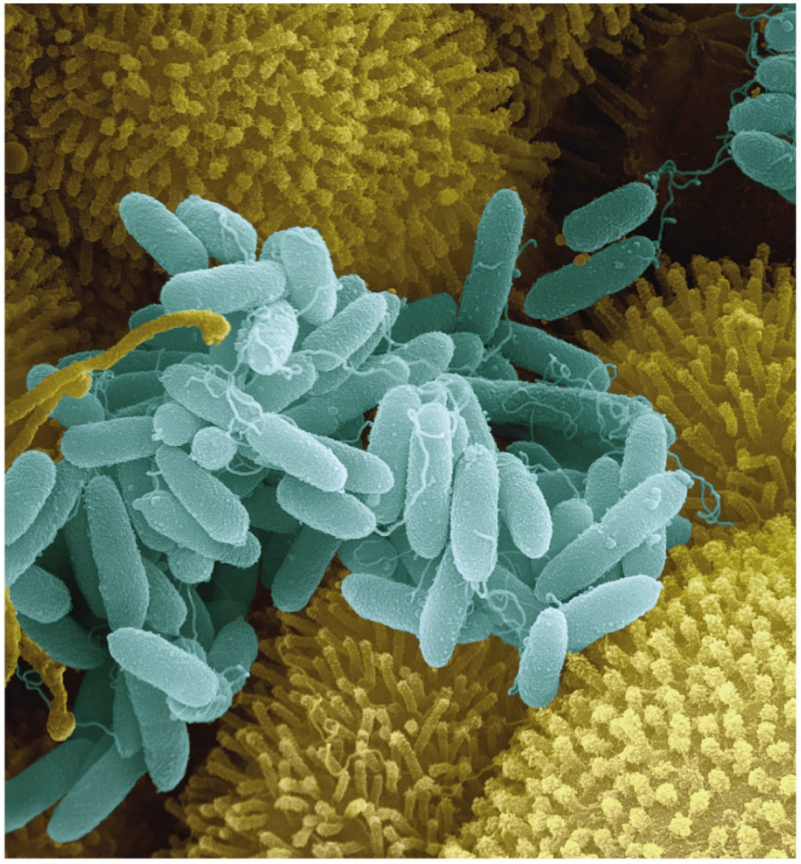
Chapter 20

Antimicrobial Drugs



Antimicrobial Drugs

- **Chemotherapy**: the use of drugs to treat a disease
- **Antimicrobial drugs**: interfere with the growth of microbes within a host
- **Antibiotic**: a substance produced by a microbe that, in small amounts, inhibits another microbe
- **Selective toxicity**: goal to kill harmful microbes without damaging the host

The Action of Antimicrobial Drugs

- **Bactericidal** // Kill microbes directly

- **Bacteriostatic** // Prevent microbes from growing

Antimicrobial Drugs

- **1928**: Fleming discovered penicillin, produced by *Penicillium*

- **1940**: Howard Florey and Ernst Chain performed first clinical trials of penicillin

Laboratory observation of antibiosis.

TABLE 20.1 Representative Sources of Antibiotics

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

The Spectrum of Antimicrobial Activity

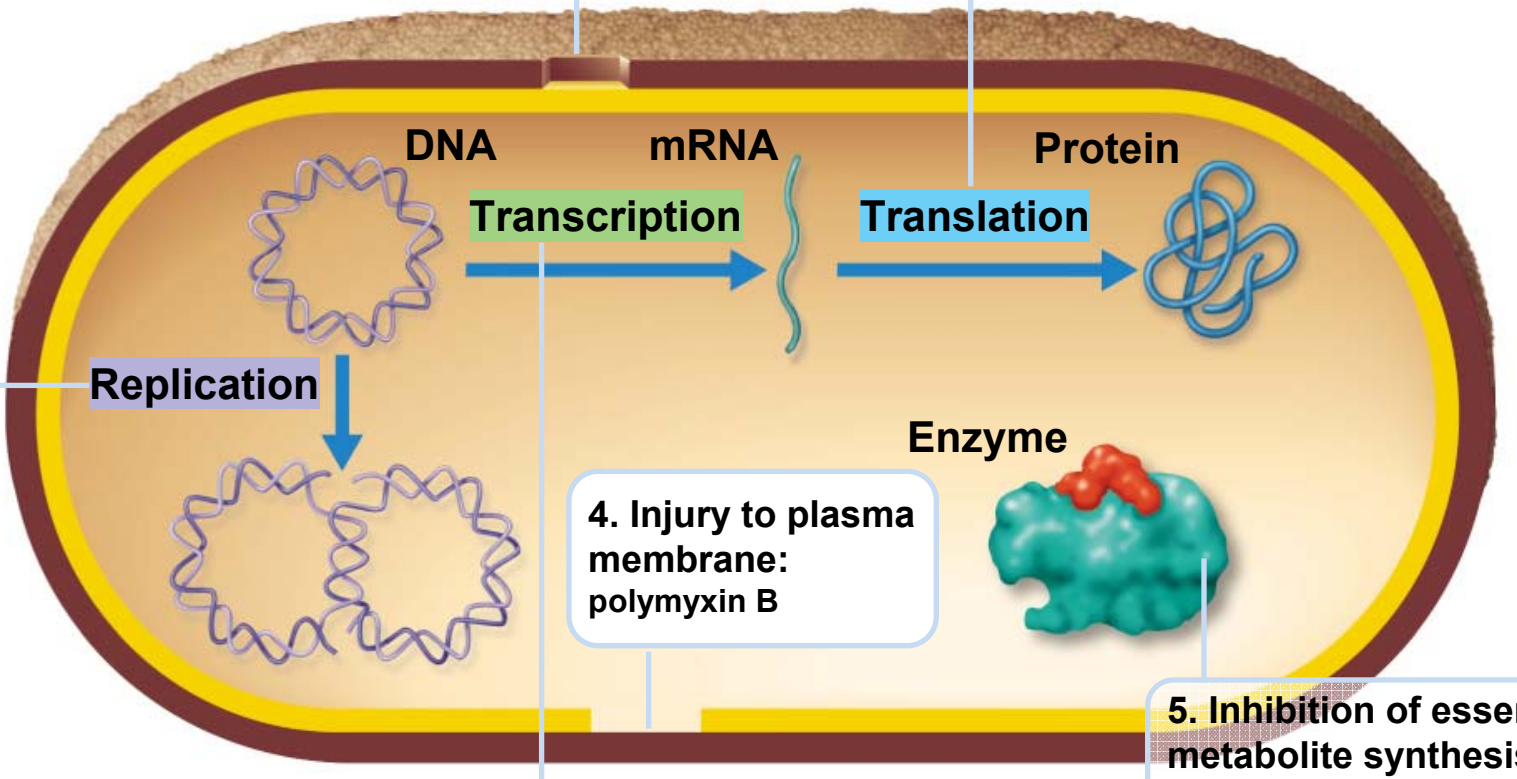
- Narrow spectrum – kills only single or select group of microoganisms
- Broad spectrum – kills wide variety of microorganisms
- Use of antibiotics may cause a "super-infection"
  - occurs when antibiotics kills normal microbe
  - remaining opportunistic microbes which are resistant to antibiotic grow rapidly
  - E.g. antibiotics kill lactobacillus in vagina // lactobacillus produce acids which limit the growth of Candida albicans // without acid yeast infection rapidly grows

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

Prokaryotes				*Eukaryotes*			
Mycobacteria*	**Gram-Negative Bacteria**	**Gram-Positive Bacteria**	**Chlamydias, Rickettsias†**	**Fungi**	**Protozoa**	**Helminths**	**Viruses**
Isoniazid ⟷		Penicillin G ⟷		Ketoconazole ⟷		Niclosamide (tapeworms) ⟷	
Streptomycin ⟷					Mefloquine (malaria) ⟷		Acyclovir ⟷
Tetracycline ⟷						Praziquantel (flukes) ⟷	

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

Major Action Modes of Antimicrobial Drugs.



1. Inhibition of cell wall synthesis: penicillins, cephalosporins, bacitracin, vancomycin

2. Inhibition of protein synthesis: chloramphenicol, erythryomycin, tetracyclines, streptomycin

4. Injury to plasma membrane: polymyxin B

5. Inhibition of essential metabolite synthesis: sulfanimide, trimethoprim

3. Inhibition of nucleic acid replication and transcription: quinolones, rifampin

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 against gram-negative bacteria, including *Pseudomonas* spp.
Imipenem	A carbapenem; very broad spectrum
Cephalosporins	
Cephalothin	First-generation cephalosporin; activity similar to penicillin; requires injection
Cefixime	Fourth-generation cephalosporin; oral administration
Polypeptide Antibiotics	
Bacitracin	Against gram-positive bacteria; topical application
Vancomycin	A glycopeptide type; penicillinase-resistant; against gram-positive bacteria
Antimycobacterial Antibiotics	
Isoniazid	Inhibits synthesis of mycolic acid component of cell wall of *Mycobacterium* spp.
Ethambutol	Inhibits incorporation of mycolic acid into cell wall of *Mycobacterium* spp.

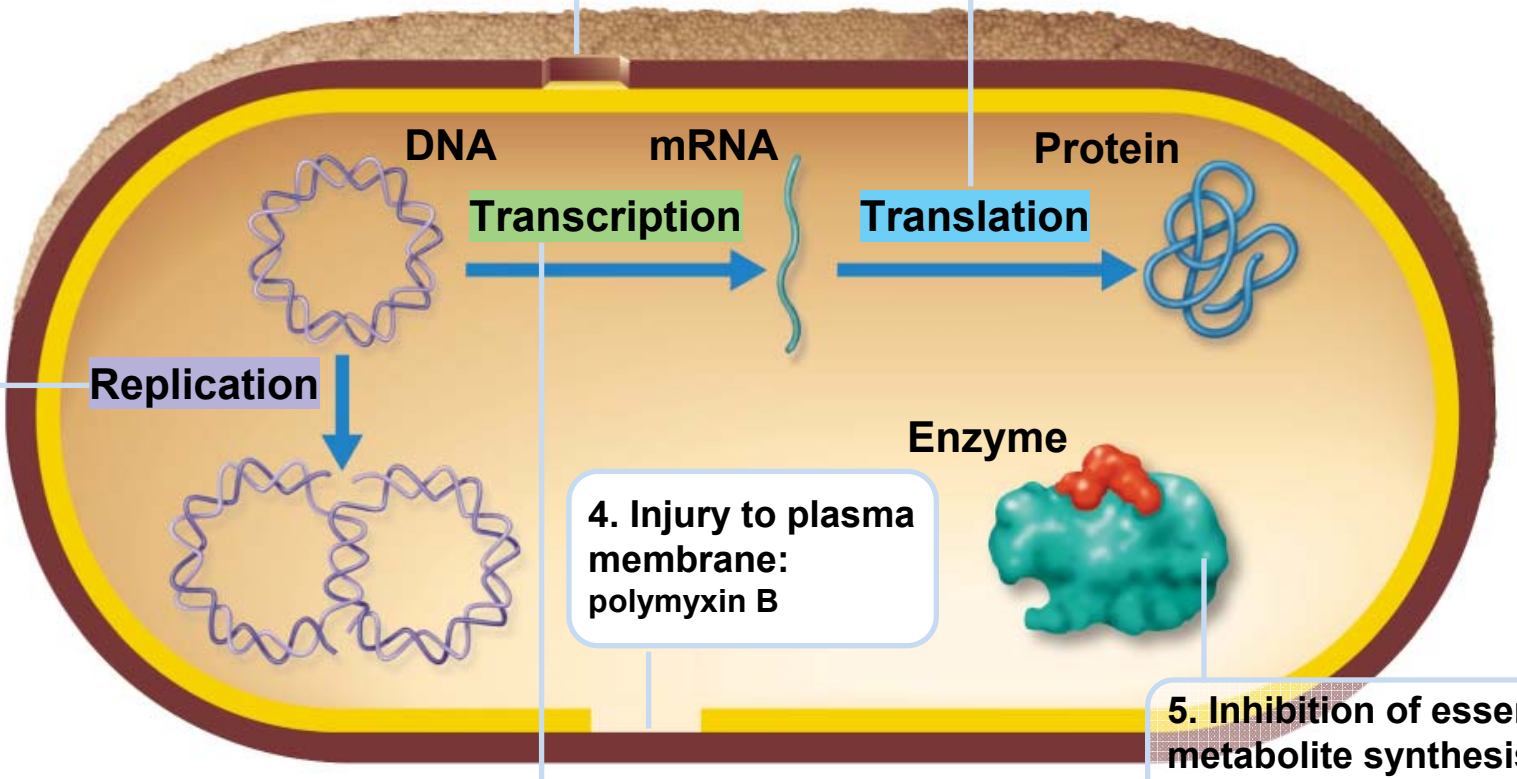
TABLE 20.3 *(continued)*

Drugs by Mode of Action	Comments
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.
Pleuromutilins	
Mutilin, retpamulin	Inhibit gram-positive bacteria
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
Streptogramins	
Quinupristin and dalfopristin (Synercid)	Alternative for treating vancomycin-resistant gram-positive bacteria
Oxazolidinones	
Linezolid (Zyvox)	Useful primarily against penicillin-resistant gram-positive bacteria
Glycylcyclines	
Tygecycline	Broad spectrum, especially MRSA and *Acinetobacter*
INJURY TO THE PLASMA MEMBRANE	
Polymyxin B	Topical use, gram-negative bacteria, including *Pseudomonas* spp.
Lipopeptides	
Daptomycin	To treat MRSA infections

TABLE **20.3** *(continued)*

Drugs by Mode of Action	Comments
INHIBITORS OF NUCLEIC ACID SYNTHESIS	
Rifamycins	
Rifampin	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

Major Action Modes of Antimicrobial Drugs.



