Chapter 20:
Antimicrobial Drugs

1. Overview of Antimicrobial Drugs
2. Antibacterial Drugs
3. Antiviral Drugs
4. Drugs for Eukaryotic Pathogens

1. Overview of Antimicrobial Drugs

Antibiotics

An antibiotic is technically a substance produced a microorganism to inhibit or kill other microorganisms:

- **e.g., the mold *Penicillium chrysogenum* produces penicillin which kills Gram^{+} bacteria**

In practice, though, the term antibiotic is used to refer to *any* substance, natural or synthetic, that inhibits or kills microorganisms:

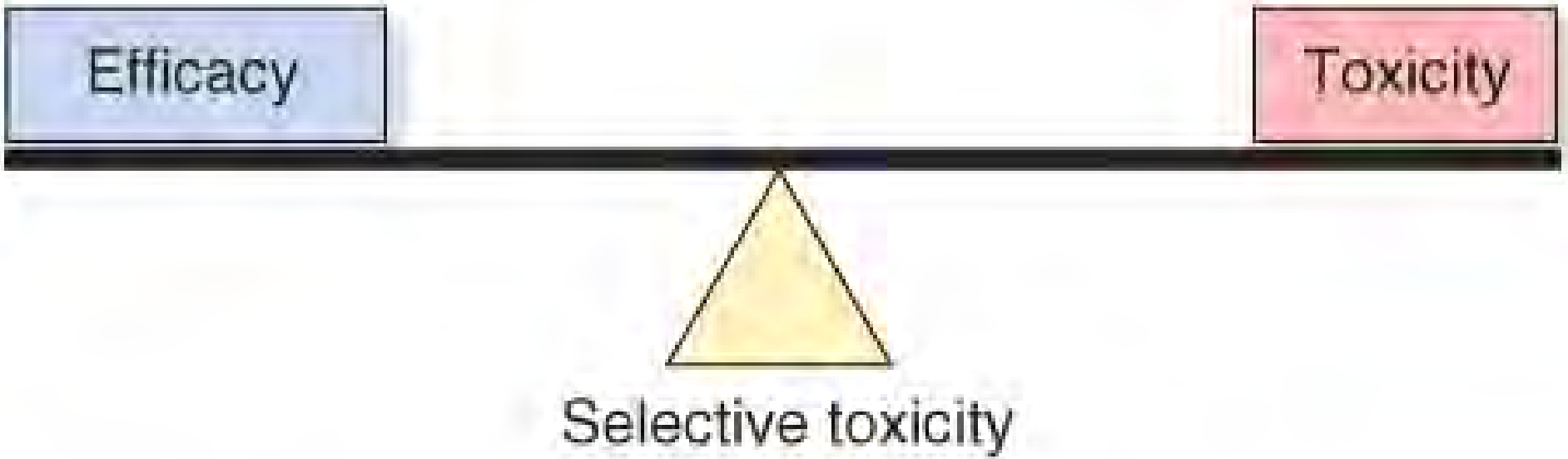
- **when used therapeutically, antibiotics are antimicrobial drugs!**

Antibiotics should not harm the Host

For an antibiotic to be an effective drug, it must cause significantly greater harm to the pathogen than to the host being treated:

- **this requires the targeting of features of the pathogen that differ from the host's cells**
- **bacteria have several such targets such as the cell wall & ribosomes**
- **viruses and eukaryotic pathogens are much more challenging to treat since they have less features that can be *safely* targeted**

Efficacy vs Toxicity



$$\text{Chemotherapeutic index} = \frac{\text{Toxic dose}}{\text{Therapeutic dose}}$$

- **the higher the chemotherapeutic index, the safer the drug…**

Spectrum of Antimicrobial Drugs

The range of pathogens targeted by a specific antibiotic is referred to as its spectrum, which can be "broad" or "narrow":

