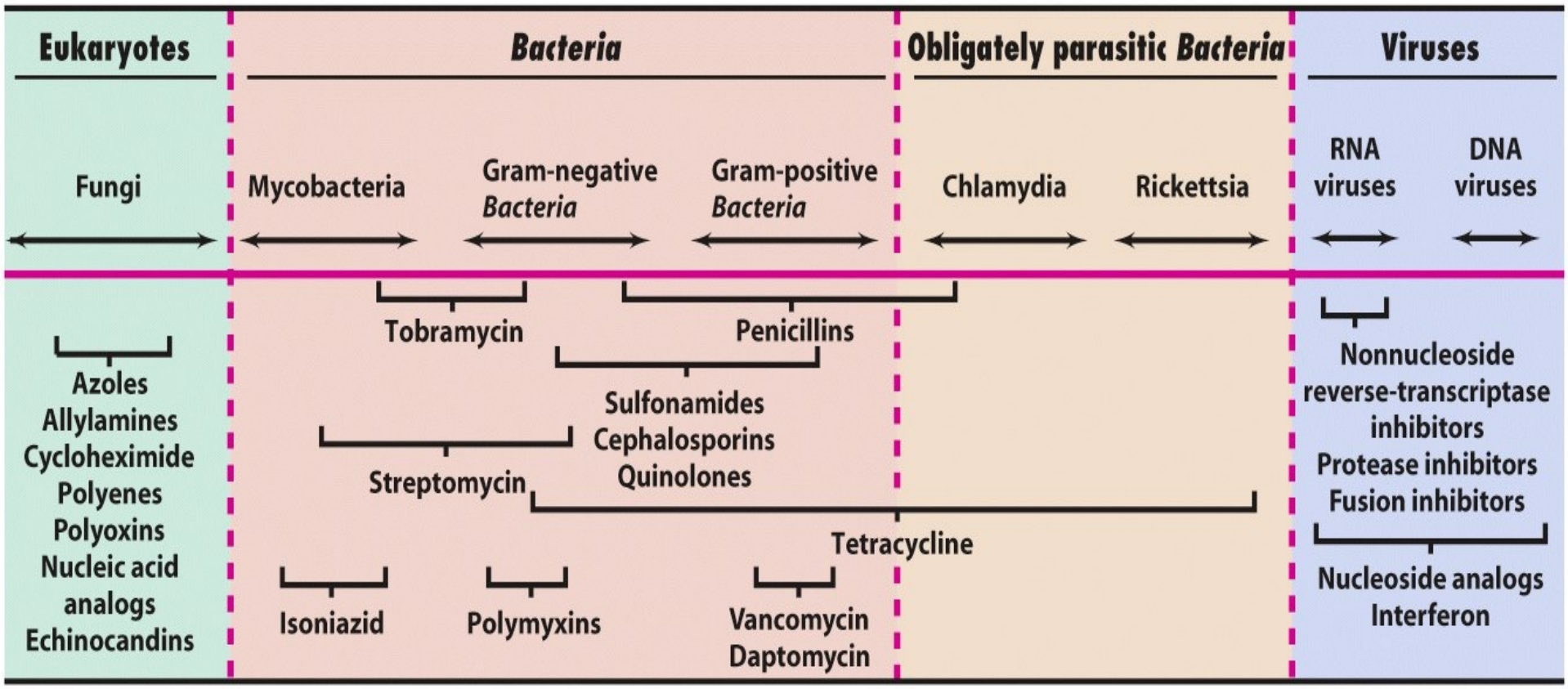


Figure 20-15 Brock Biology of Microorganisms 11/e

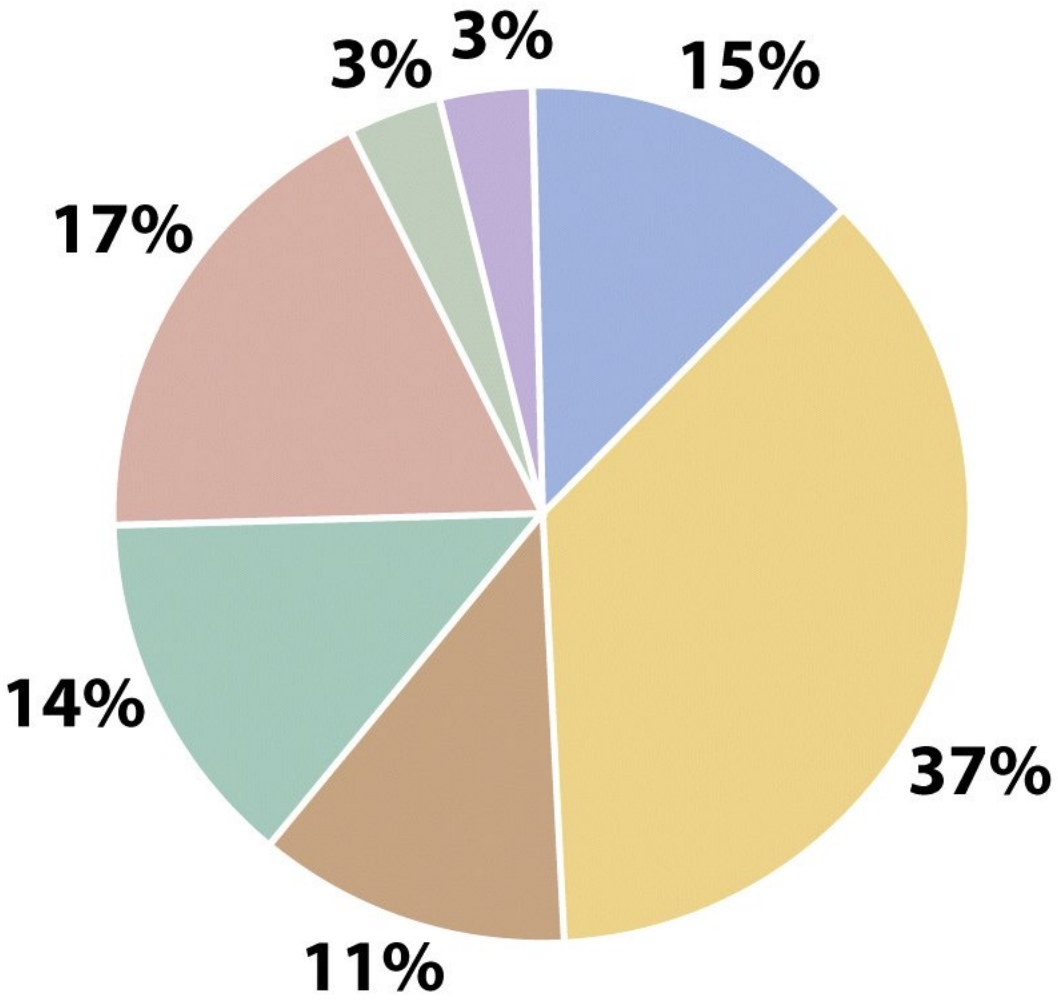


Figure 20-16 Brock Biology of Microorganisms 11/e

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	Third-generation cephalosporin; oral administration

TABLE 20.3 Antibacterial Drugs *(continued)*

Drugs by Mode of Action	Comments
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.
Inhibitors of Protein Synthesis	
Chloramphenicol	Broad spectrum, potentially toxic
Aminoglycosides	
Streptomycin	Broad spectrum, including mycobacteria
Neomycin	Topical use, broad spectrum
Gentamicin	Broad spectrum, including *Pseudomonas* spp.
Tetracyclines	
Tetracycline, oxytetracycline, chlortetracycline	Broad spectrum, including chlamydias and rickettsias; animal feed additives
Macrolides	
Erythromycin	Alternative to penicillin
Azithromycin, clarithromycin	Semisynthetic; broader spectrum and better tissue penetration than erythromycin
Telithromycin (Ketek)	New generation of semisynthetic macrolides; used to cope with resistance to other macrolides

TABLE 20.3 Antibacterial Drugs *(continued)*

Drugs by Mode of Action	Comments
Streptogramins	
Quinupristin and dalfopristin (Synercid)	Alternative for treating vancomycin-resistant gram-positive bacteria
Oxazolidinones	
Linezolid (Zyvox)	Useful primarily against penicillin-resistant gram-positive bacteria
Injury to the Plasma Membrane	
Polymyxin B	Topical use, gram-negative bacteria, including *Pseudomonas* spp.
Inhibitors of Nucleic Acid Synthesis	
Rifamycins	
Rifampin (or rifampicin)	Inhibits synthesis of mRNA; treatment of tuberculosis
Quinolones and Fluoroquinolones	
Nalidixic acid, nofloxacin, ciprofloxacin	Inhibit DNA synthesis; broad spectrum; urinary tract infections
Gatifloxacin	Newest generation quinolone; increased potency against gram-positive bacteria
Competitive Inhibitors of the Synthesis of Essential Metabolites	
Sulfonamides	
Trimethoprim-sulfamethoxazole	Broad spectrum; combination is widely used