1. Inhibition of cell wall synthesis: penicillins, cephalosporins, bacitracin, vancomycin

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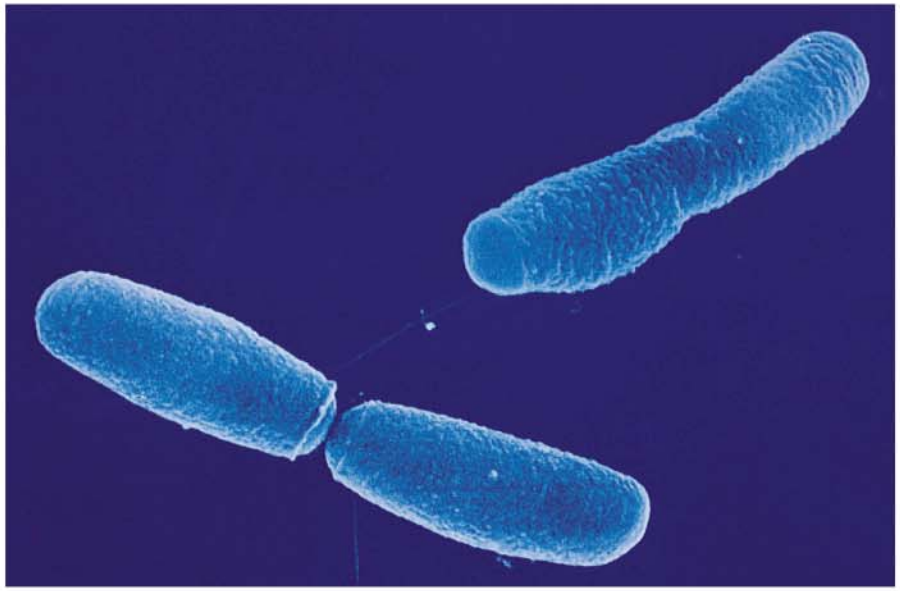
Inhibitors of Cell Walls

Inhibitors of Cell Wall Synthesis

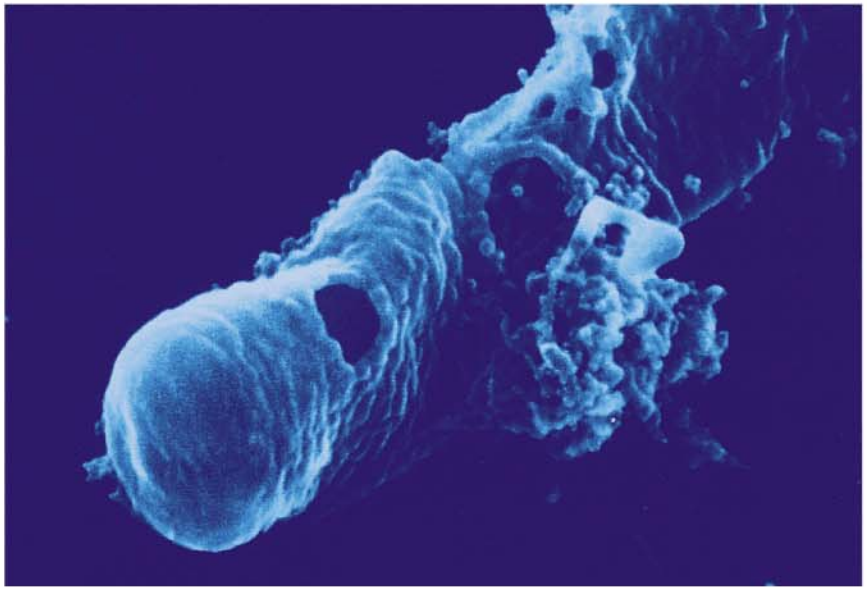
- Penicillin
  - Natural penicillins / extracted from the mold Penicillium / drug of choice for staphylococci, streptococci, some spirochetes // narrow spectrum & susceptibility to penicillinases
  - Semisynthetic penicillins // partly made by mold and then modified to increase range and length of action or resistance to penicillinases
  - Extended-spectrum penicillins

The inhibition of bacterial cell synthesis by penicillin.



(a) **Rod-shaped bacterium before penicillin.**

SEM 1 μm

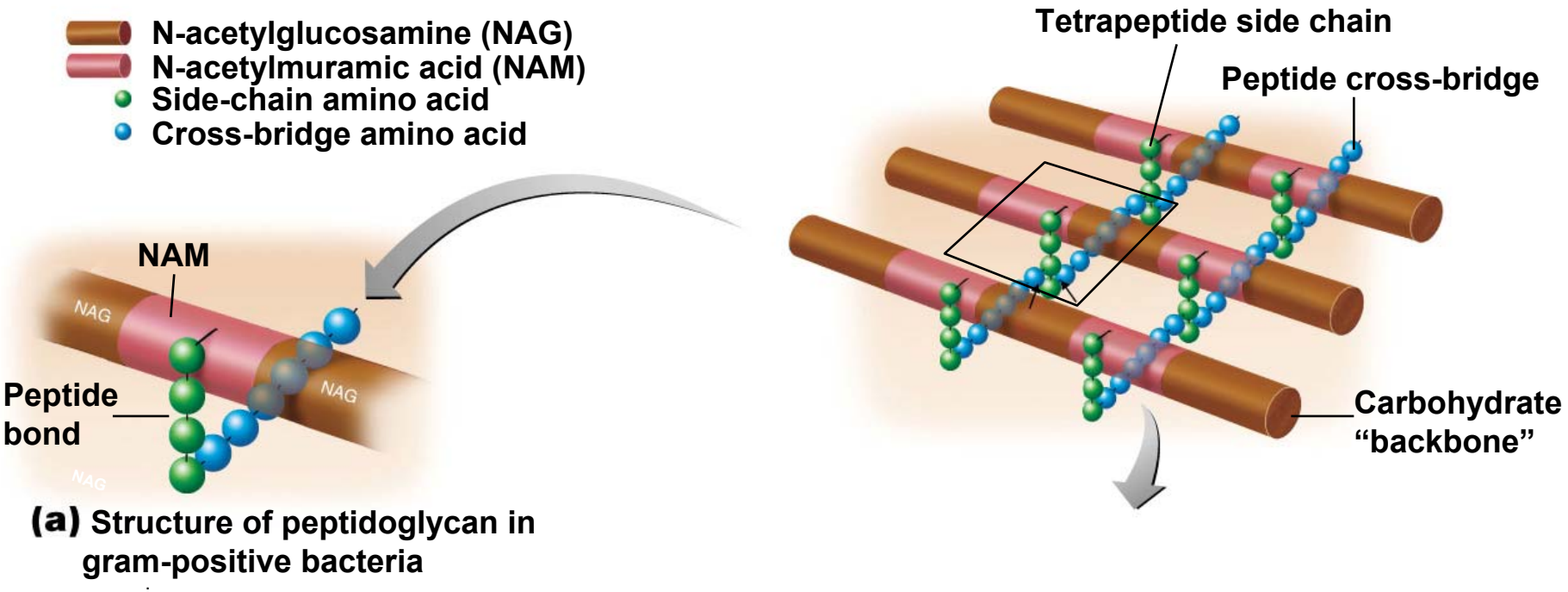


(b) **The bacterial cell lysing as penicillin weakens the cell wall.**

SEM 1 μm

Note: lysozyme also disrupts bacterial cell wall

Bacterial cell walls.

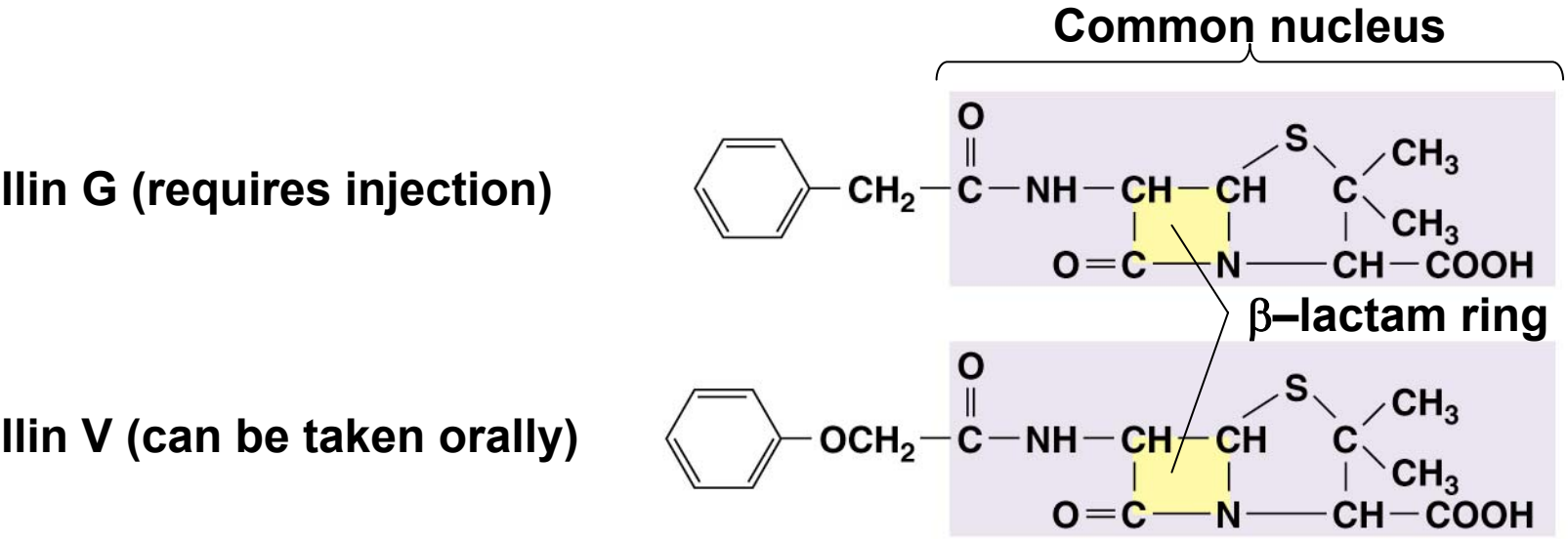


(a) Structure of peptidoglycan in gram-positive bacteria

Penicillin and lysoyme inhibit synthesis of bacterial cell walls

The structure of penicillins, antibacterial antibiotics.

(a) Natural penicillins



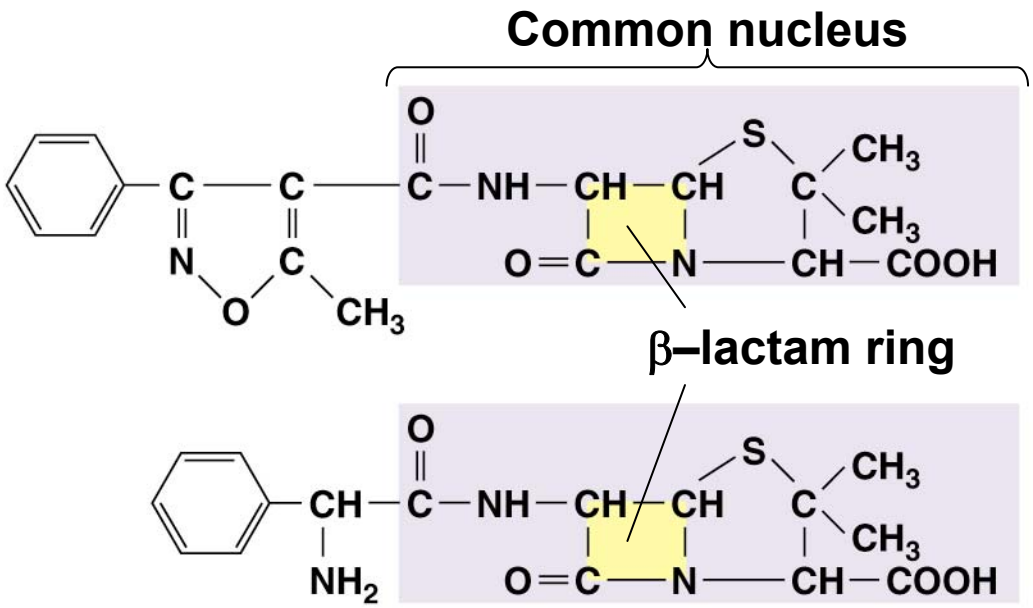
Note: characteristic beta-lactam ring structure / beta-lactamases break ring structure to deactivate antibiotic

The structure of penicillins, antibacterial antibiotics.