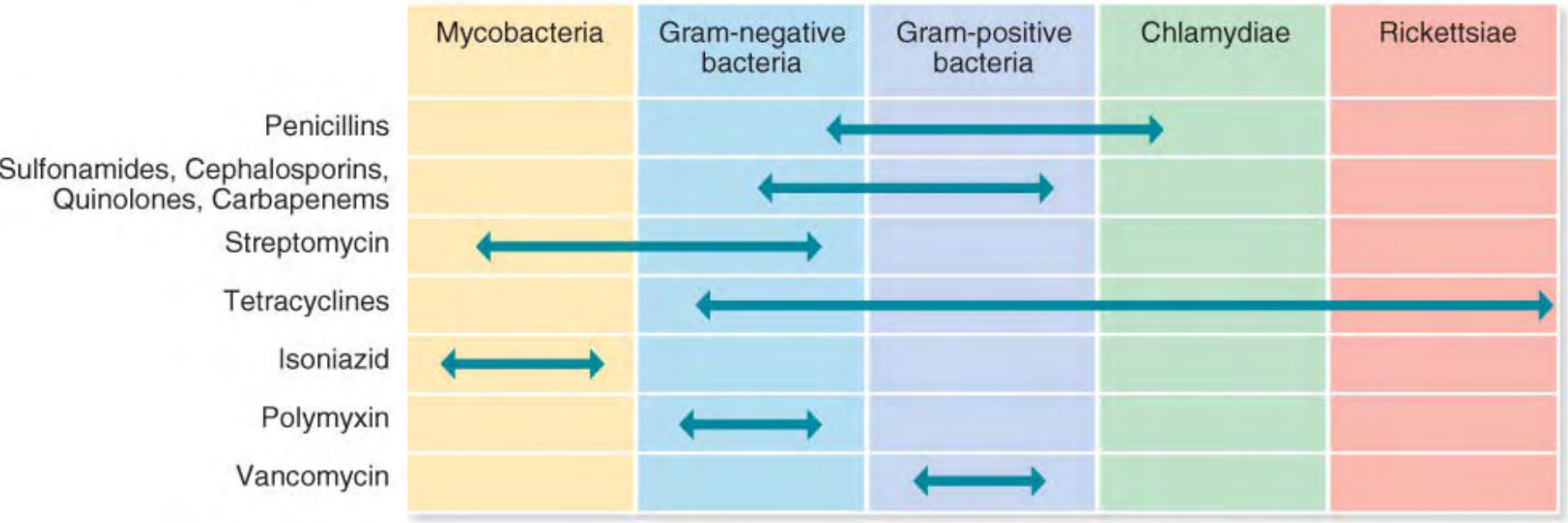
Broad-spectrum antibiotics

- usually refers to drugs effective against more that one general category of pathogens
- e.g., Gram$^-$ & Gram$^+$ bacteria

Narrow-spectrum antibiotics

- usually refers to drugs effective against only one general category of pathogens
- e.g., Gram$^+$ bacteria, or mycobacteria

Examples of Spectrum of Activity



- **vancomycin is “narrow spectrum”**
- **tetracyclines are “broad spectrum**

Antimicrobial Drug Resistance

The introduction of an antibiotic into the microbial environment is a selective factor that over time can select for resistant pathogens.

The main ways to minimize this problem are:

1) **administer the antibiotic at the prescribed dose for the prescribed duration**
   - **premature stoppage allows the more resistant pathogens to survive**

2) **use antibiotics in combination**
   - **much lower odds of resistance to multiple antibiotics**

How is Resistance Obtained?

Resistance to an antibiotic is generally obtained by the acquisition of antibiotic resistance genes:

e.g., transformation, conjugation, transduction, or a fortuitous mutation

Resistance genes can be of several types:

- **enzymes that degrade the antibiotic**
- **pumps which rapidly expel the antibiotic**
- **barriers which resist penetration of antibiotic**
- **molecular changes which prevent binding of the antibiotic to the target site**

2. Antibacterial Drugs

Antibacterial Targets

A variety of unique bacterial features can be targeted by antibiotics w/o harming host cells:

1) bacterial cell wall

- **peptidoglycan and outer membrane**

2) protein synthesis

- **prokaryotic ribosomes differ from those of eukaryotes**

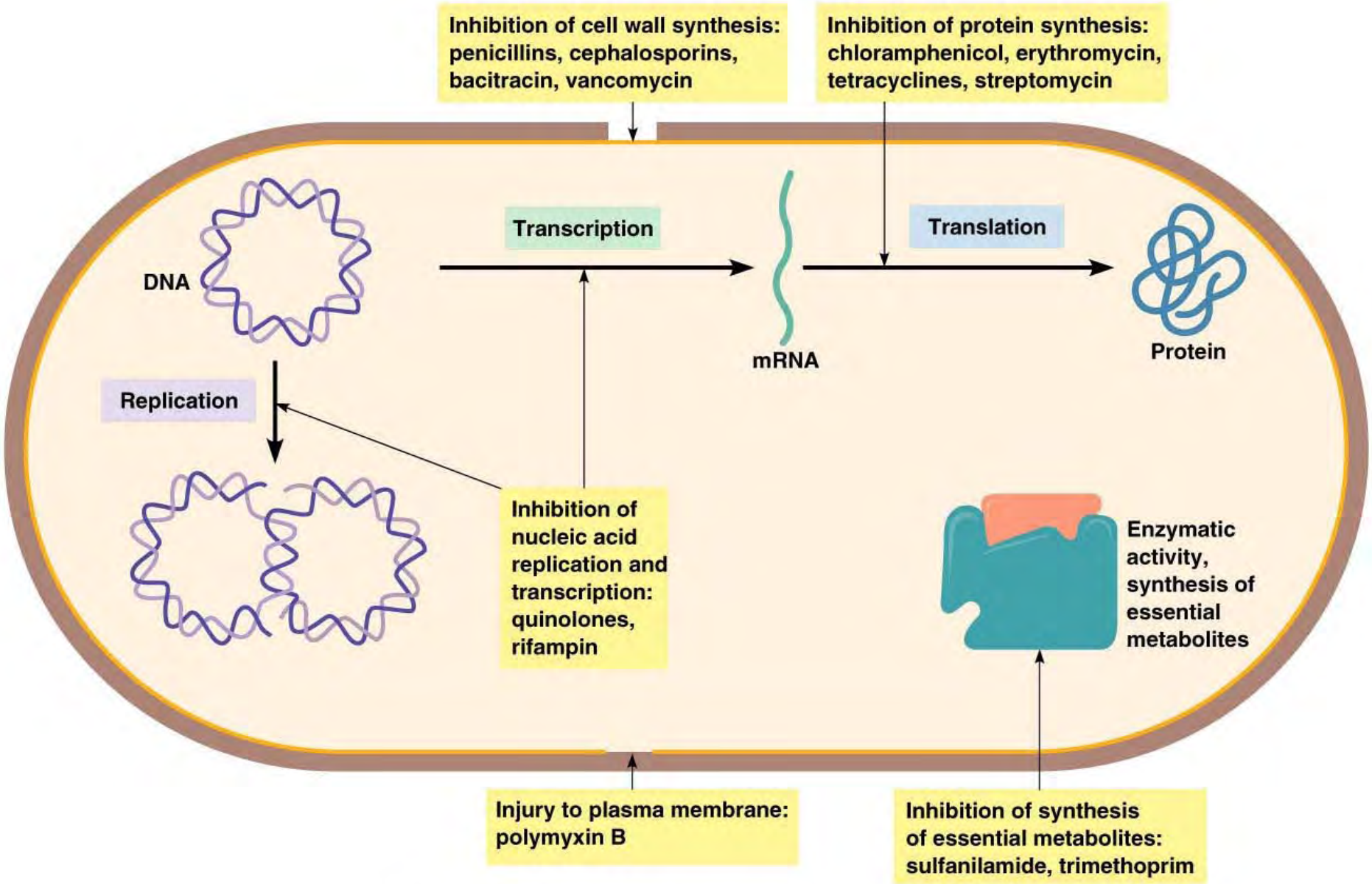
3) plasma membrane

- **there are unique features to bacterial membranes**

4) nucleic acid synthesis

- **unique features of prokaryotic DNA, RNA polymerases**

5) metabolic inhibitors



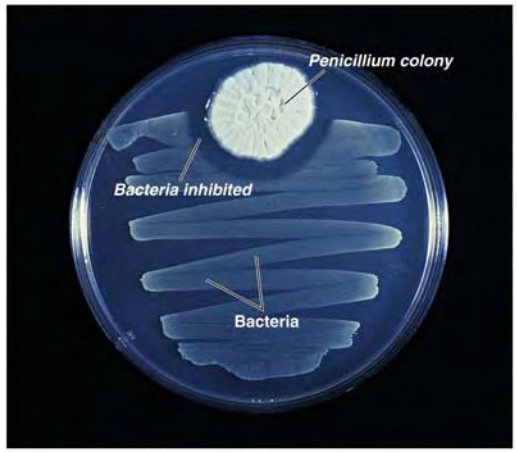
Antibacterial Targets

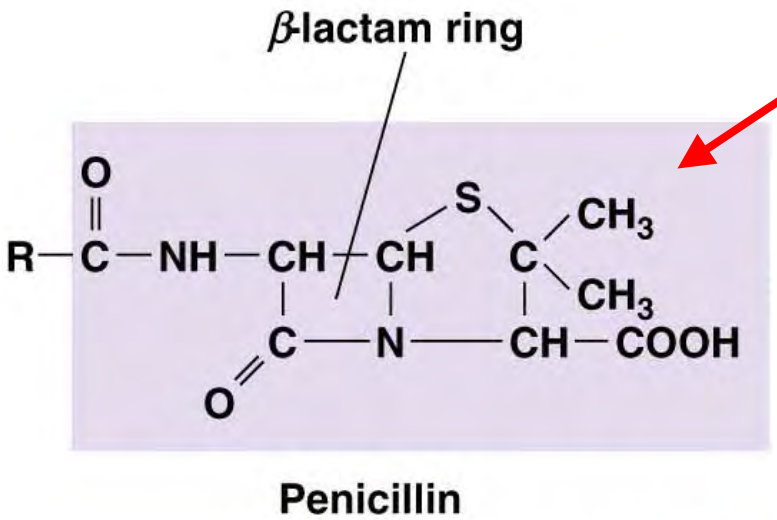
Drugs that Target the Cell Wall

Inhibitors of peptidoglycan synthesis:

Penicillin & its derivatives

- over 50 related compounds
- some are natural, some are semisynthetic



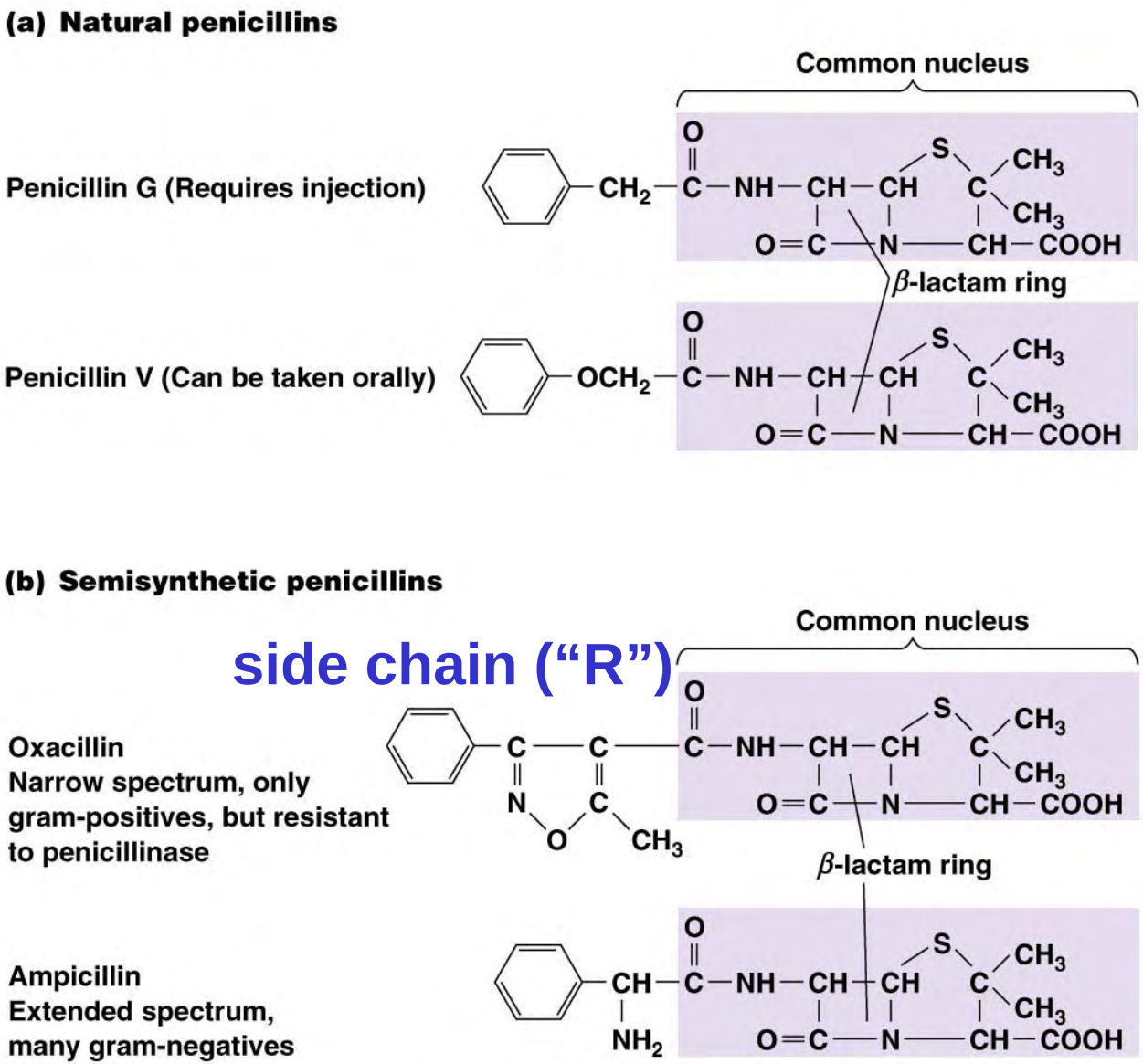


Penicillin

- all penicillin-based compounds have this same core structure
- prevent cross-linking of carbohydrate & peptide components of peptidoglycan

more effective against Gram$^+$ bacteria (no outer membrane)