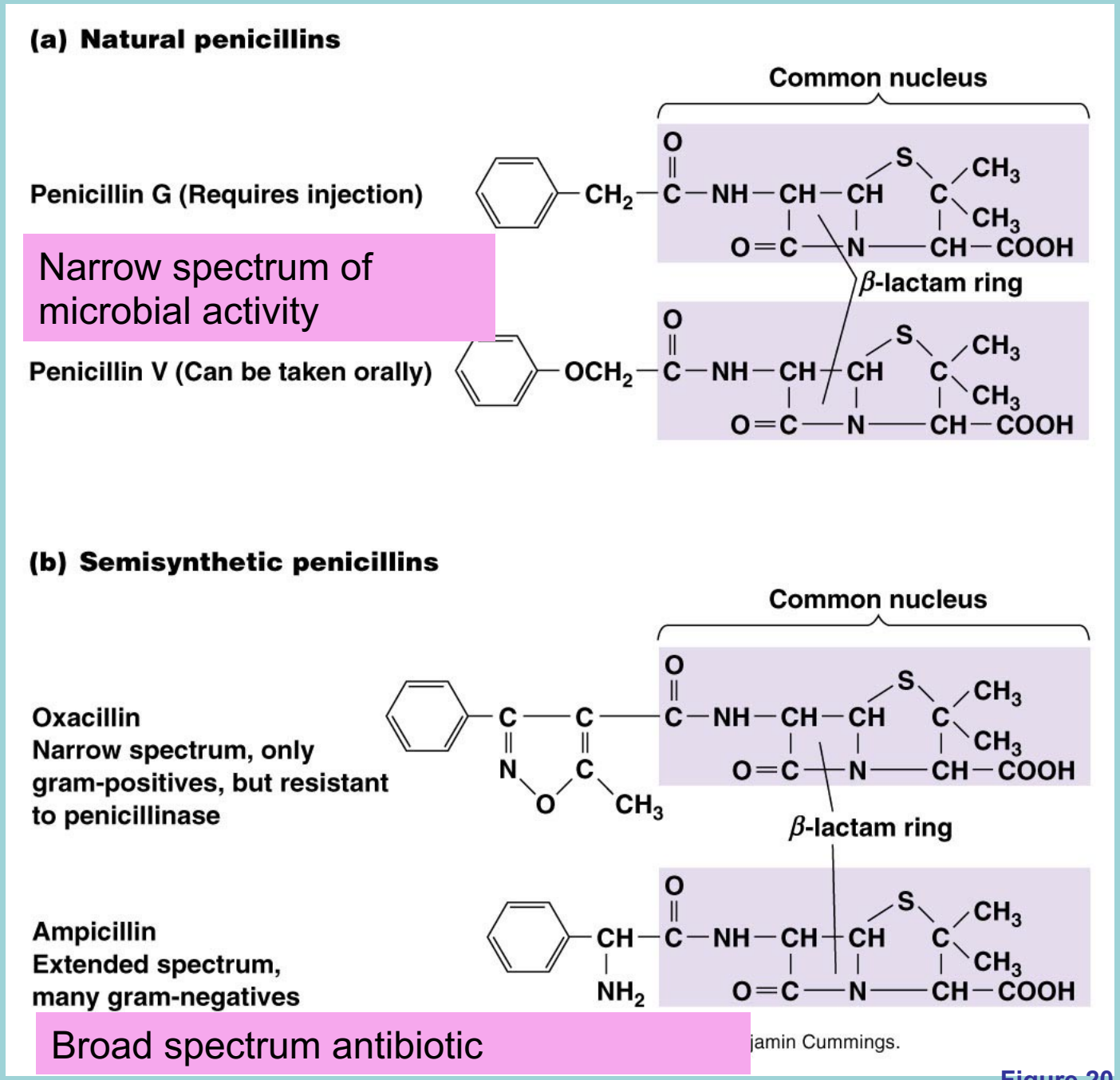


Figure 20.6 - Overview

Structure of peptidoglycan

glycan tetrapeptide

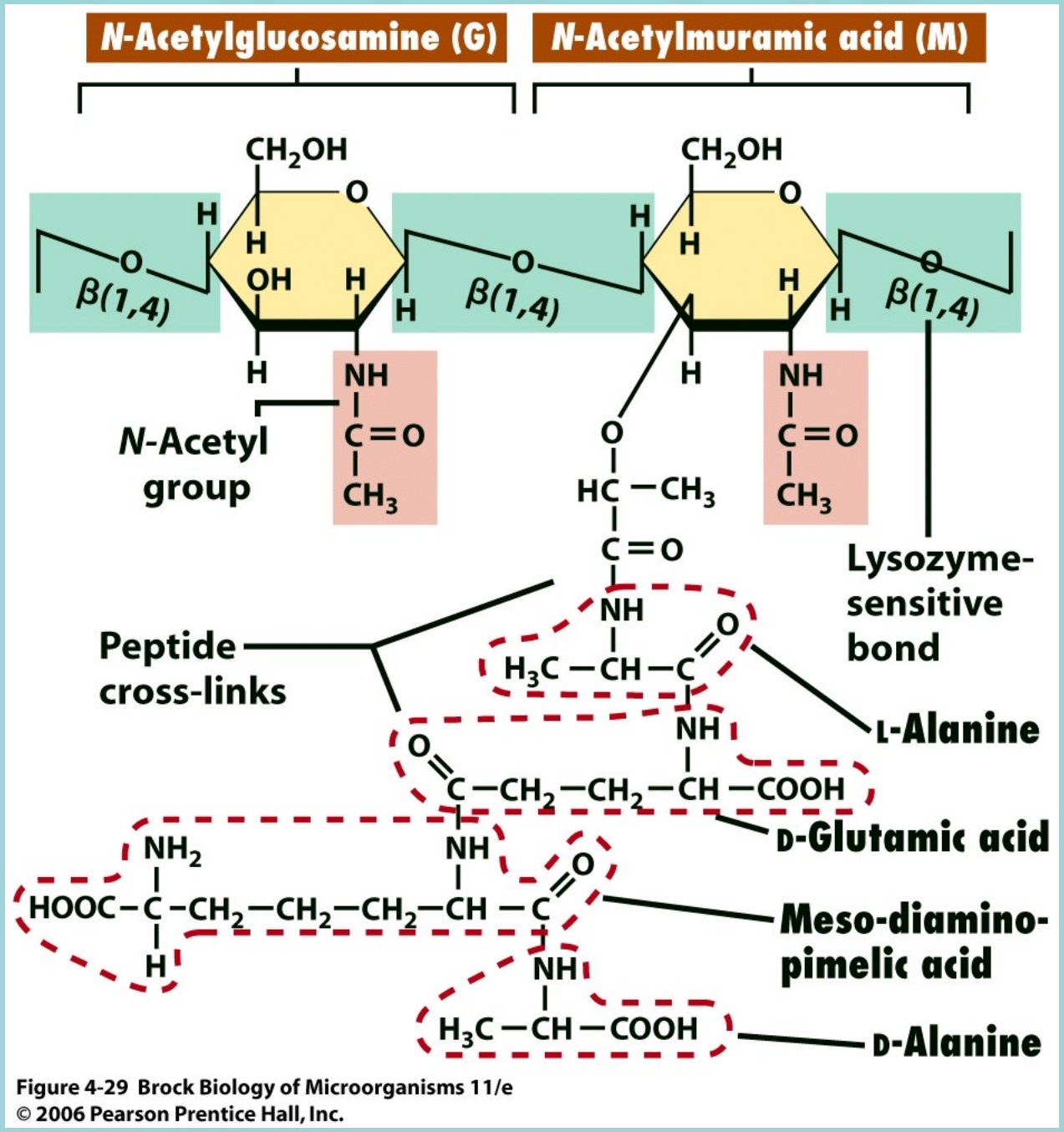


Figure 4-29 Brock Biology of Microorganisms 11/e