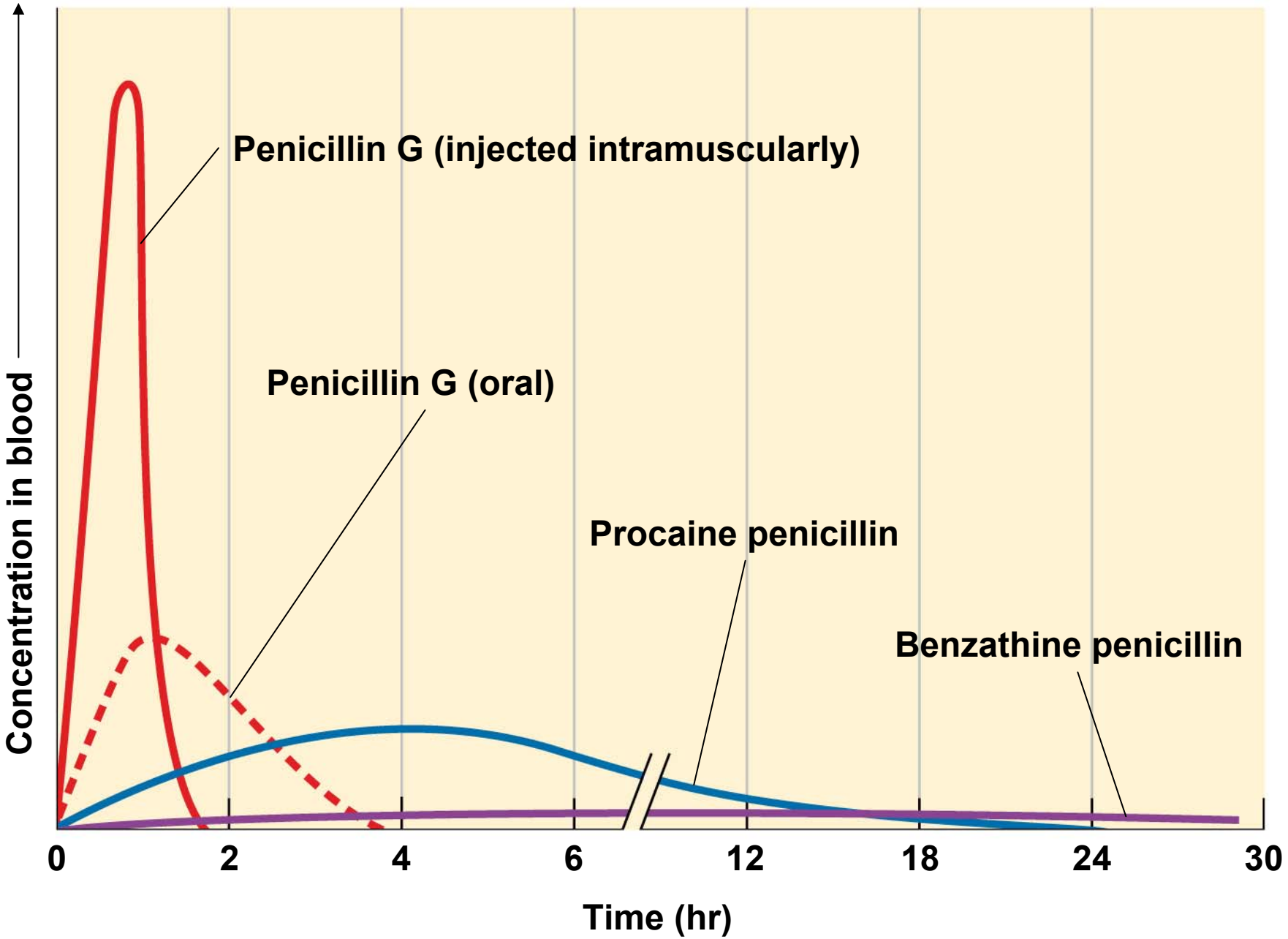
(b) Semisynthetic penicillins

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

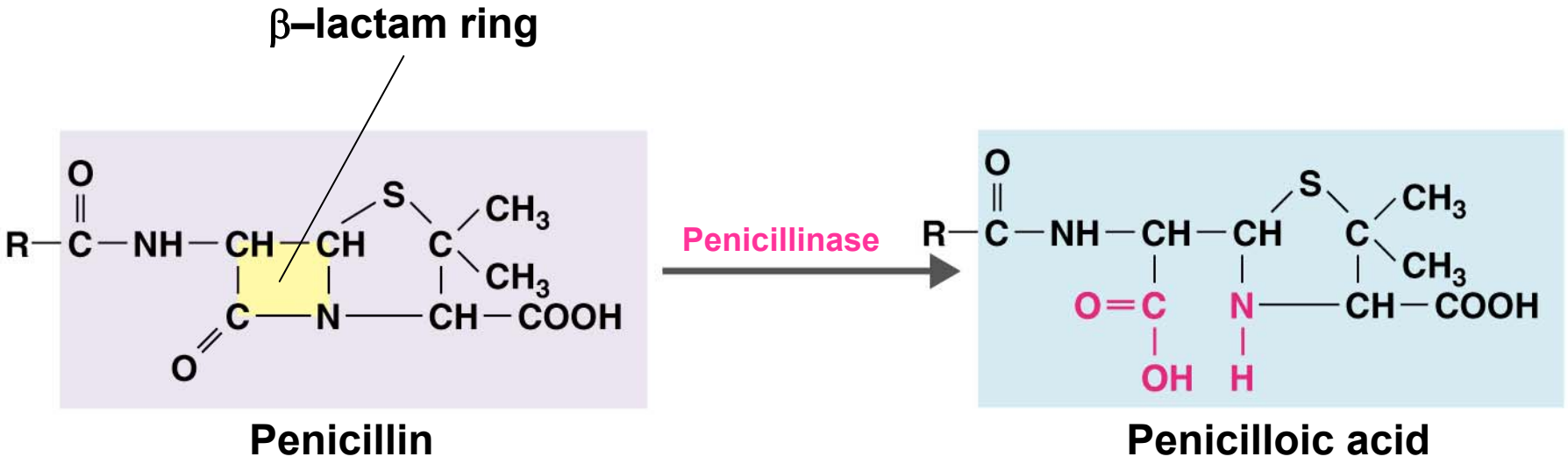
Ampicillin:
Extended spectrum, many gram-negatives.



Retention of penicillin G.



The effect of penicillinase on penicillins.



Bacteria carry enzyme as plasmid.

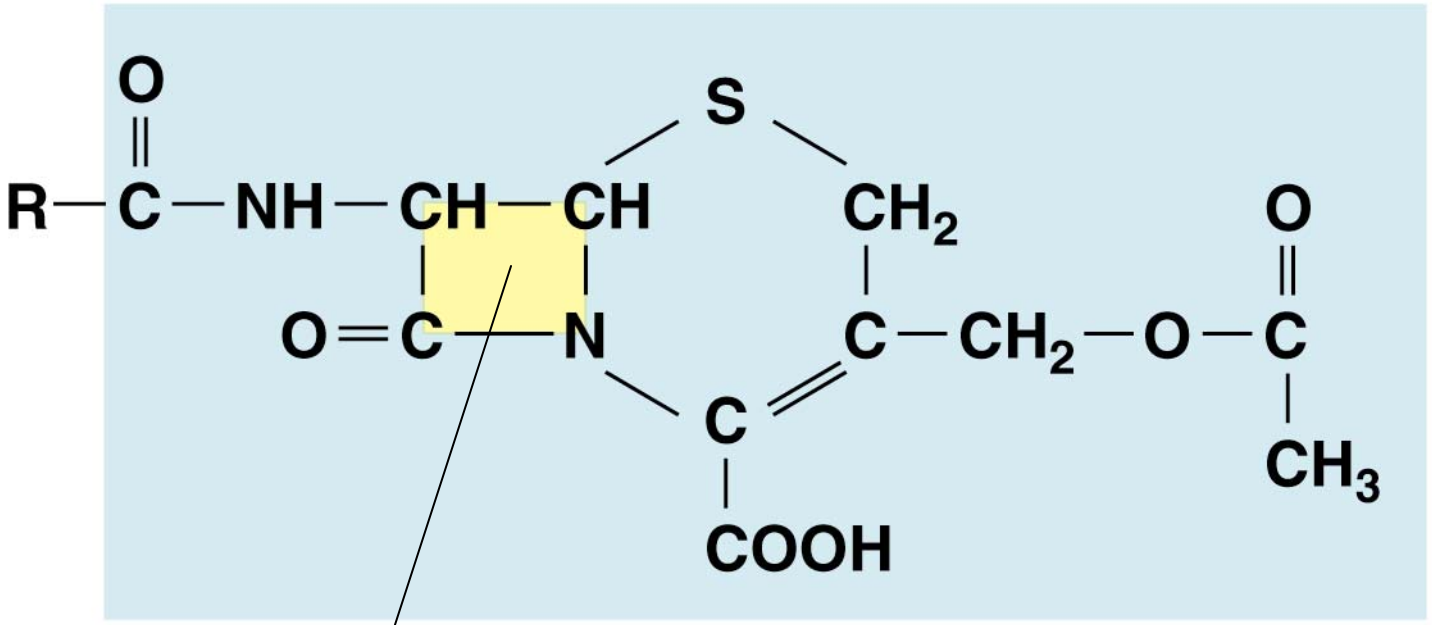
β–Lactam Antibiotics /// Penicillinase-Resistant

- Penicillins + β-lactamase inhibitors
- **Carbapenems //** Substitute a C for an S, add a double bond
- **Monobactam //** Single ring

Inhibitors of Cell Wall Synthesis
How Antibiotics Modified Over Time

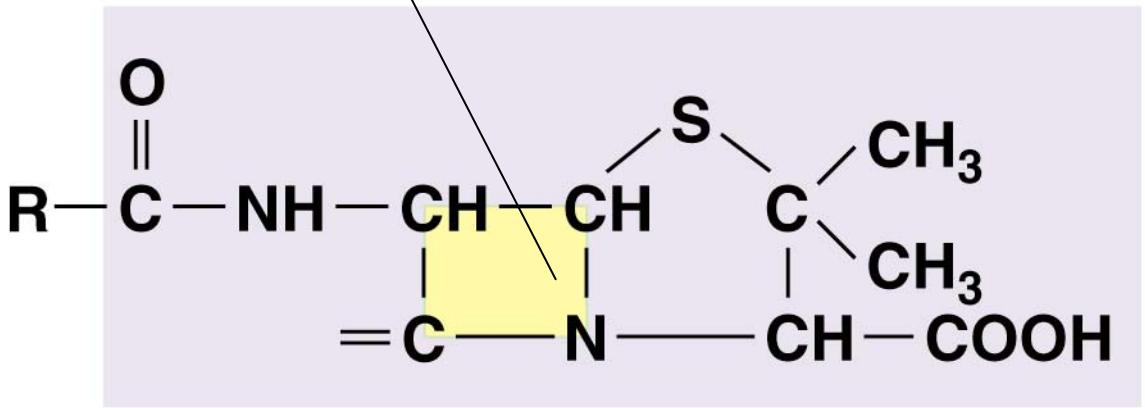
- **Cephalosporins**
  - First-generation was narrow spectrum // act against only gram-positive bacteria
  - Second-generation: extended spectrum includes gram-negative bacteria
  - Third-generation: includes pseudomonads // injected
  - Fourth-generation // oral

The nuclear structures of a cephalosporin and penicillin compared.



Cephalosporin nucleus

β–lactam ring



Penicillin nucleus

Inhibitors of Cell Wall Synthesis

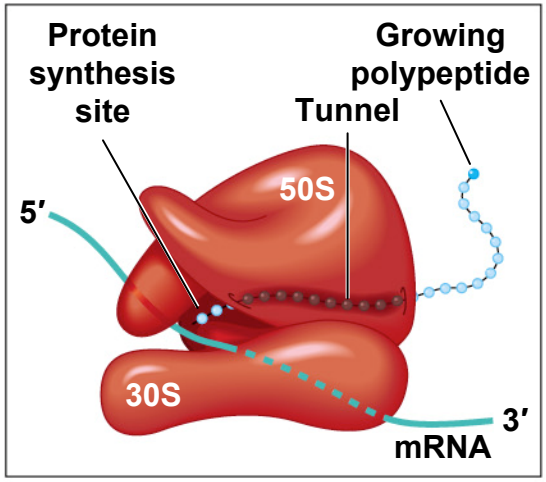
- **Polypeptide antibiotics**
  - **Bacitracin** // Topical application - effective against gram-positives
  - **Vancomycin** // Glycopeptide - Important "last line" against antibiotic-resistant *S. aureus*