Some Penicillin Derivatives



Natural

- produced by fungi
- narrow spectrum
- subject to degradation

Semisynthetic

- side chain only is synthetic
- broader spectrum
- resistant to degradation

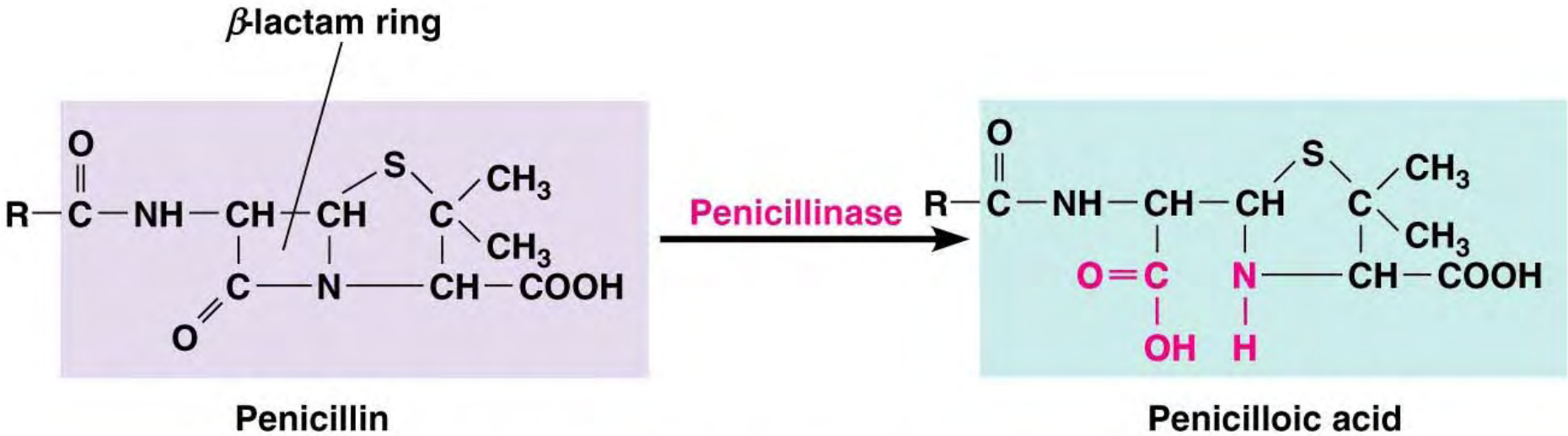
Effects of Penicillin

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

(b) The bacterial cell is lysing as penicillin weakens the cell wall. SEM 1 μm

- **penetrates cells (mostly Gram$^+$) and interferes with peptidoglycan synthesis**
- **without an intact peptidoglycan layer, bacterial cells are prone to lysis by osmosis**

Microbial Defenses to Penicillin



- some bacteria can avoid the effects of penicillin by the production of penicillinases (e.g., β-lactamase), enzymes that break the β-lactam ring