Peptidoglycan sheet in *Escherichia coli* and *Staphylococcus aureus*

Glycine interbridge in *S. aureus*

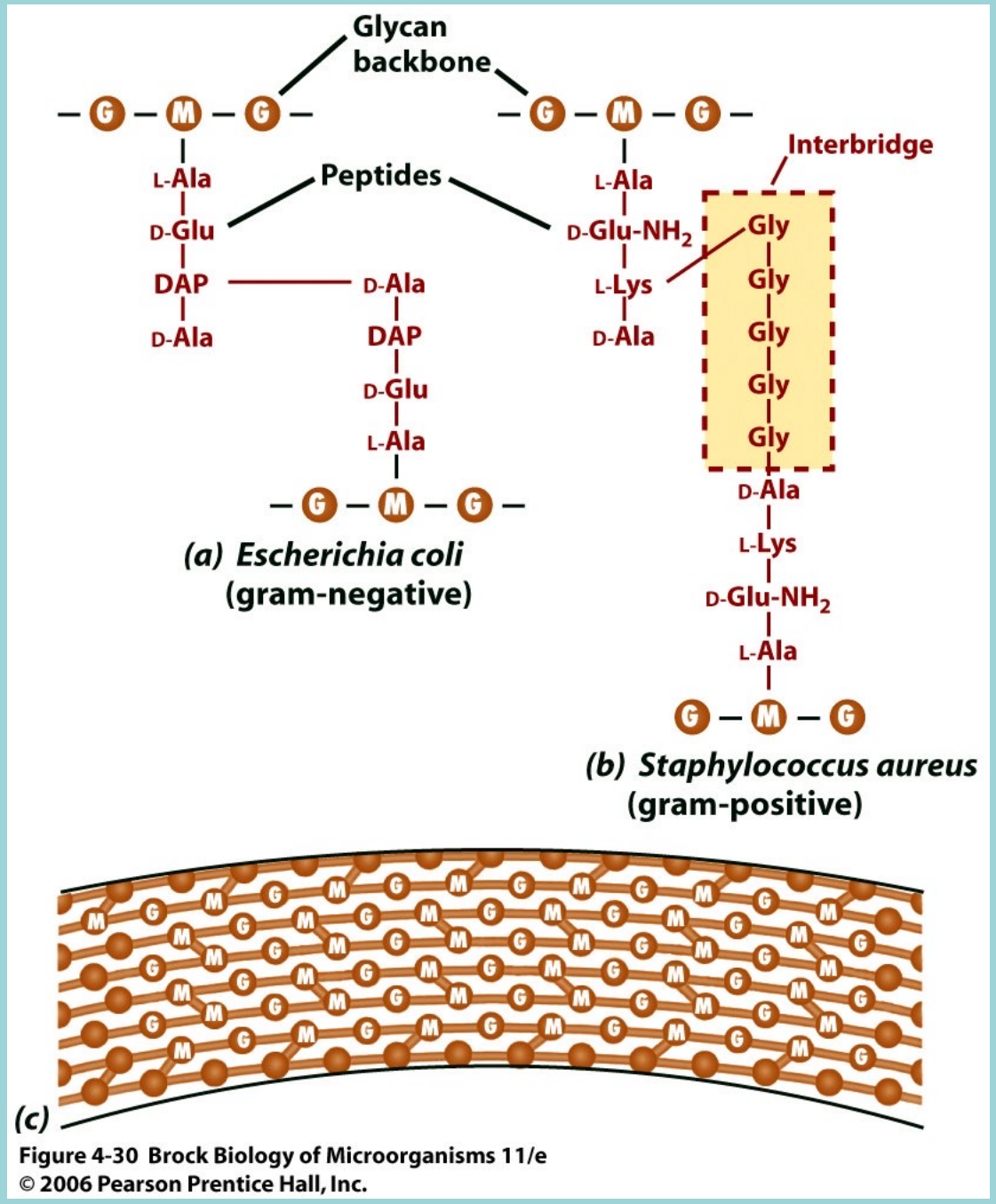
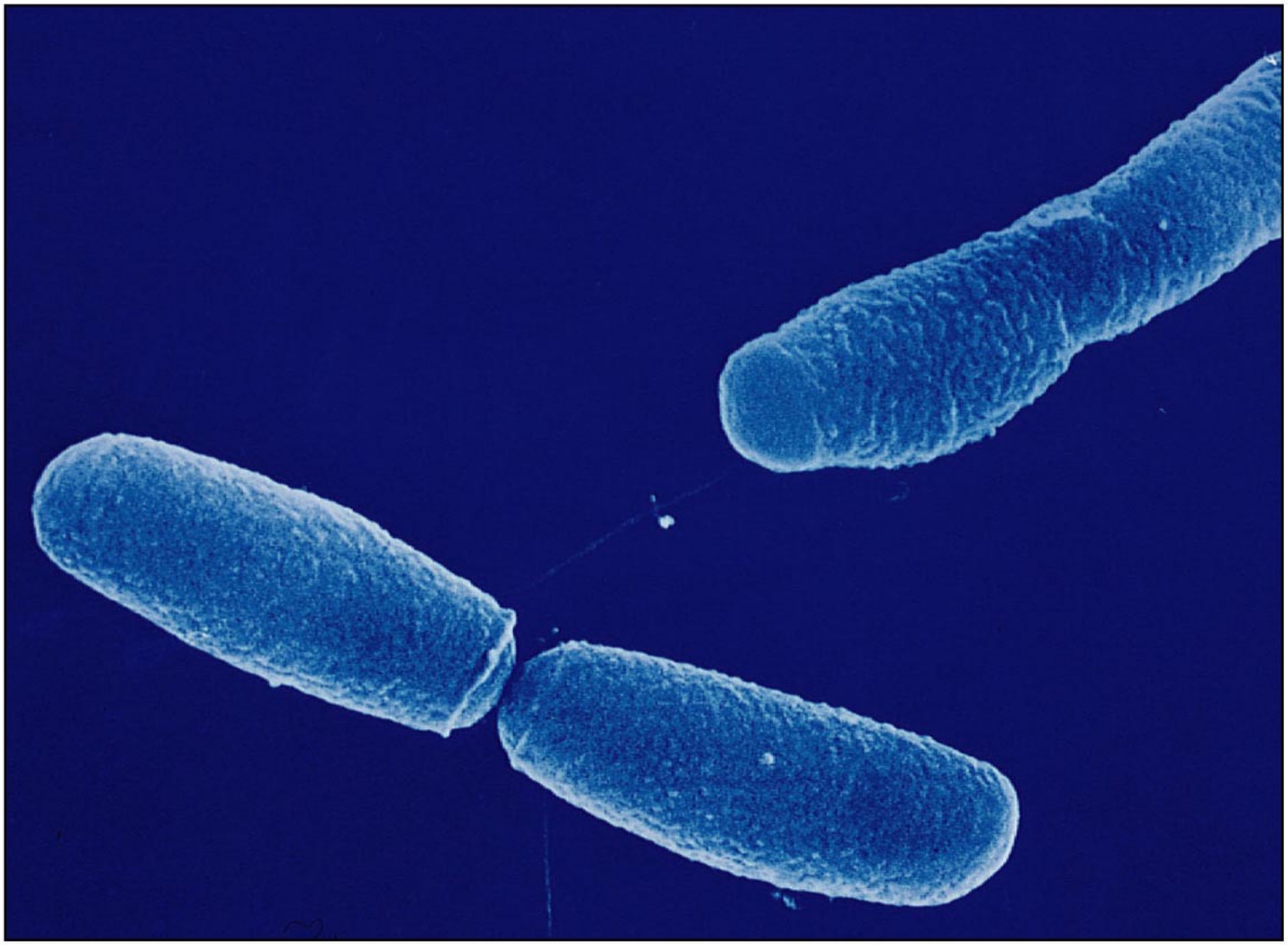
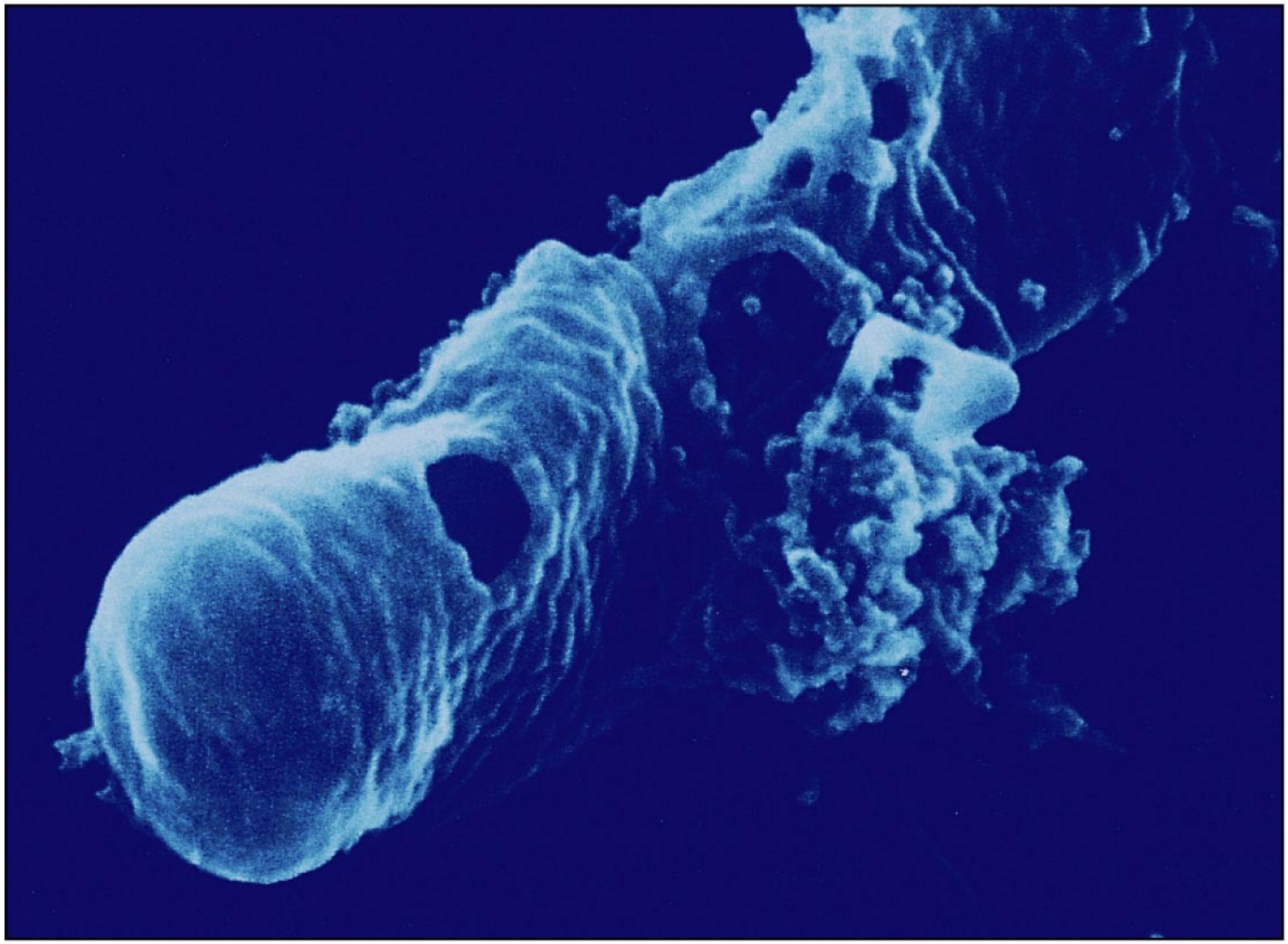