Inhibitors of Cell Wall Synthesis

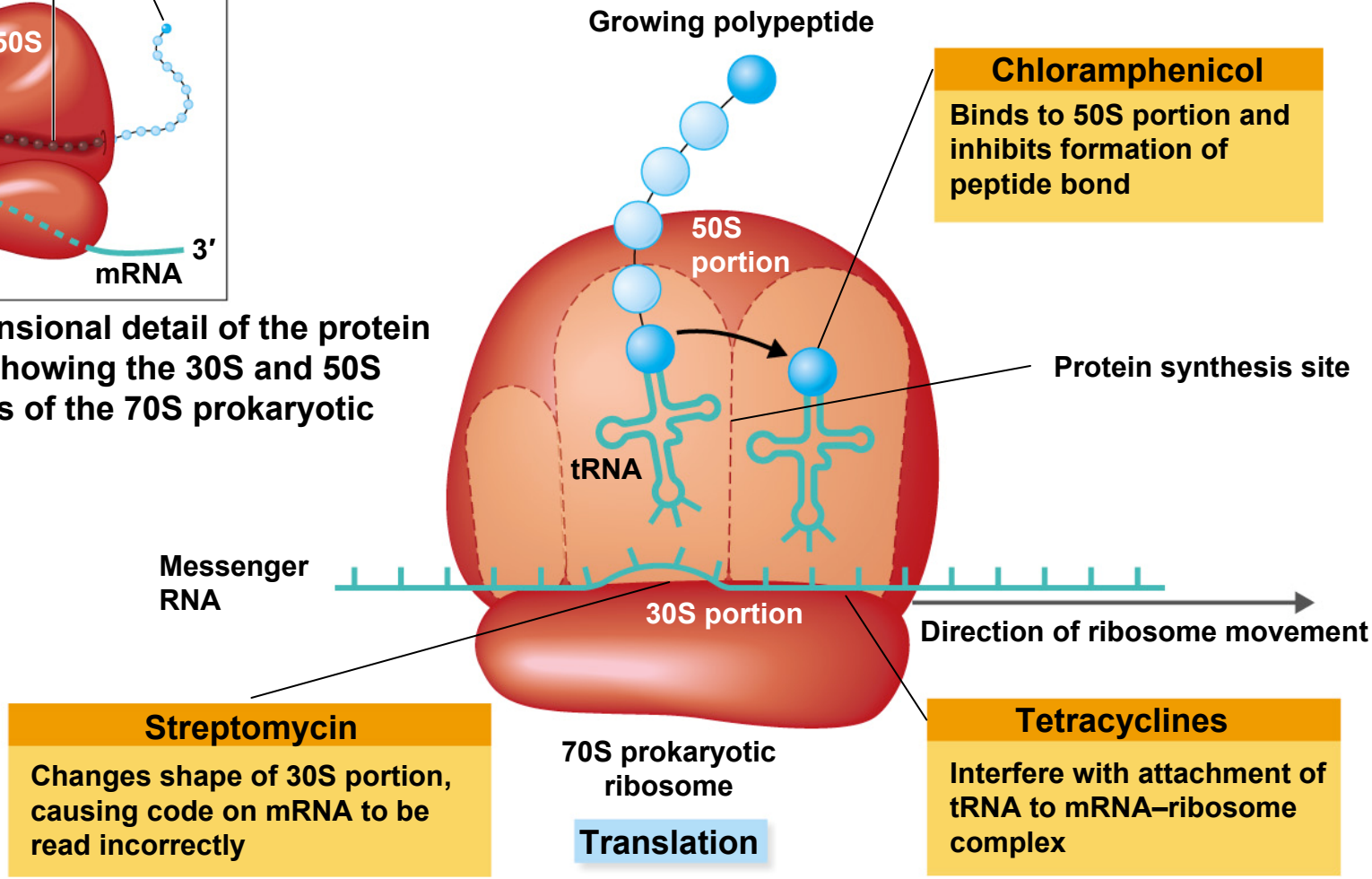
- Antimycobacterial antibiotics
  - **Isoniazid (INH)** // Inhibits mycolic acid synthesis
  - **Ethambutol** // Inhibits incorporation of mycolic acid
  - Note: tuberculosis and leprosy microbes have mycolic acid in their cell walls

Inhibitors of Protein Synthesis

The inhibition of protein synthesis by antibiotics.



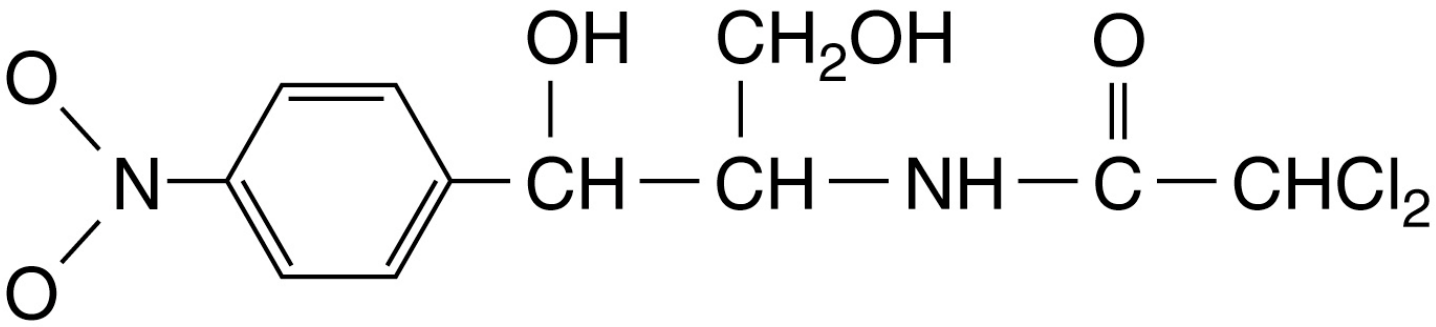
(a) Three-dimensional detail of the protein synthesis site showing the 30S and 50S subunit portions of the 70S prokaryotic ribosome



(b) Diagram indicating the different points at which chloramphenicol, the tetracyclines, and streptomycin exert their activities

Inhibitors of Protein Synthesis

- **Chloramphenicol**
  - Broad spectrum
  - Binds 50S subunit - inhibits peptide bond formation



Chloramphenicol

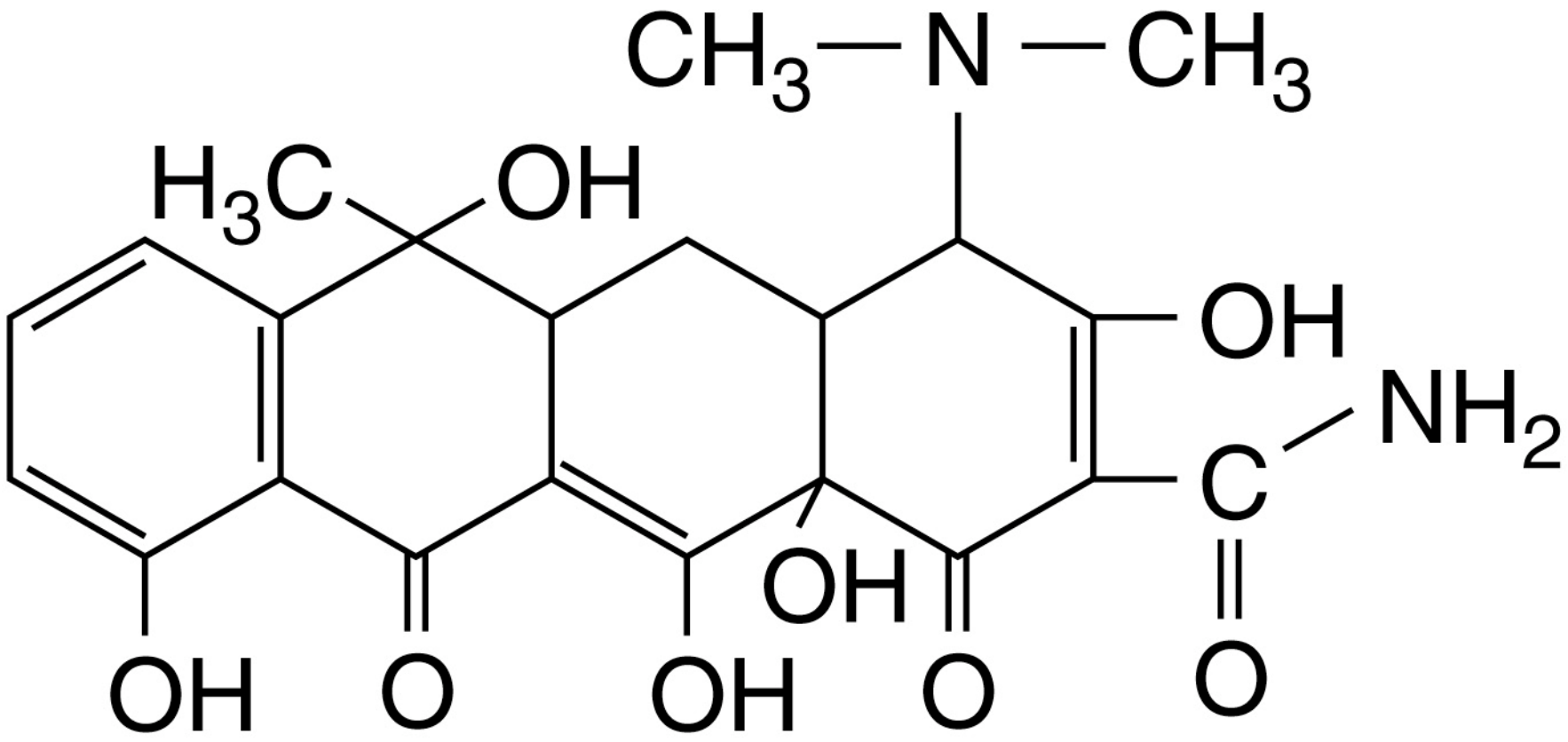
Inhibitors of Protein Synthesis

- **Aminoglycosides**
  - Streptomycin, neomycin, gentamicin
    - Broad spectrum
    - Change shape of 30S subunit

Inhibitors of Protein Synthesis

- **Tetracyclines**
  - Broad spectrum
  - Interfere with tRNA attachment

The structure of the antibacterial antibiotic tetracycline.



Tetracycline

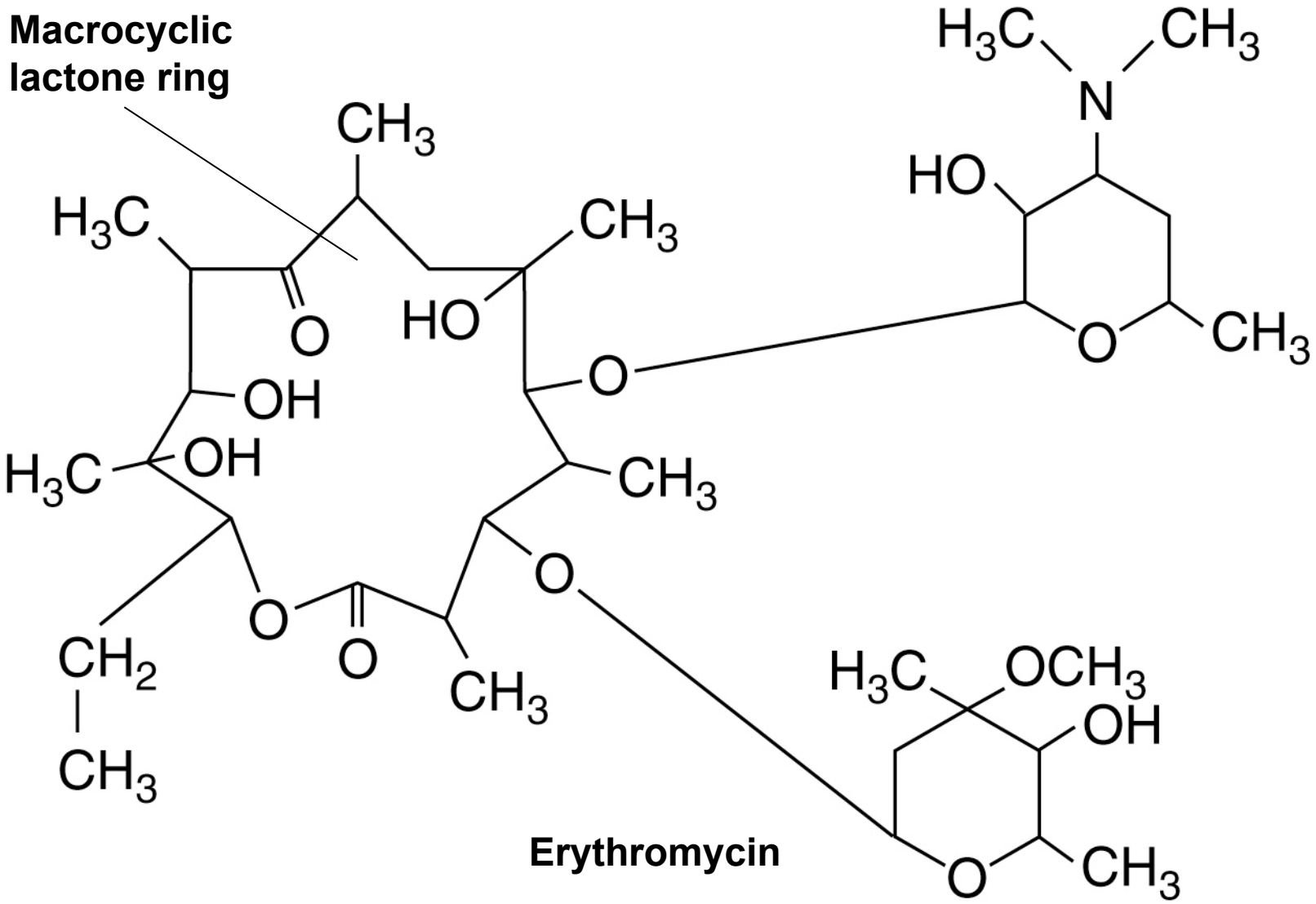
Inhibitors of Protein Synthesis

- **Glycylcyclines**
  - MRSA and *Acinetobacter baumanii*
  - Bind 30S subunit // inhibit translation

Inhibitors of Protein Synthesis

- **Macrolides (e.g. erythromycin)**
  - Gram-positives
  - Bind 50S // prevent translocation

The structure of the antibacterial antibiotic erythromycin, a representative macrolide.