- semisynthetic derivatives such as Oxacillin are resistant to penicillinases

Other Peptidoglycan Inhibitors

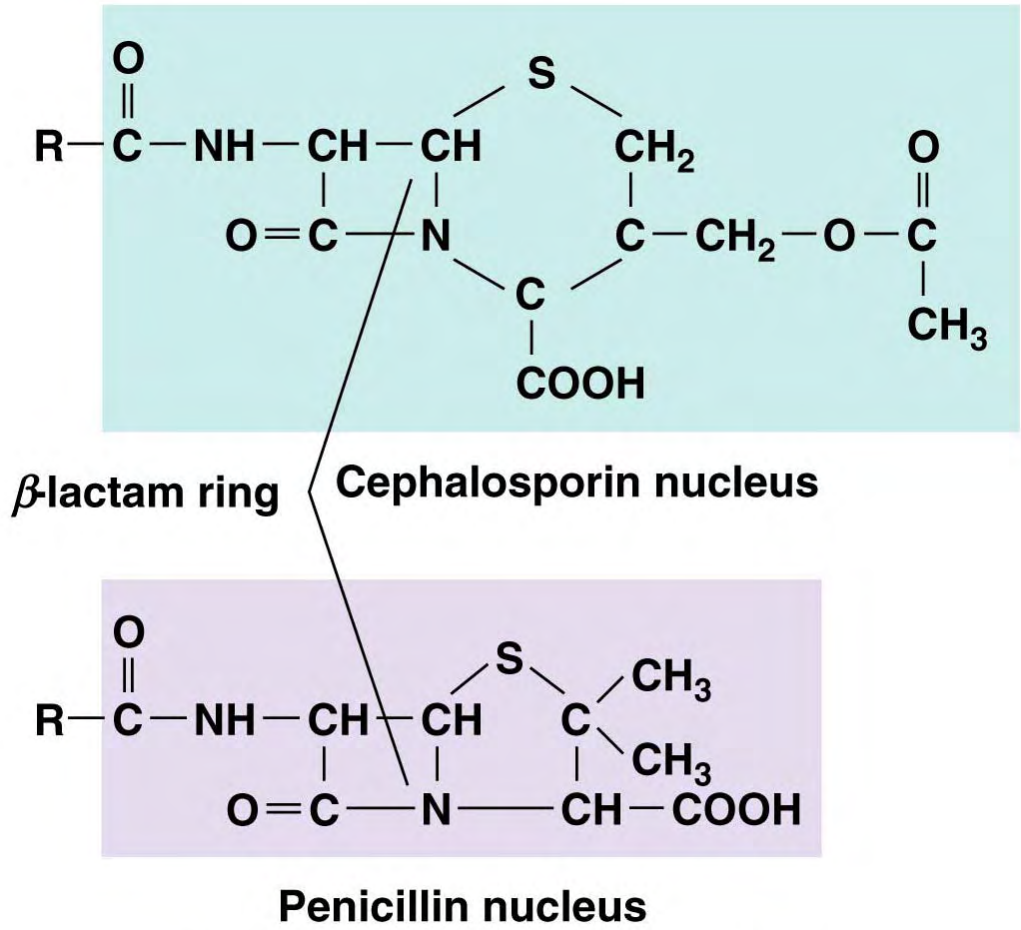
Cephalosporin & its derivatives (over 70!)

- inhibits peptidoglycan synthesis much like penicillin

- resistant to penicillinases
- vulnerable to cleavage by a similar yet distinct class of enzymes