Figure 4-30 Brock Biology of Microorganisms 11/e



(a) Rod-shaped bacterium before penicillin. SEM 1 μm

Figure 20.3a

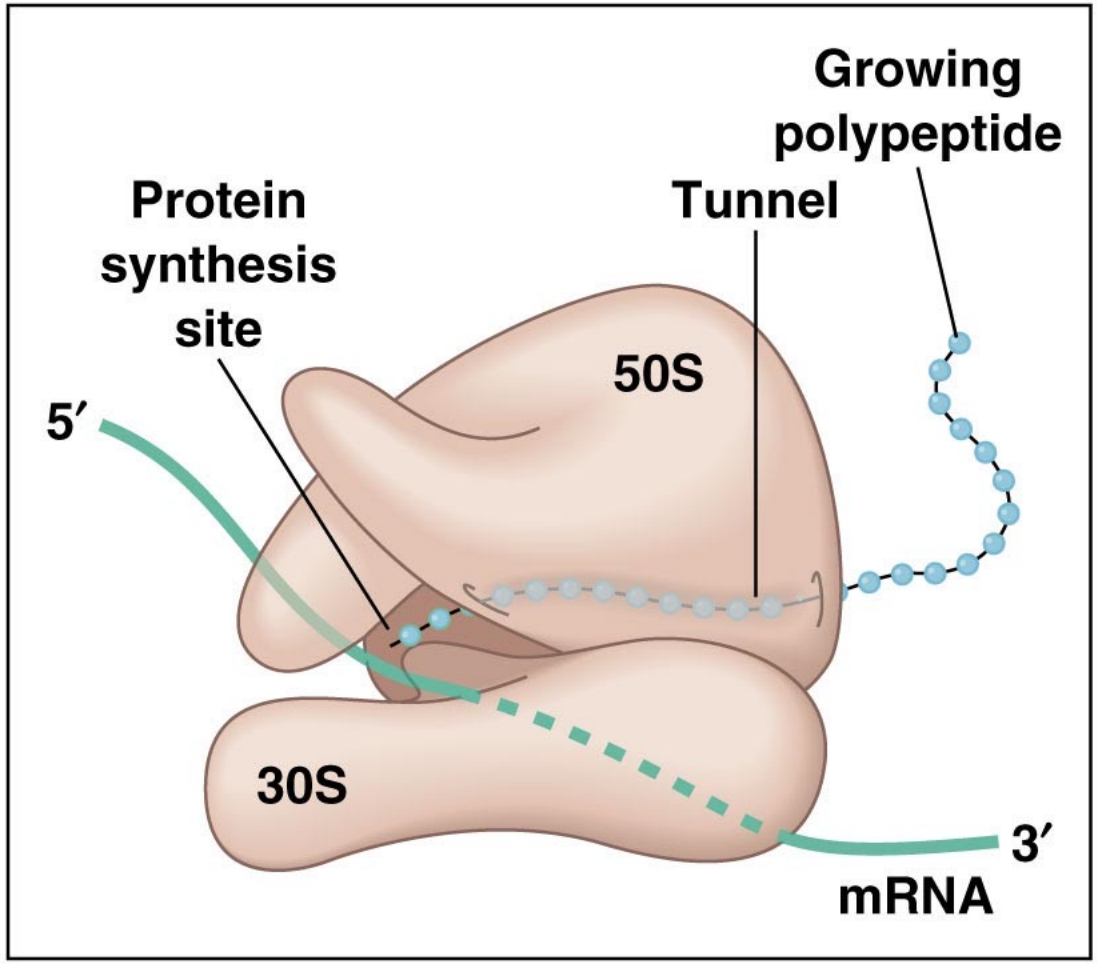


(b) The bacterial cell is lysing as penicillin weakens the cell wall.