Inhibitors of Protein Synthesis

- **Streptogramins**
  - Gram-positives
  - Bind 50S subunit // inhibit translation

Inhibitors of Protein Synthesis

- **Oxazolidinones**
  - Linezolid // MRSA
  - Bind 50S subunit
  - prevent formation of 70S ribosome

Inhibitors of Protein Synthesis

- **Pleuromutilins**
  - From the mushroom *Pleurotis mutilus*
  - MRSA
  - Bind 50S // prevent translocation

Injury to the Plasma Membrane

Injury to the Plasma Membrane

- **Lipopeptides**
  - Structural changes in the membrane
  - Followed by arrest of the synthesis of DNA, RNA, and protein
  - MRSA
- **Polymyxin B** // Topical
  - Combined with bacitracin and neomycin in over-the-counter preparation

Inhibitors of Nucleic Acid Replication

Inhibitors of Nucleic Acid Synthesis

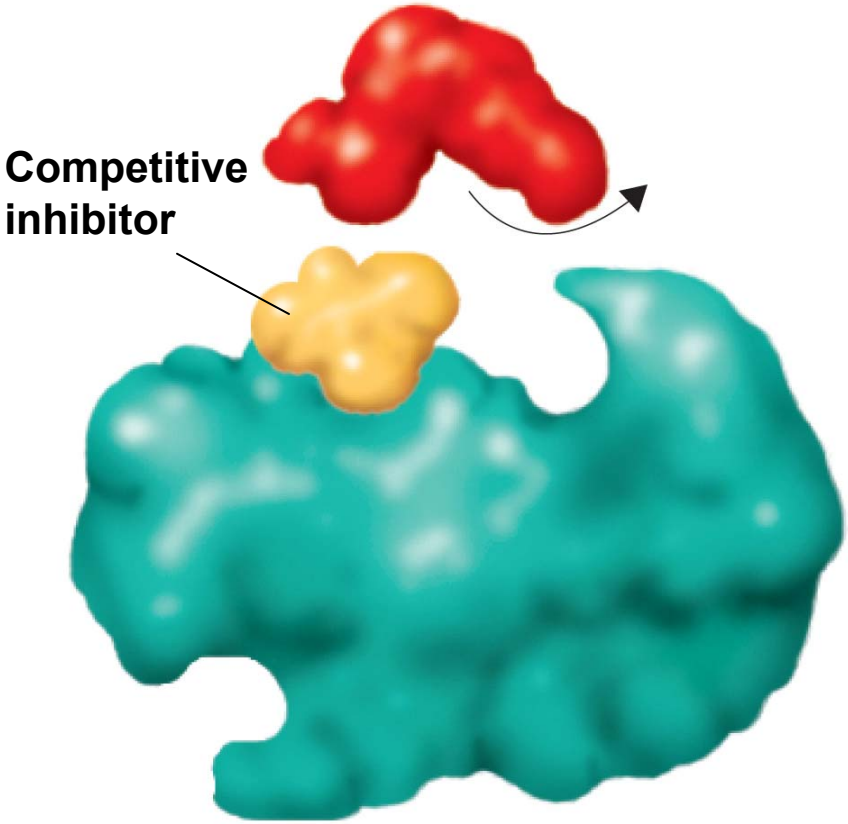
- **Rifamycin**
  - Inhibits RNA synthesis // Antituberculosis
- **Quinolones** and **fluoroquinolones**
  - Nalidixic acid: urinary infections
  - Ciprofloxacin // Inhibit DNA gyrase - Urinary tract infections

Inhibitors of Essential Metabolite Synthesis

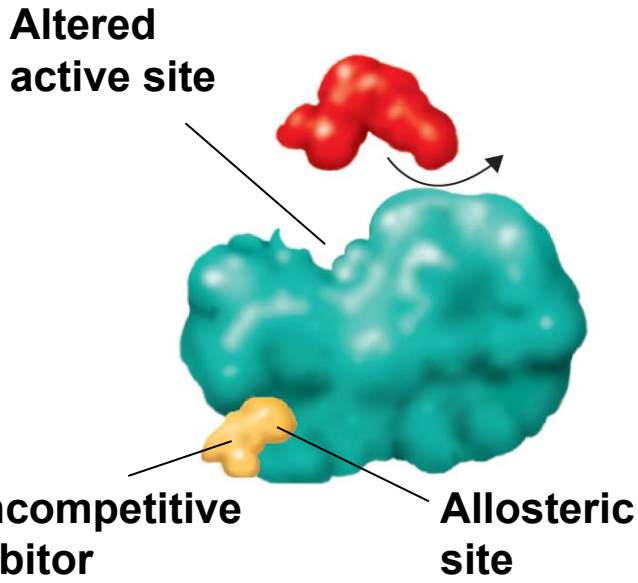
Competitive Inhibitors

- **Sulfonamides (sulfa drugs)**
  - Inhibit folic acid synthesis
  - Broad spectrum

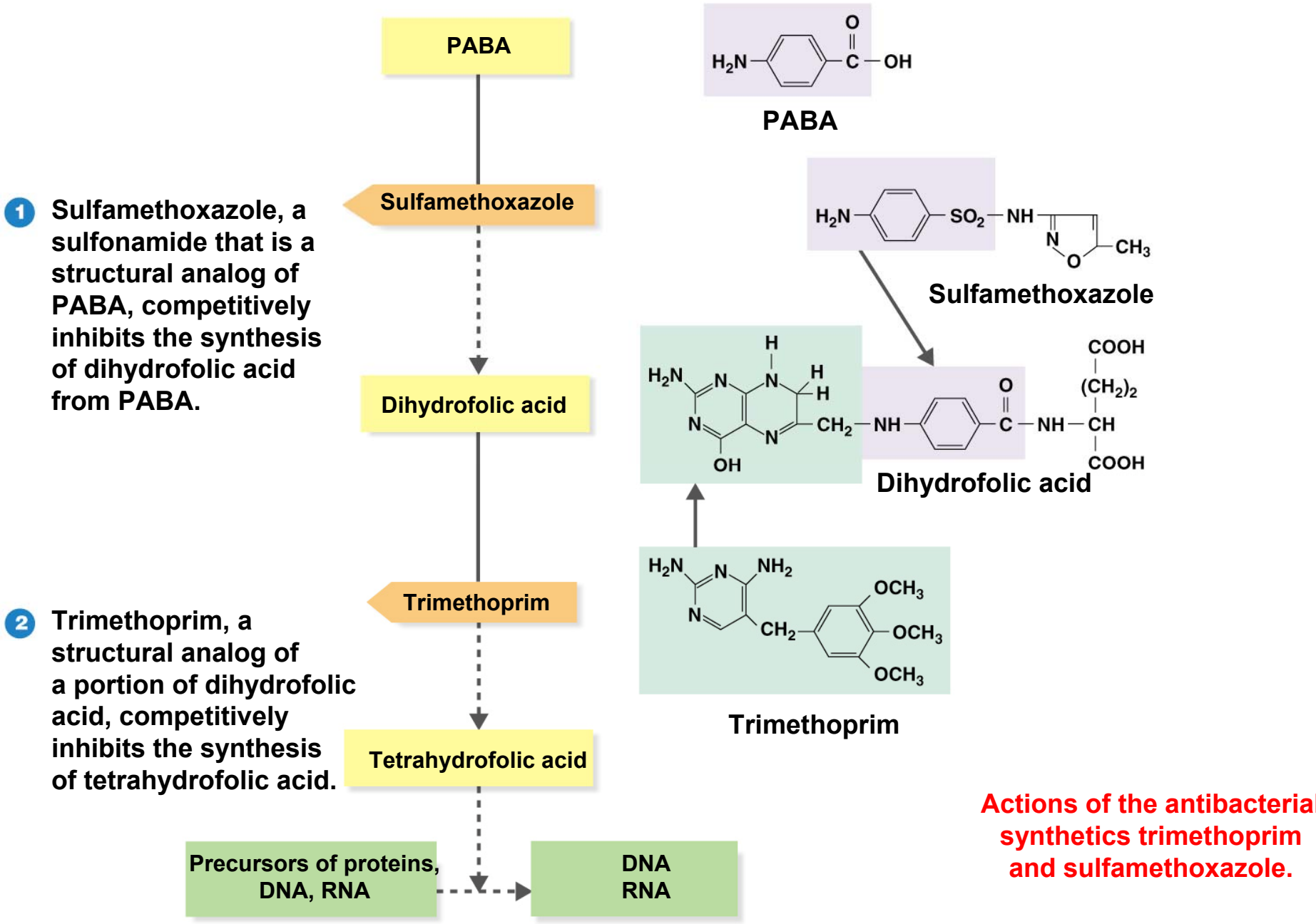
Action of Enzyme Inhibitors



(b)

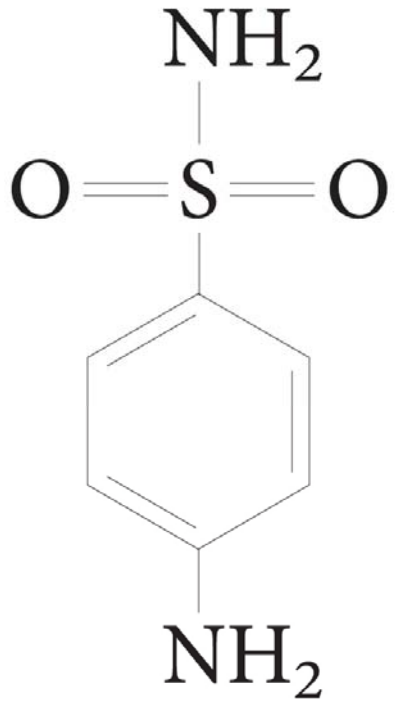


(c)

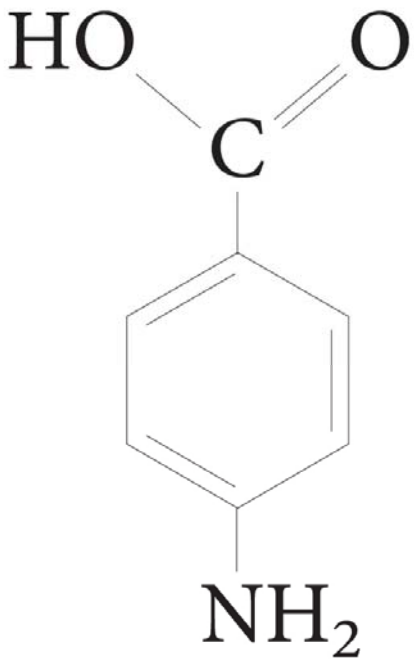


Actions of the antibacterial synthetics trimethoprim and sulfamethoxazole.

Inhibiting the Synthesis of Essential Metabolites



Sulfanilamide

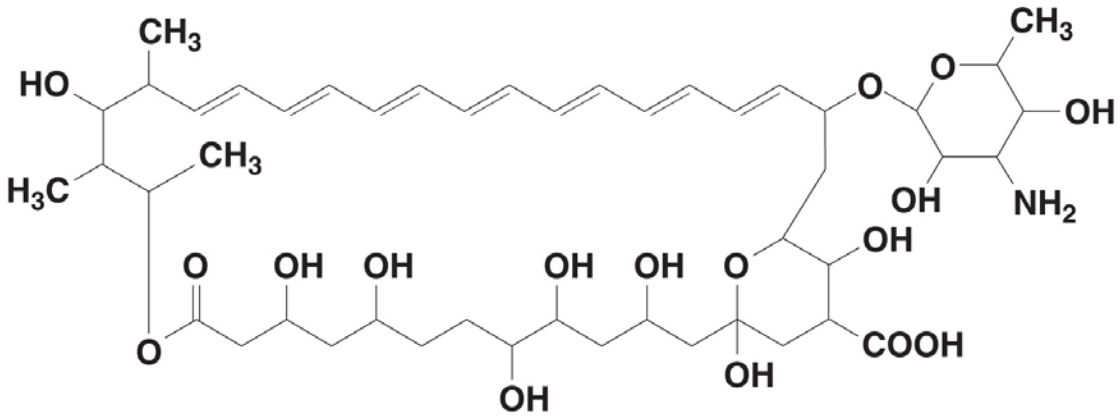


PABA

Para-aminobenzoic acid / substrate which leads to formation of folic acid – essential bacterial nutrient // sulfer drugs act as a competitive inhibitor

Antifungal Drugs:
Inhibition of Ergosterol Synthesis

- **Polyenes** // Amphotericin B

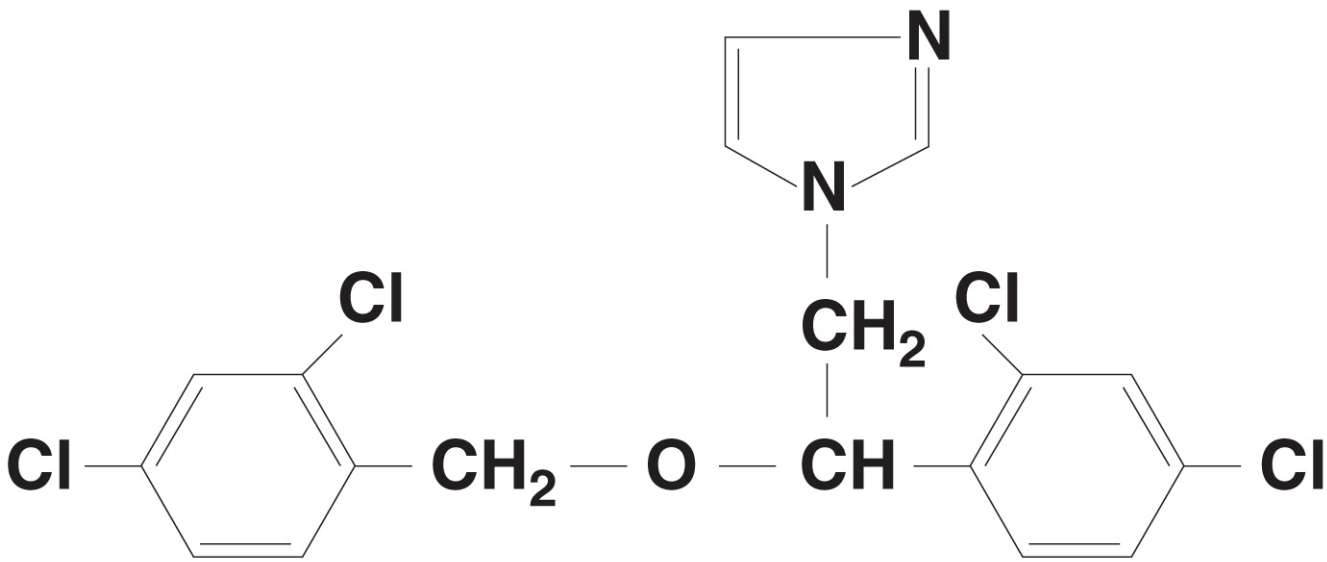


The structure of the antifungal drug amphotericin B, representative of the polyenes.