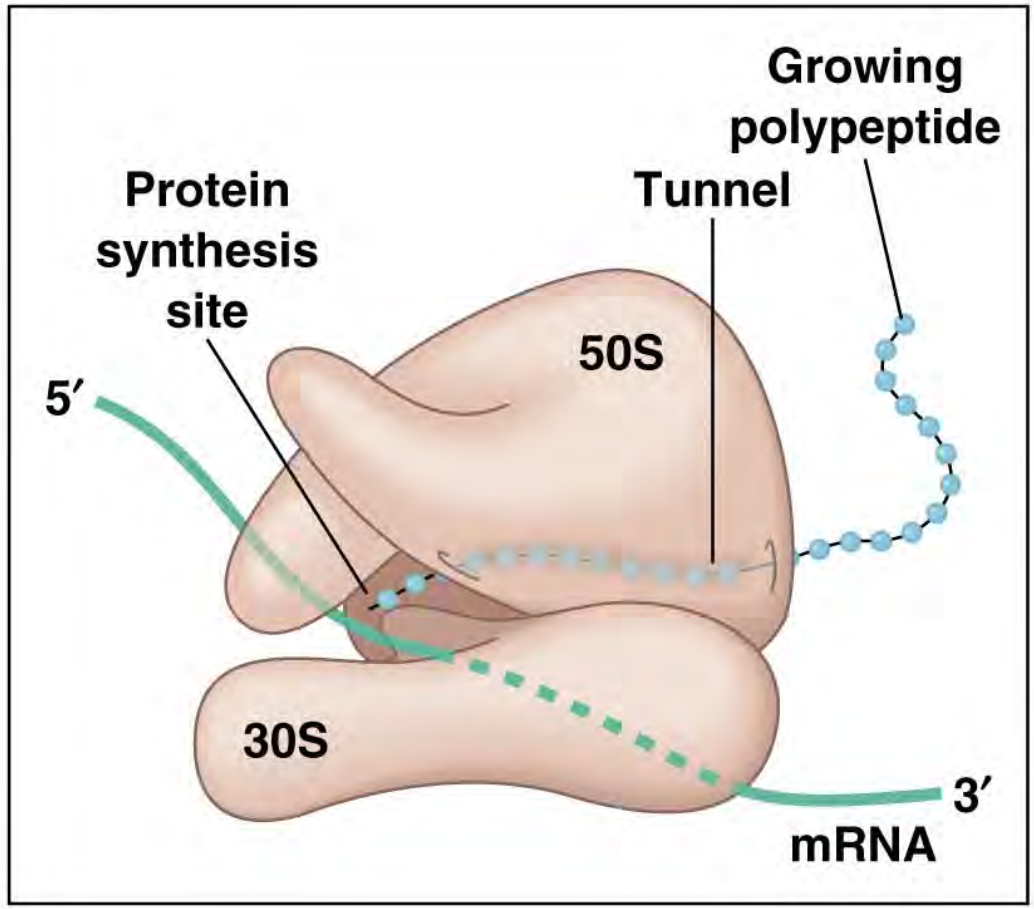
Vancomycin & Bacitracin

- polypeptides that inhibit peptidoglycan synthesis in a different manner



Drugs that Target Protein Synthesis

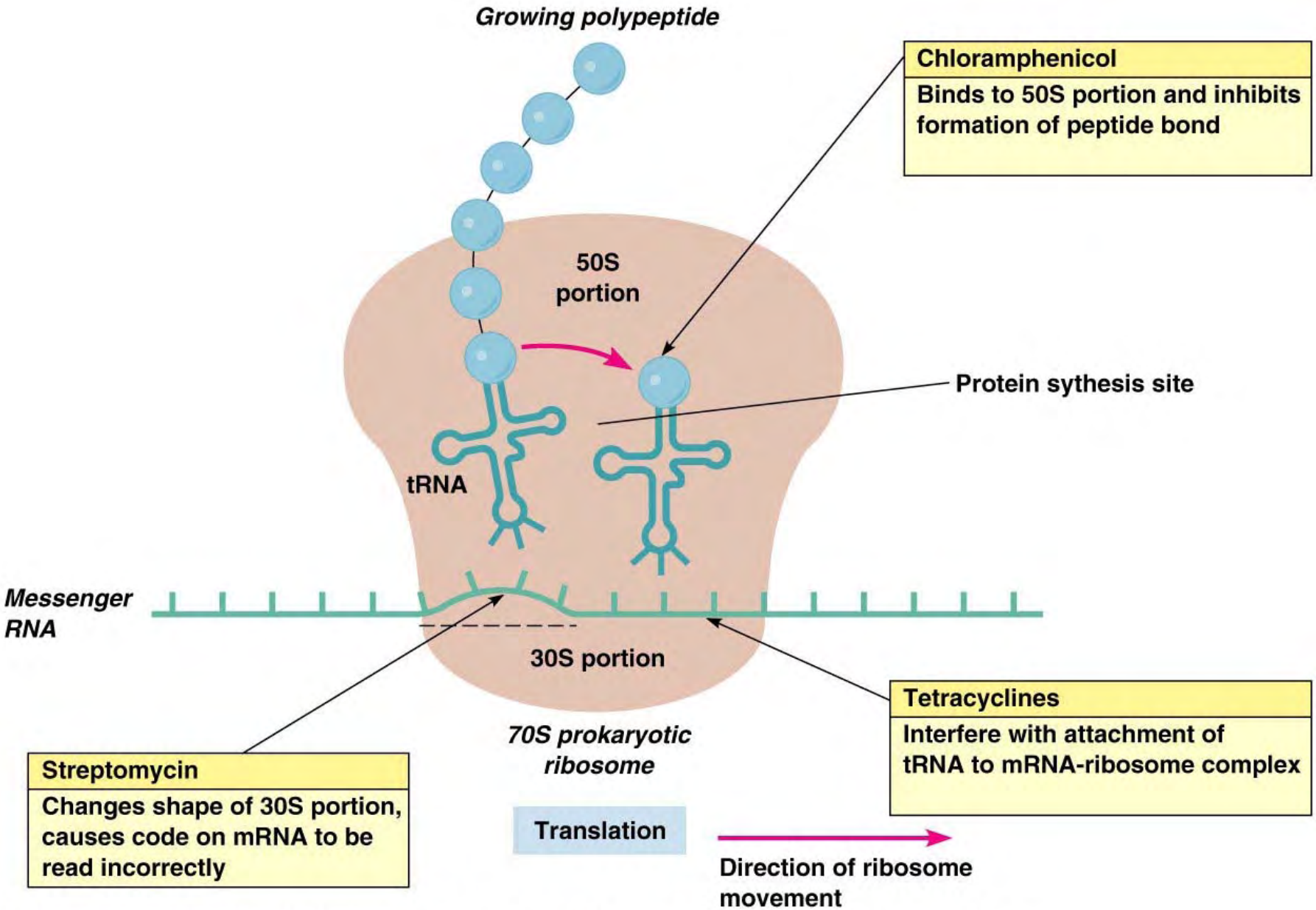
Bacterial ribosomes are slightly smaller than eukaryotic ribosomes and have enough structural differences to make them good targets for antibiotics