SEM

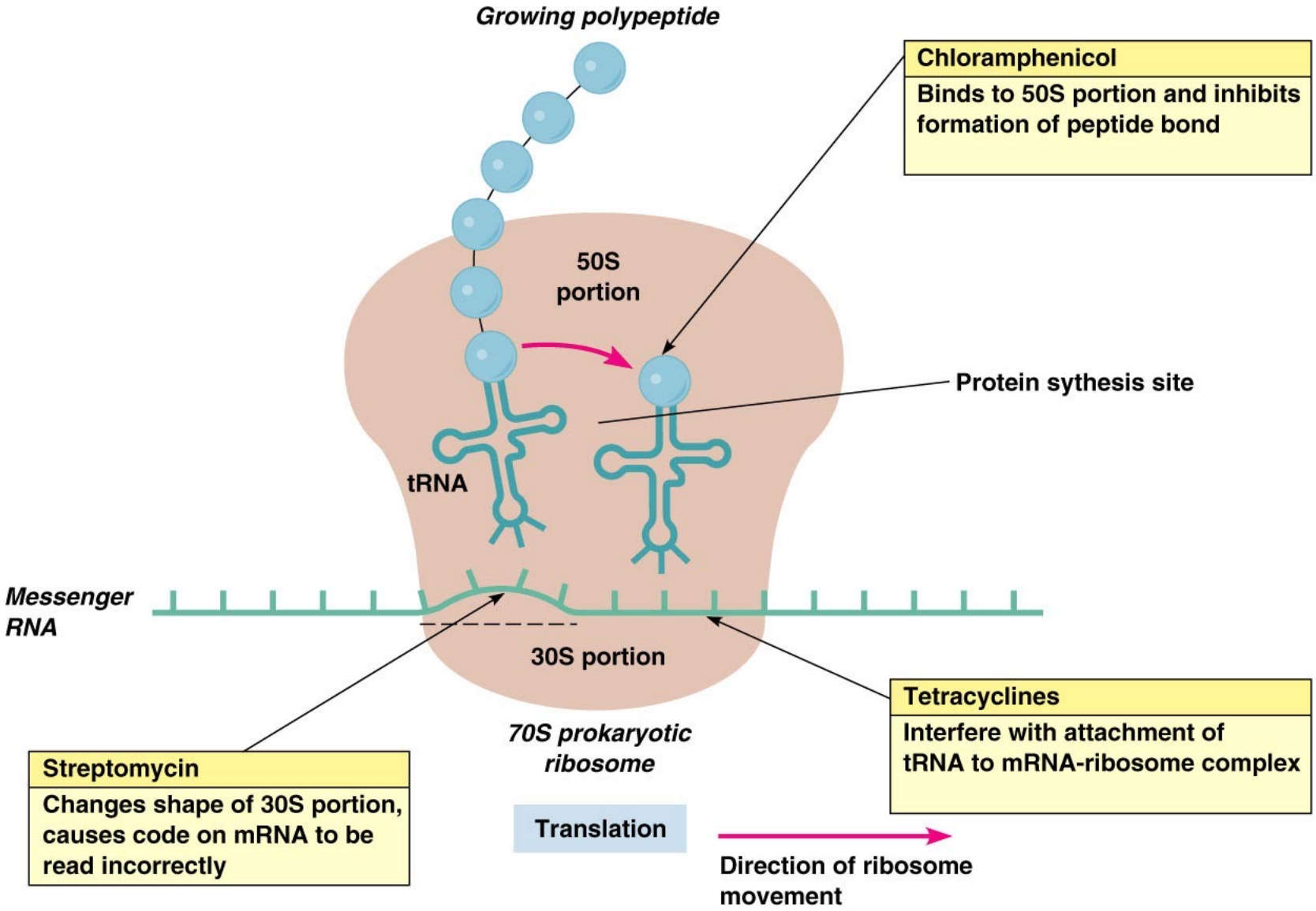
1 μm

Figure 20.3b



(a) Three-dimensional detail of the protein synthesis site showing the 30S and 50S subunit portions of the 70S prokaryotic ribosome.

Figure 20.4a



(b) In the diagram the black arrows indicate the different points at which chloramphenicol, the tetracyclines, and streptomycin exert their activities.