Antifungal Drugs:
Inhibition of Ergosterol Synthesis

- **Azoles** // Miconazole & Triazole
- **Allylamines** // For azole-resistant infections

The structure of the antifungal drug miconazole, representative of the imidazoles.

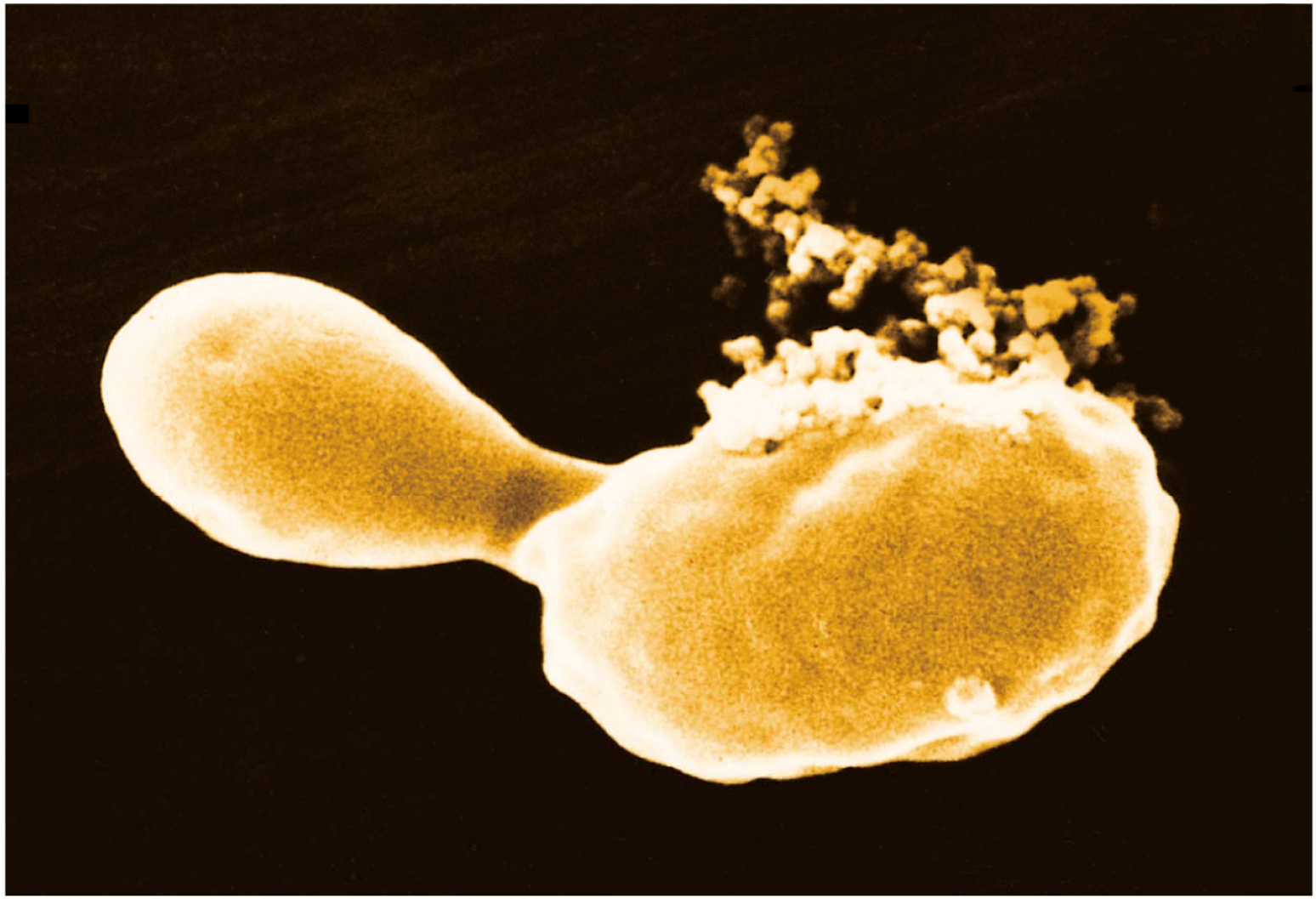


Miconazole

Antifungal Drugs: Inhibiting Cell Wall Synthesis

- **Echinocandins**
  - Inhibit synthesis of β-glucan
  - Cancidas is used against *Candida* and *Pneumocystis*

Injury to the plasma membrane of a yeast cell caused by an antifungal drug.



Inhibition of Nucleic Acids

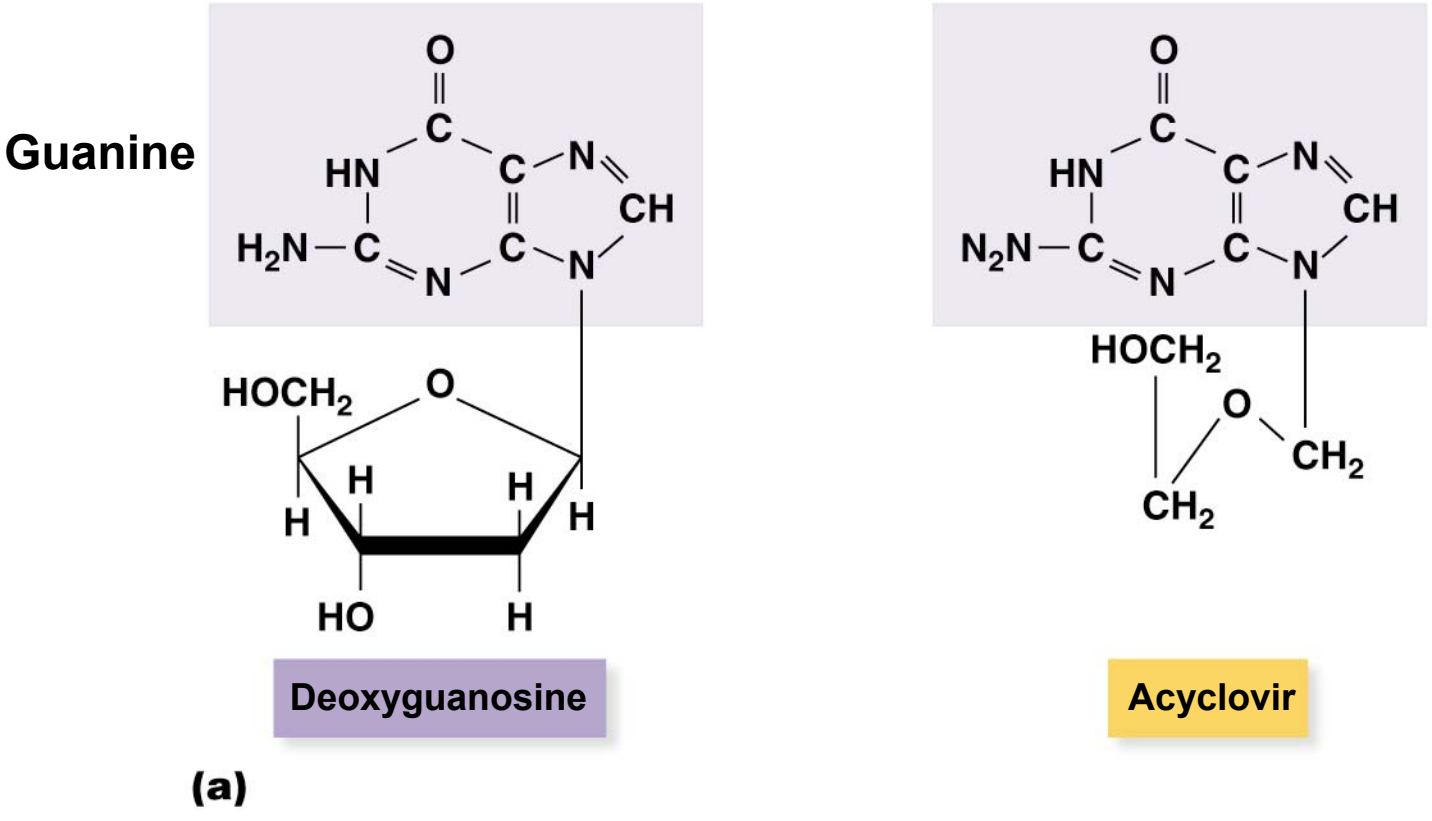
- **Flucytosine** // Cytosine analog interferes with RNA synthesis
- **Pentamidine isethionate** // Anti-*Pneumocystis*; may bind DNA

Other Antifungal Drugs

- **Griseofulvin** // Inhibits microtubule formation
  - Superficial dermatophytes
- **Tolnaftate** // Action unknown

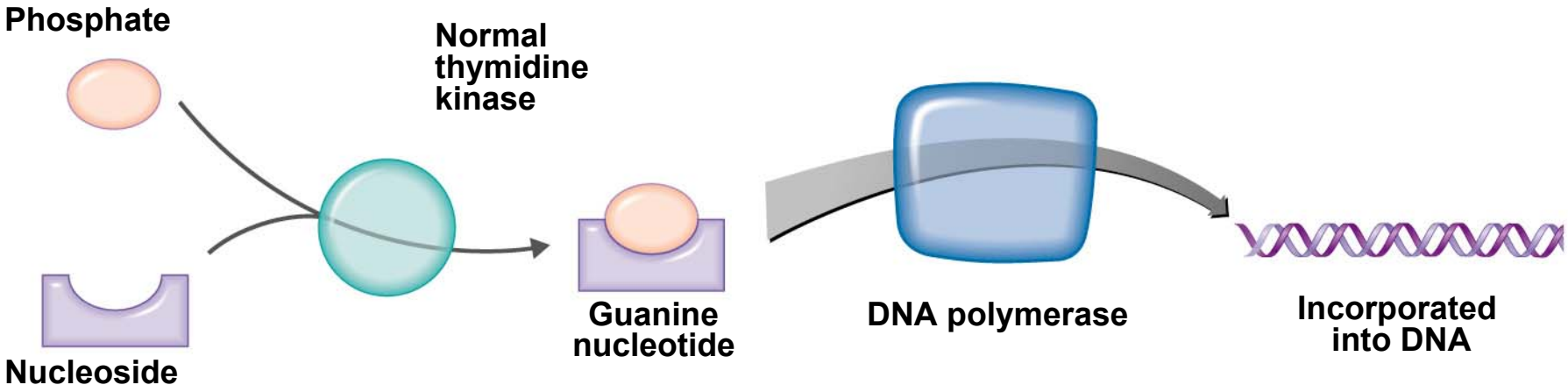
Antiviral Drug

The structure and function of the antiviral drug acyclovir.