Figure 20.4b

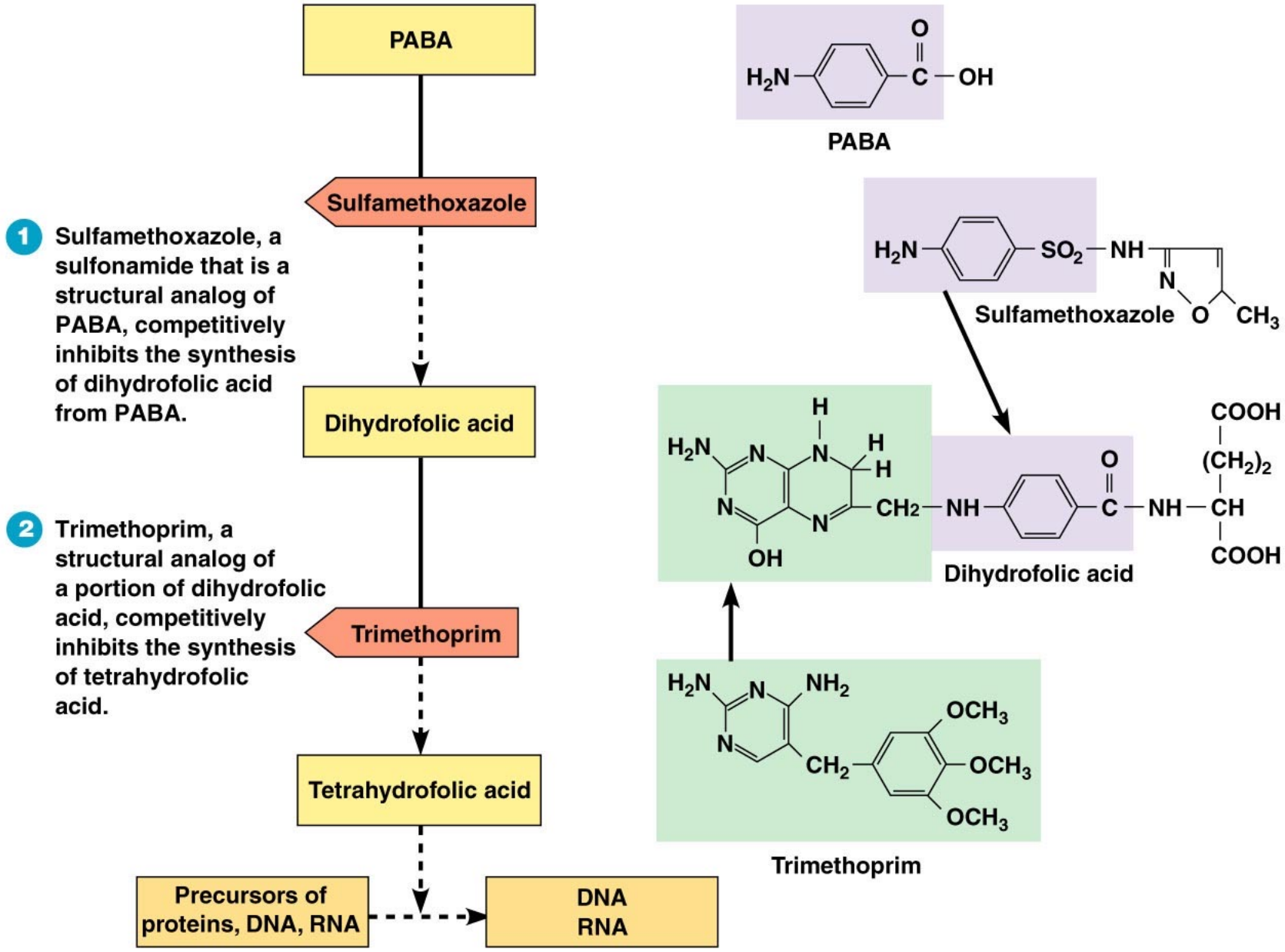


Figure 20.13 - Overview

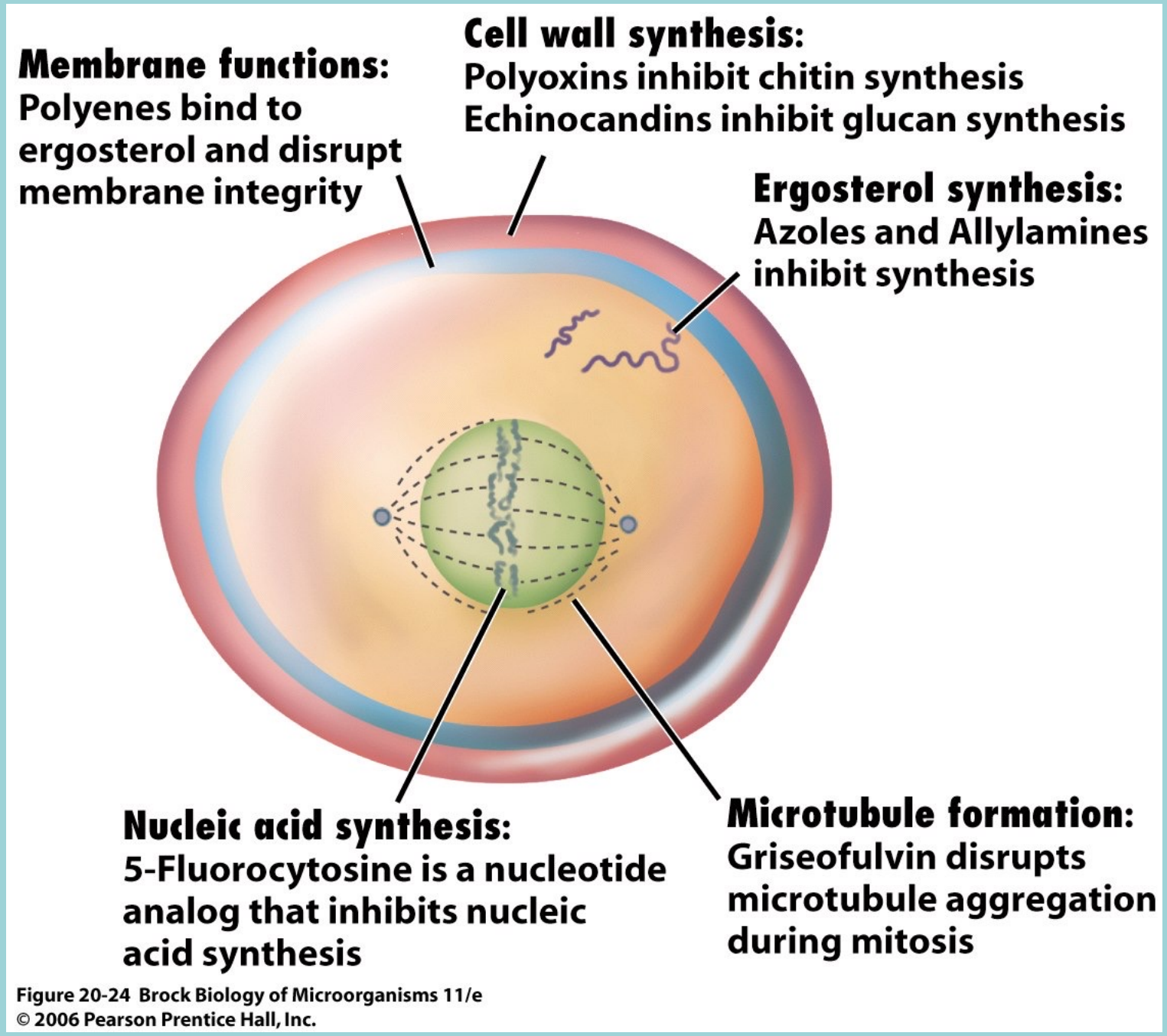


Figure 20-24 Brock Biology of Microorganisms 11/e

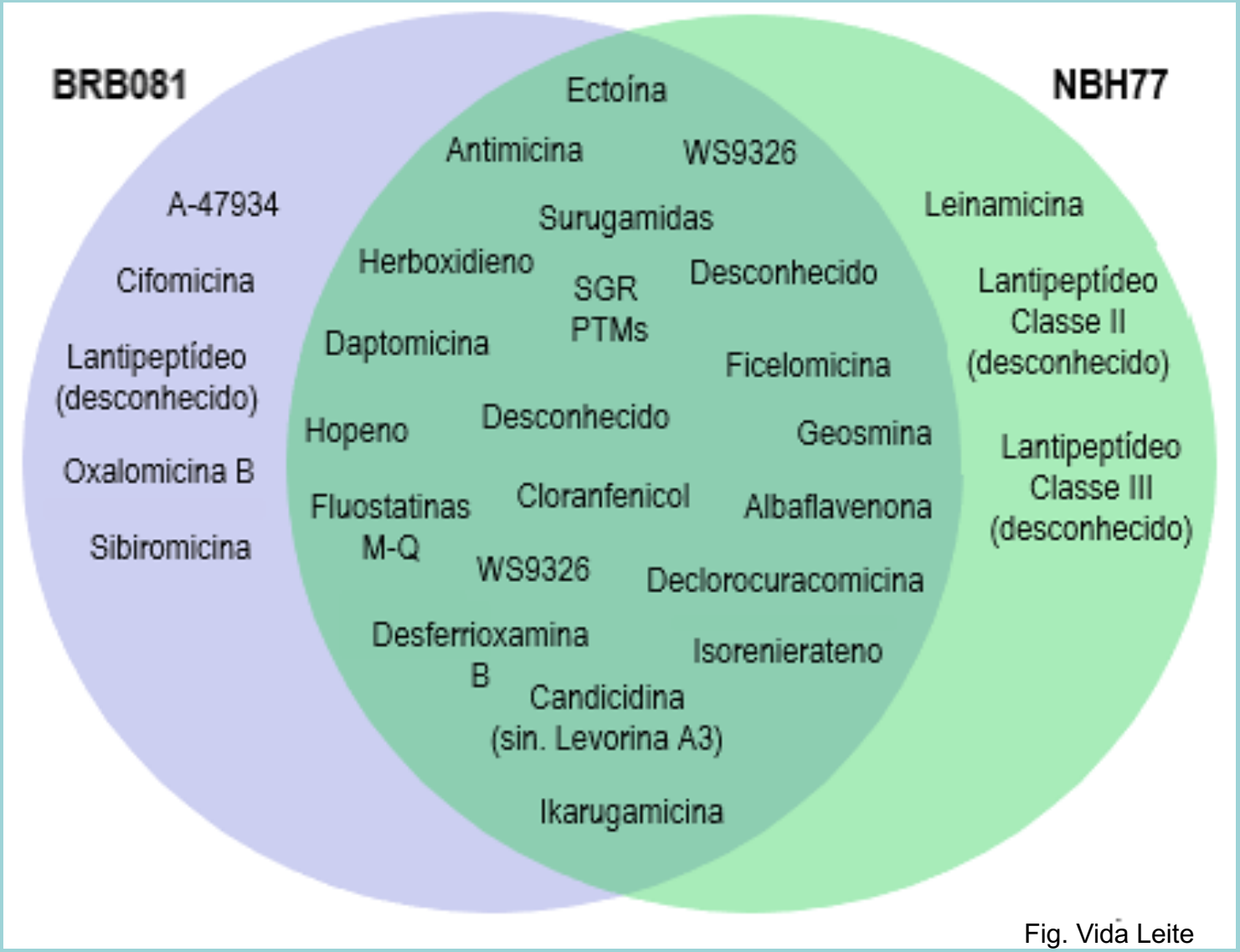
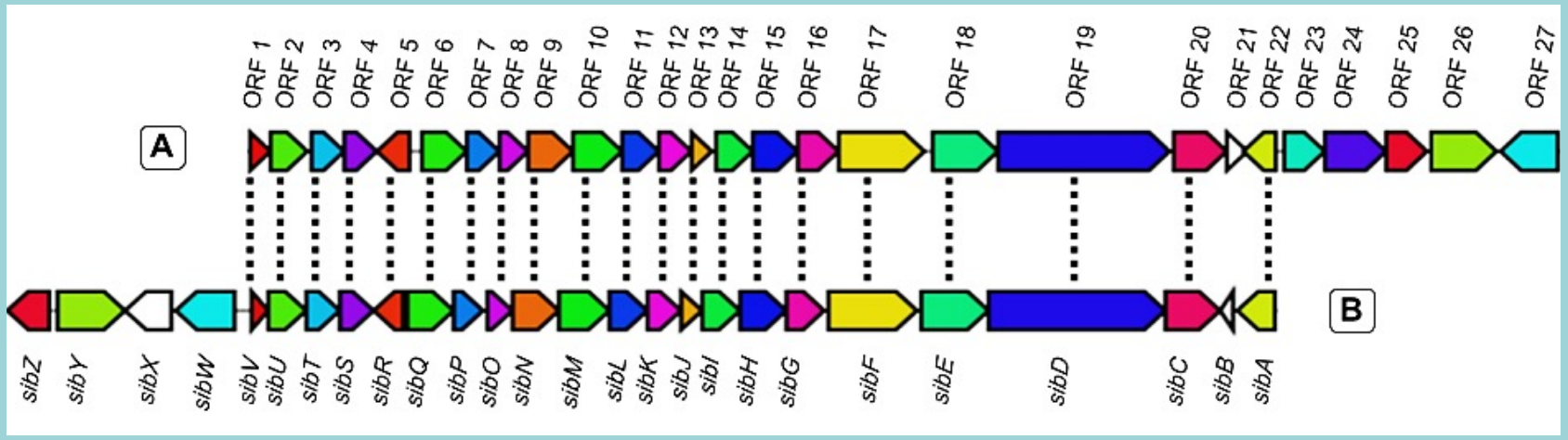


Fig. Vida Leite

Comparação entre (A) BGC putativo de sibiromicina de BRB081 e (B) BGC de sibiromicina de *Streptosporangium sibiricum* (LI et al., 2009). Os limites de A foram definidos com base em homologia. As ORFs correlacionadas entre A e B são representadas pela mesma cor. As linhas pontilhadas conectam ORFs relacionadas e dispostas na mesma ordem.



Injury of plasma membrane of a yeast caused by antifungal drug

Figure 20.5

TABLE 20.4 Antifungal, Antiviral, Antiprotozoan, and Antihelminthic Drugs

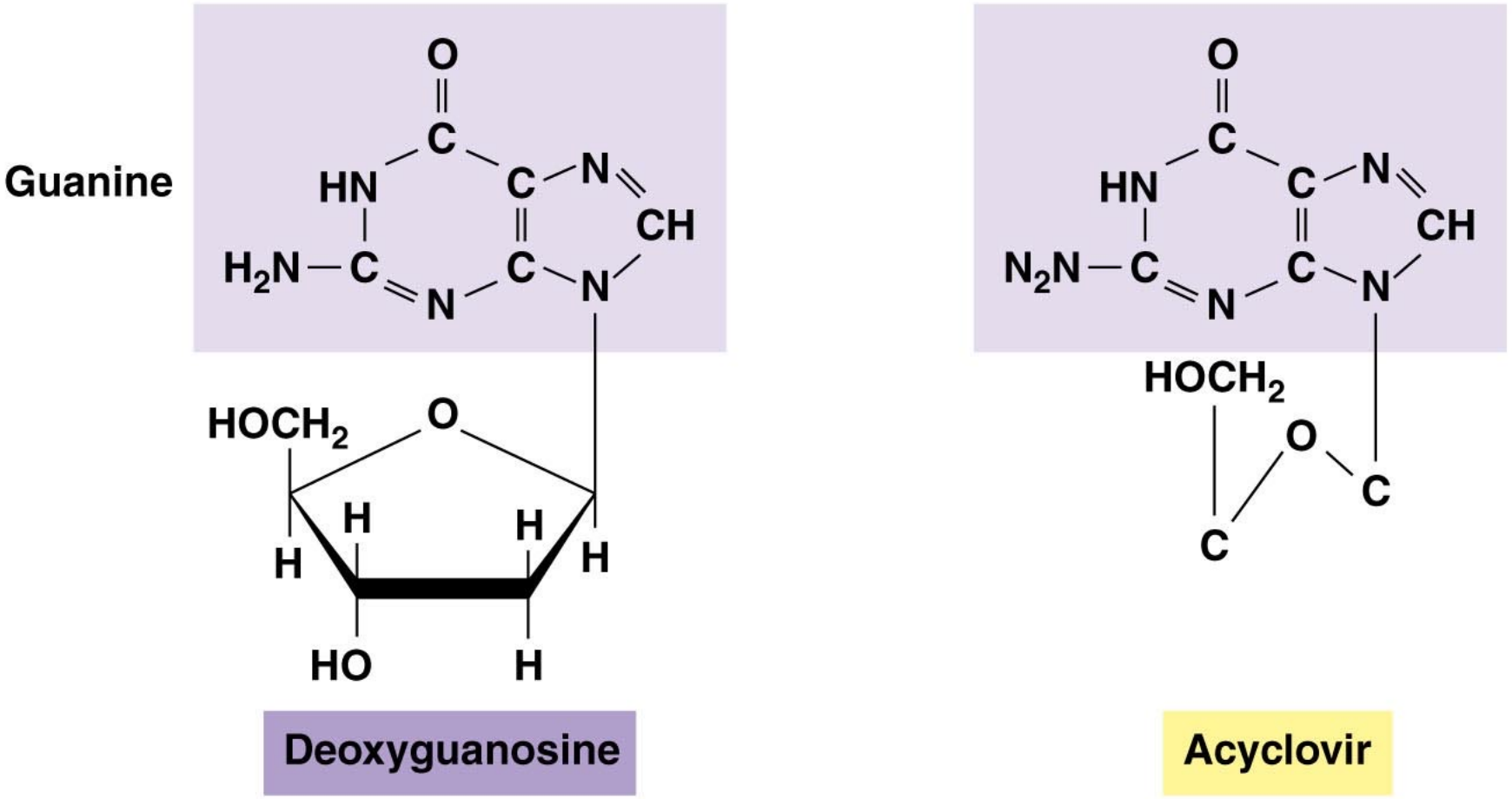
	Mode of Action	Comments
Antifungal Drugs		
Agents Affecting Fungal Sterols (Plasma Membrane)		
Polyenes		
Amphotericin B	Injury to plasma membrane	Systemic fungal infections; fungicidal
Azoles		
Clotrimazole, miconazole	Inhibit synthesis of plasma membrane	Topical use
Ketoconazole	Inhibits synthesis of plasma membrane	Can be taken orally for systemic fungal infections
Voriconazole	Inhibits synthesis of plasma membrane	Can penetrate blood–brain barrier to treat aspergillosis of the central nervous system
Allylamines		
Terbinafine, naftifine	Inhibits synthesis of plasma membrane	New class of antifungals frequently used to treat diseases resistant to azoles
Agents Affecting Fungal Cell Walls		
Echinocandins		
Caspofungin (Cancidas)	New class of antifungals that inhibit synthesis of cell wall	

TABLE 20.4 **Antifungal, Antiviral, Antiprotozoan, and Antihelminthic Drugs** *(continued)*

	Mode of Action	Comments
Agents Inhibiting Nucleic Acids		
Flucytosine	Inhibits synthesis of RNA and therefore protein synthesis	
Other Antifungal Drugs		
Griseofulvin	Inhibition of mitotic microtubules	Fungal infections of the skin
Tolnaftate	Unknown	Athlete's foot
Antiviral Drugs (See also Table 20.5, Drugs for Chemotherapy of HIV)		
Nucleoside and Nucleotide Analogs		
Acyclovir, ganciclovir, ribavirin, lamivudine	Inhibit DNA or RNA synthesis	Used primarily against herpesviruses
Cidofovir	Inhibits DNA or RNA synthesis	Cytomegalovirus infections; possibly effective against smallpox
Adefovir dipivoxil (Hepsera)		For resistance against lamivudine
Attachment and Uncoating		
Zanamivir, oseltamivir	Inhibit neuraminidase on influenza virus	Treatment of influenza
Amantadine, zimantadine	Inhibit uncoating	Treatment of influenza
Interferons		
alpha-interferon	Inhibits spread of virus to new cells	Viral hepatitis

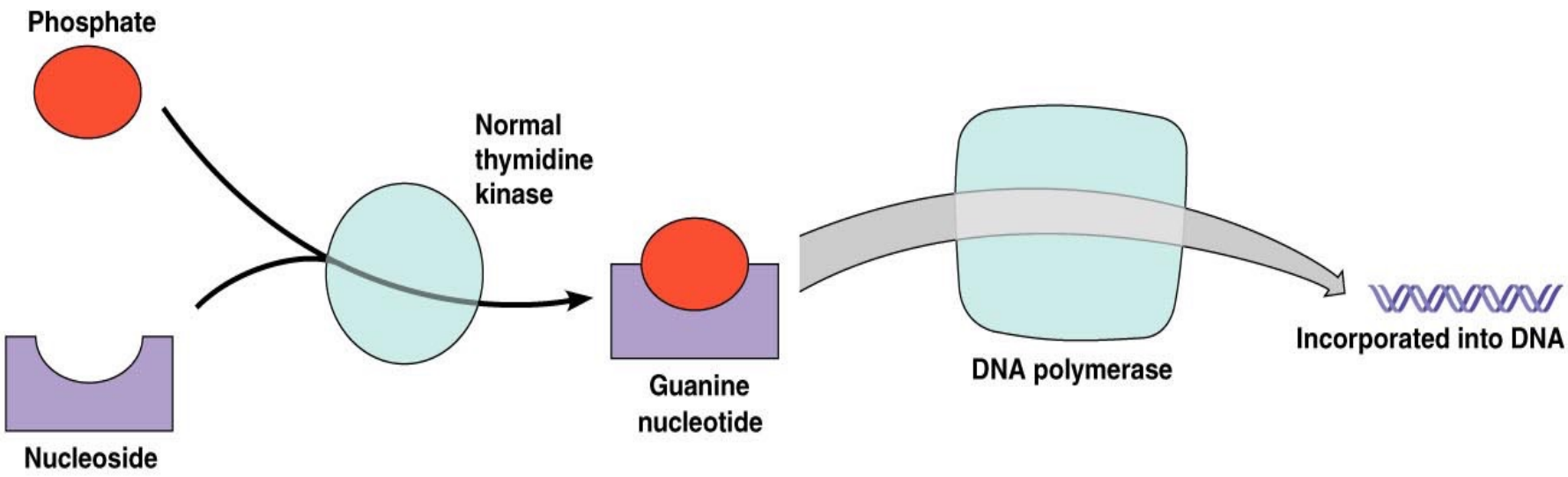
TABLE 20.4 **Antifungal, Antiviral, Antiprotozoan, and Antihelminthic Drugs** *(continued)*