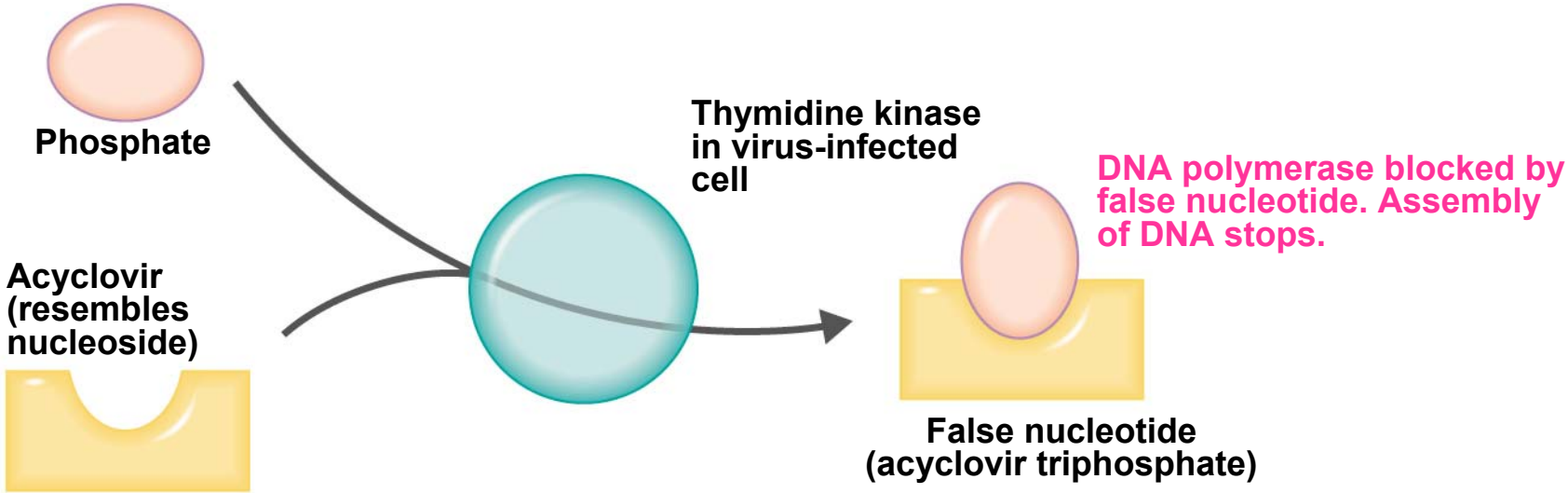


Acyclovir structurally resembles the nucleoside deoxyguanosine.

The structure and function of the antiviral drug acyclovir.



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



(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) to a false nucleotide, which blocks DNA synthesis by DNA polymerase.

Antiviral Drugs:
Enzyme Inhibitors

- **Protease inhibitors** //
  Indinavir: HIV

- **Integrase inhibitors** // HIV

Antiviral Drugs:
Entry Inhibitors

- **Entry inhibitors** // Amantadine: influenza

- **Fusion inhibitors** // Zanamivir: influenza - Block CCR5: HIV

Antiviral Drugs: Interferons

- Prevent spread of viruses to new cells // Alpha interferon: Viral hepatitis

- **Imiquimod** // Promotes interferon production

Antiprotozoan Drugs

- Chloroquine // Inhibits DNA synthesis - Malaria
- Artemisinin // Kills *Plasmodium* sporozoites
- Metronidazole// Interferes with anaerobic metabolism - *Trichomonas* and *Giardia*

Antihelminthic Drugs

- Niclosamide // Prevents ATP generation – Tapeworms
- Praziquantel // Alters membrane permeability - Flatworms
- Mebendazole and albendazole // Interfere with nutrient absorption - Intestinal roundworms
- Ivermectin // Paralysis of helminths - Intestinal roundworms

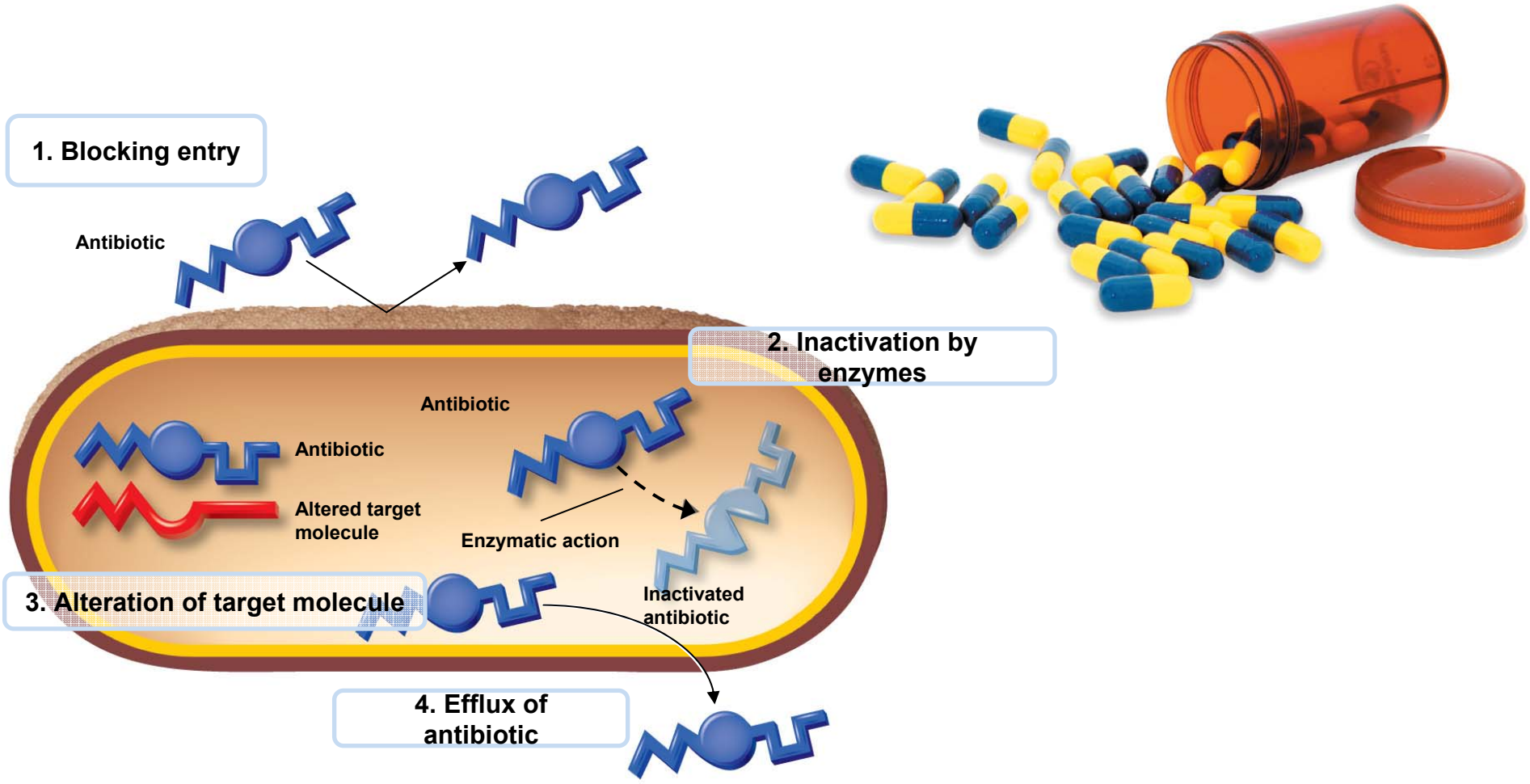
Antibiotic Resistance

- A variety of mutations can lead to antibiotic resistance
- Resistance genes are often on plasmids or transposons that can be transferred between bacteria

Antibiotic Resistance

- Misuse of antibiotics selects for resistance mutants
- Misuse includes:
  - Using outdated or weakened antibiotics
  - Using antibiotics for the common cold and other inappropriate conditions
  - Using antibiotics in animal feed
  - Failing to complete the prescribed regimen
  - Using someone else’s leftover prescription

Bacterial Resistance to Antibiotics.

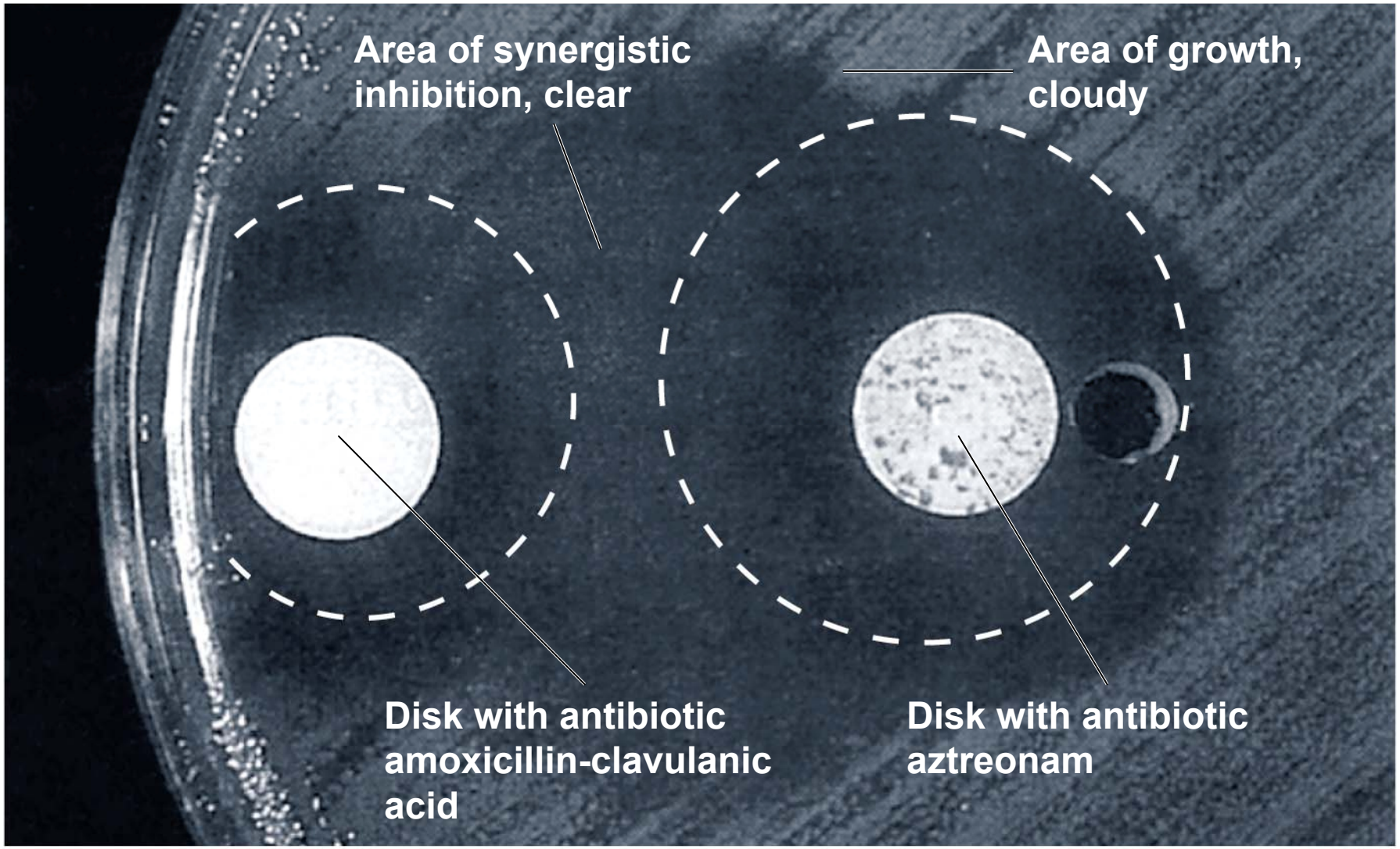


Effects of Combinations of Drugs

- **Synergism** occurs when the effect of two drugs together is greater than the effect of either alone

- **Antagonism** occurs when the effect of two drugs together is less than the effect of either alone

An example of synergism between two different antibiotics.



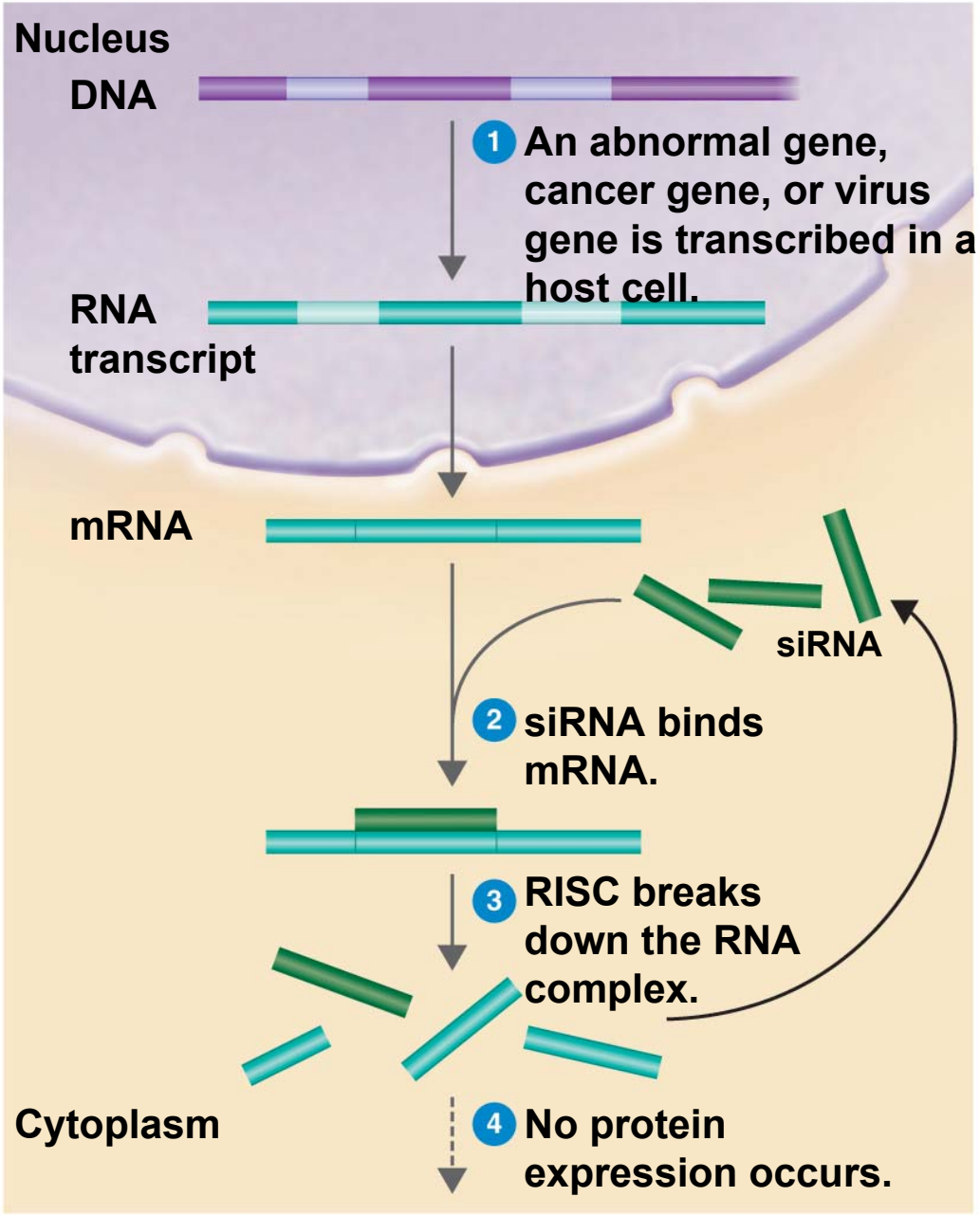
Antibiotic Safety

- Therapeutic index: risk versus benefit

Future of Chemotherapeutic Agents

- **Antimicrobial peptides**
  - Broad-spectrum antibiotics
    - Nisin (lactic acid bacteria)
    - Defensins (human)
    - Magainin (frogs)
    - Squalamine (sharks)
- **Phage therapy**