	Mode of Action	Comments
Antiprotozoan Drugs		
Chloroquine	Inhibits DNA synthesis	Malaria; effective against red blood cell stage only
Diiodohydroxyquin	Unknown	Amoebic infections; amoebicidal
Metronidazole, Tinidazole	Interferes with anaerobic metabolisms	Giardiasis, amebiasis, trichomoniasis
Nitazoxanide	Interferes with anaerobic metabolism	Giardiasis; only drug approved for cryptosporidiosis
Antihelminthic Drugs		
Niclosamide	Prevents ATP generation in mitochondria	Tapeworm infections; kills tapeworms
Praziquantel	Alters permeability of plasma membranes	Tapeworm and fluke infections; kills flatworms
Pyantel pamoate	Neuromuscular block	Intestinal roundworms; kills roundworms
Mebendazole, albendazole	Inhibit absorption of nutrients	Intestinal roundworms
Ivermectin	Paralyzes worm	Intestinal roundworms primarily; occasional use for scabies mite and lice



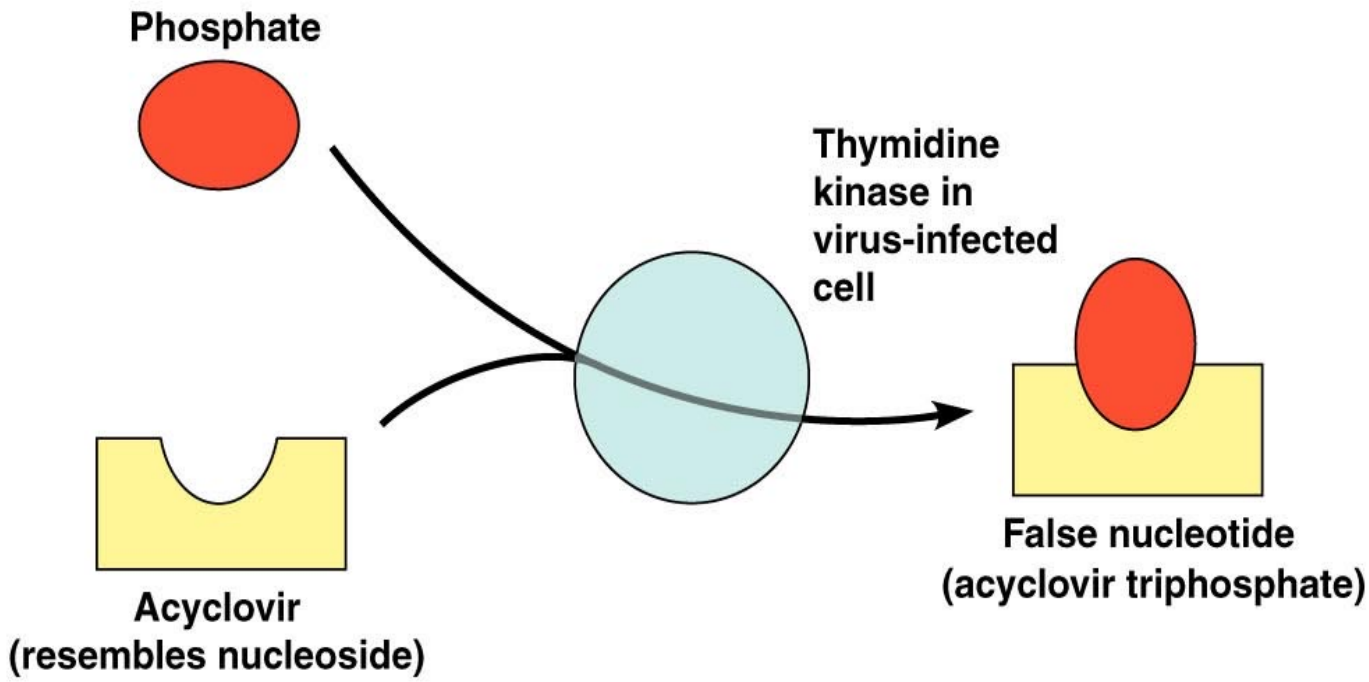
(a) Acyclovir structurally resembles the nucleoside deoxyguanosine.

Figure 20.16a



(b) The enzyme thymidine kinase combines phosphates with nucleosides to form nucleotides, which are then incorporated into DNA.

Figure 20.16b



(c) Acyclovir has no effect on a cell not infected by a virus, that is, with normal thymidine kinase. In a virally infected cell, the thymidine kinase is altered and converts the acyclovir (which resembles the nucleoside deoxyguanosine) into a false nucleotide—which blocks DNA synthesis by DNA polymerase.

Figure 20.16c

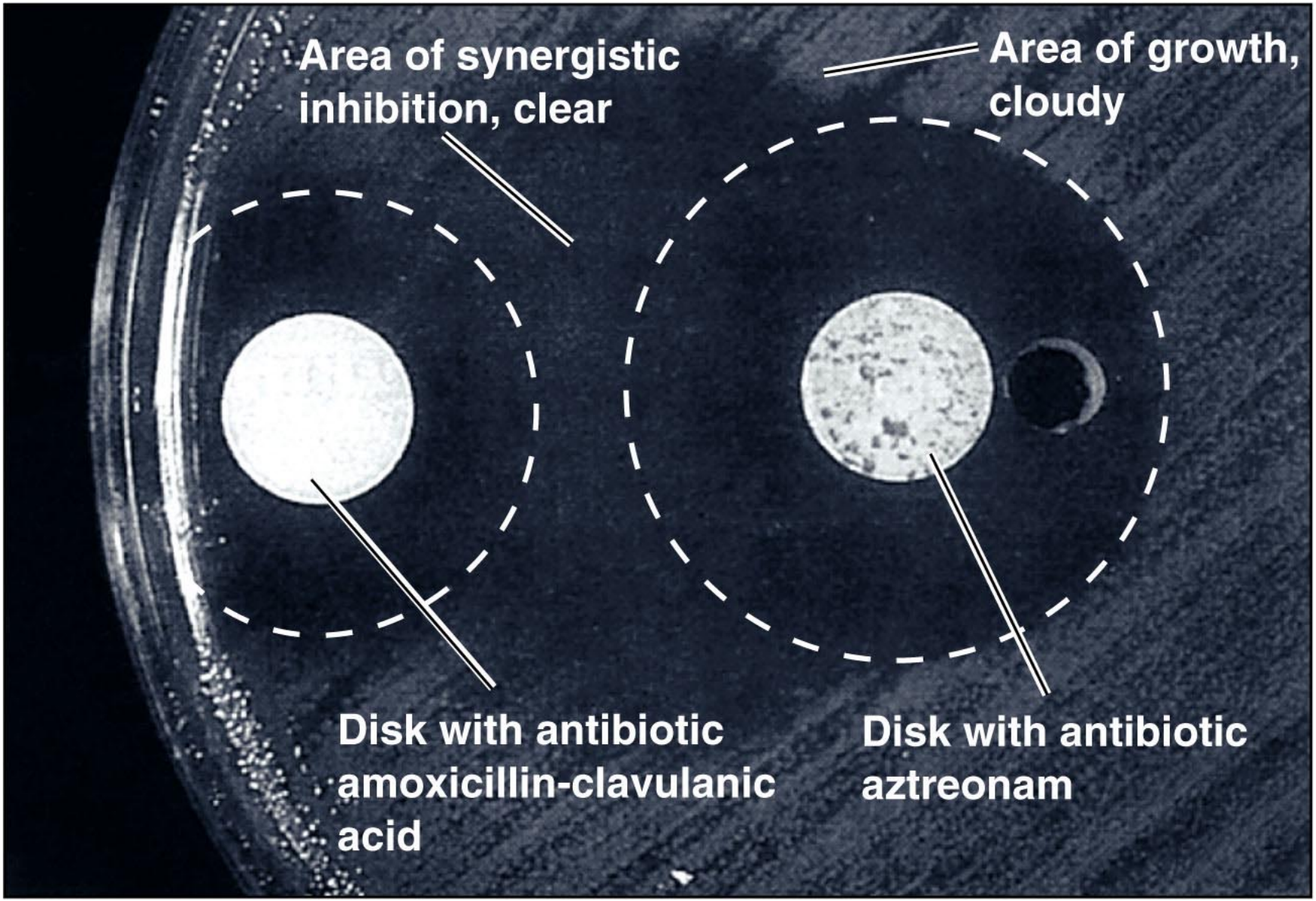


Figure 20.22