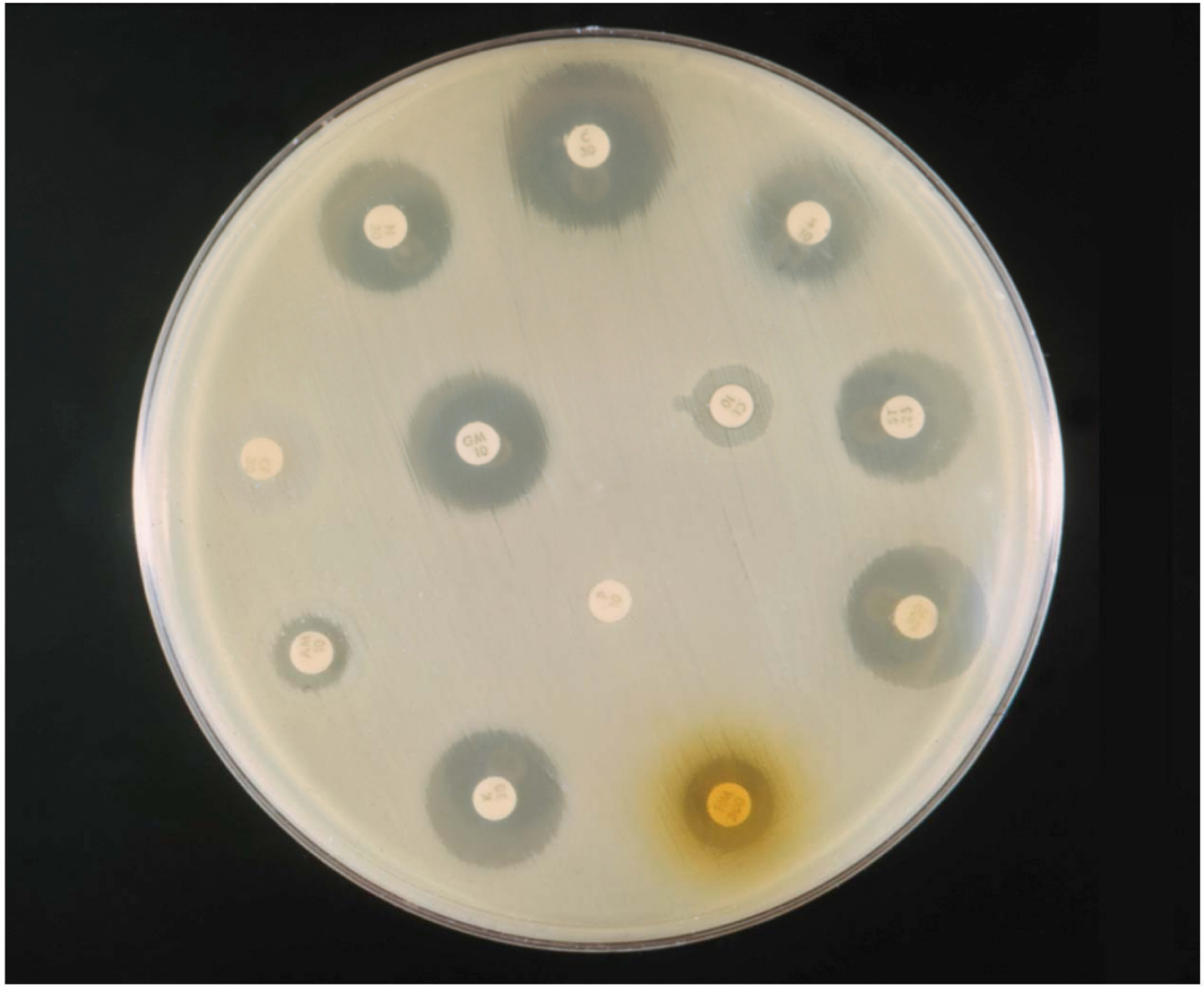
Gene silencing could provide treatments for a wide range of diseases.



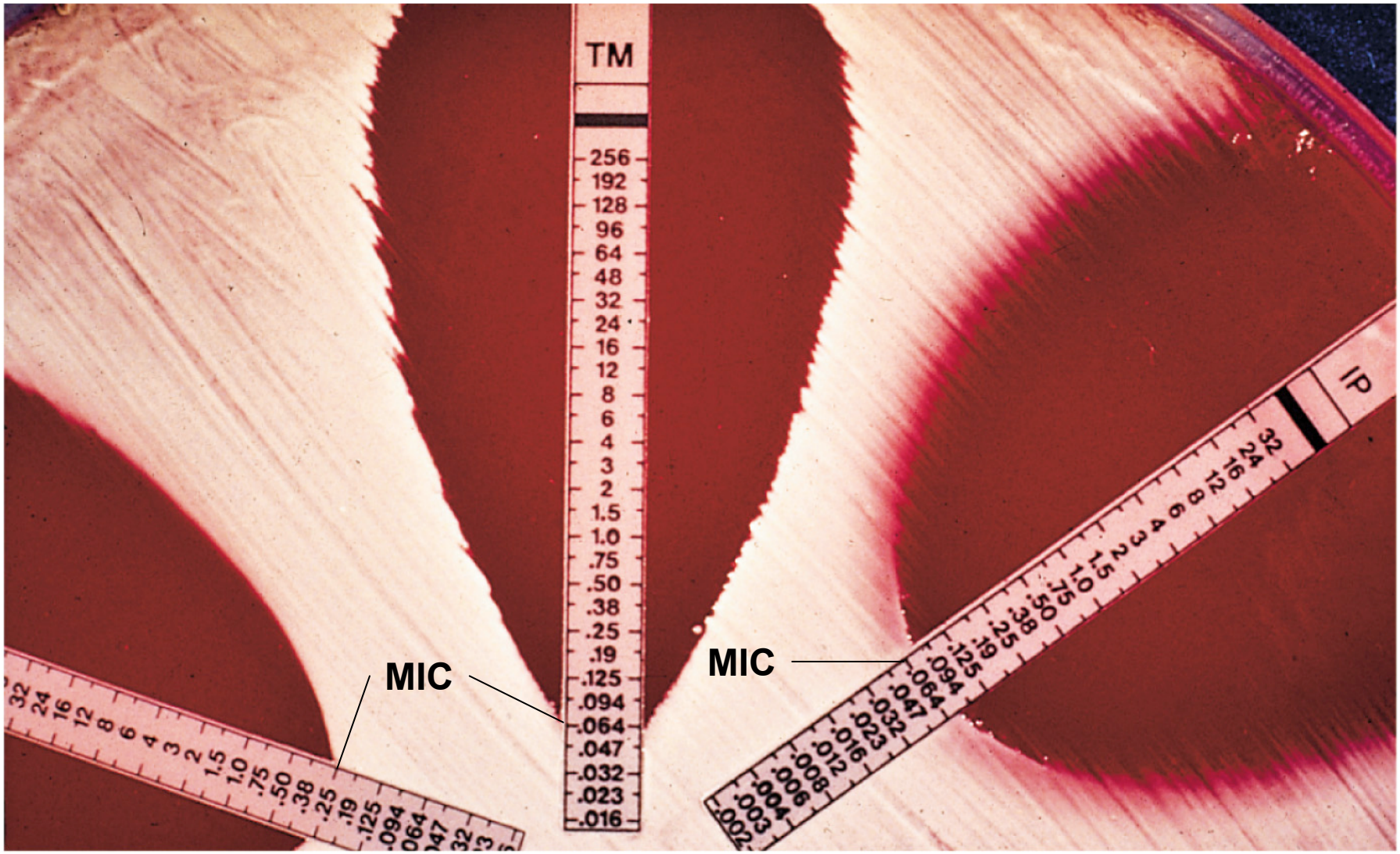
Tests to Guide Chemotherapy

- **MIC**: minimal inhibitory concentration
- **MBC**: minimal bactericidal concentration
- **Antibiogram**

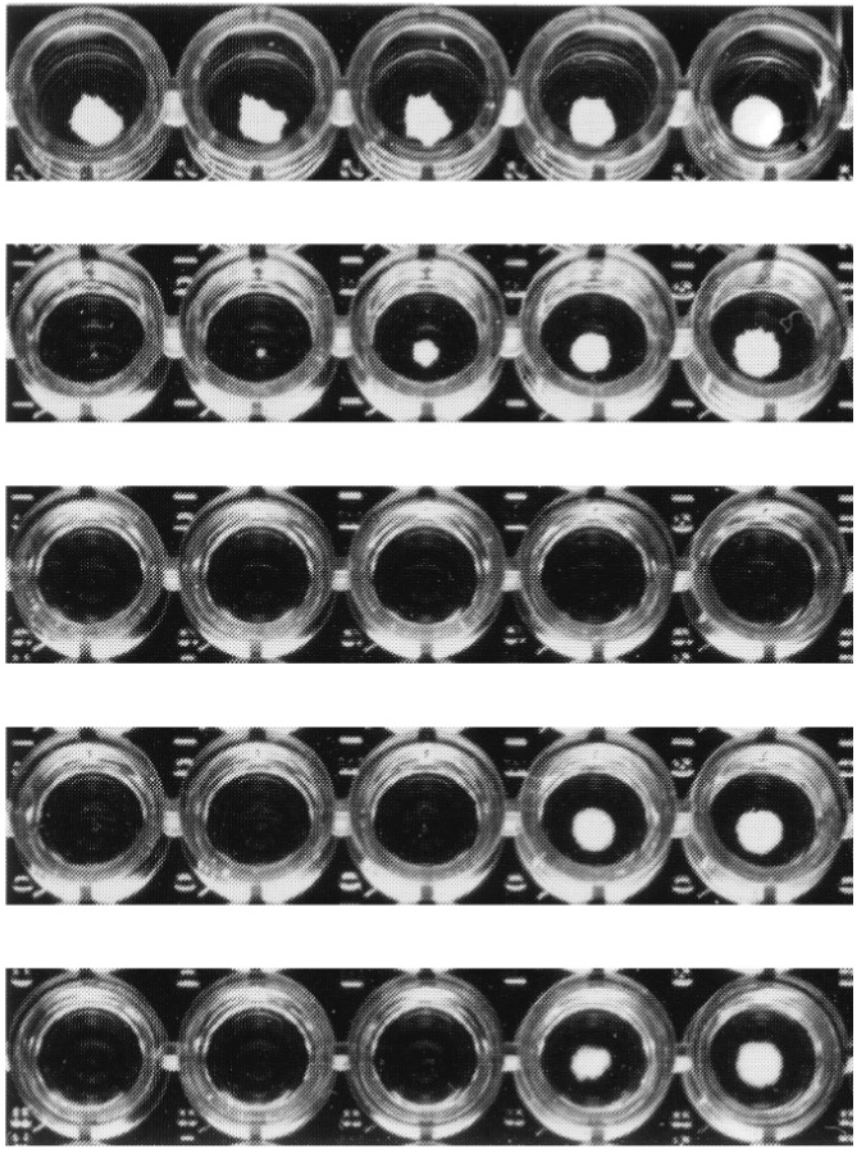
The disk-diffusion method for determining the activity of antimicrobials.



The E test (for epsilometer), a gradient diffusion method that determines antibiotic sensitivity and estimates minimal inhibitory concentration (MIC).



A microdilution, or microtiter, plate used for testing for minimal inhibitory concentration (MIC) of antibiotics.



Doxycycline
(Growth in all wells, resistant)

Sulfamethoxazole
(Trailing end point; usually read where there is an estimated 80% reduction in growth)

Streptomycin
(No growth in any well; sensitive at all concentrations)

Ethambutol

Kanamycin

(Growth in fourth wells; equally sensitive to ethambutol and kanamycin)

Decreasing concentration of drug →

The development of an antibiotic-resistant mutant during antibiotic therapy.