<u>Tetracyclines</u> – block binding of tRNAs to ribosome

<u>Chloramphenicol</u> – blocks peptide bond formation

<u>Aminoglycosides</u> – disrupt “reading” of mRNA



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

Inhibitors of Nucleic Acid Synthesis

Rifamycins

- e.g., rifampicin
- inhibit bacterial transcription (mRNA synthesis)
- penetrates host cells well, effective against intracellular bacteria such as Mycobacteria

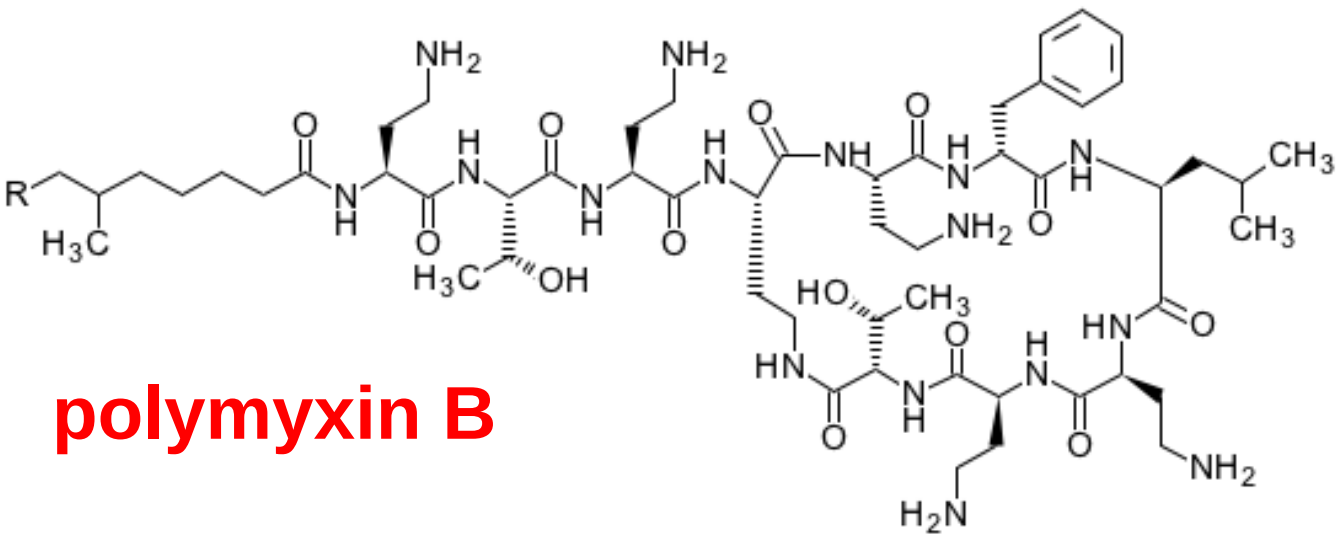
Quinolones

- e.g., ciprofloxacin
- inhibit the bacterial DNA gyrase - DNA replication
- broad spectrum antibiotic, more effective against Gram^{+} bacteria

Drugs that target Plasma Membrane

Polymyxin B

- disrupts plasma membrane, outer membrane
- especially effective against Gram$^-$ bacteria
- usually in topical ointments (“over the counter”) though can be given internally



polymyxin B

C11612

Metabolic Inhibitors

Some drugs selectively inhibit metabolic processes in bacteria:

Sulfonamides ("sulfa drugs")

- **inhibit folic acid synthesis from PABA (para-aminobenzoic acid)**
- **different from folic acid synthesis in animals**
- **have a bacteriostatic effect**
- **synthetic compounds that have a broad spectrum of antimicrobial activity**

Antimycobacterial Drugs

Mycobacteria are difficult targets due to their unique “acid-fast” outer membrane containing mycolic acids, and being intracellular pathogens.

The most effective antibiotics for mycobacterial infections are:

Rifamycins

- **penetrate outer membrane, inhibit transcription**

Isoniazid

- **directly inhibits mycolic acid synthesis**

3. Antiviral Drugs

Limits of Antiviral Drugs

Viruses are especially difficult to target with drugs for several reasons:

1) viruses use host cell metabolic processes

- **it's difficult to target viral processes w/o harming host**

2) viruses are intracellular parasites

- **the drug must effectively enter host cells**

3) viruses can be latent

- **there's very little a drug can do to combat a provirus**

4) viruses mutate very rapidly

- **thus their molecular targets can change rapidly**

Nevertheless, there are a several antiviral drugs in use…

Targets of Antiviral Drugs

Antiviral drugs generally target the following:

Virus-specific enzymes

- e.g., reverse transcriptase, integrase (inserts viral DNA into host DNA), proteases (process viral proteins)

Viral DNA replication, transcription

- drugs inhibiting these processes may kill host cell also

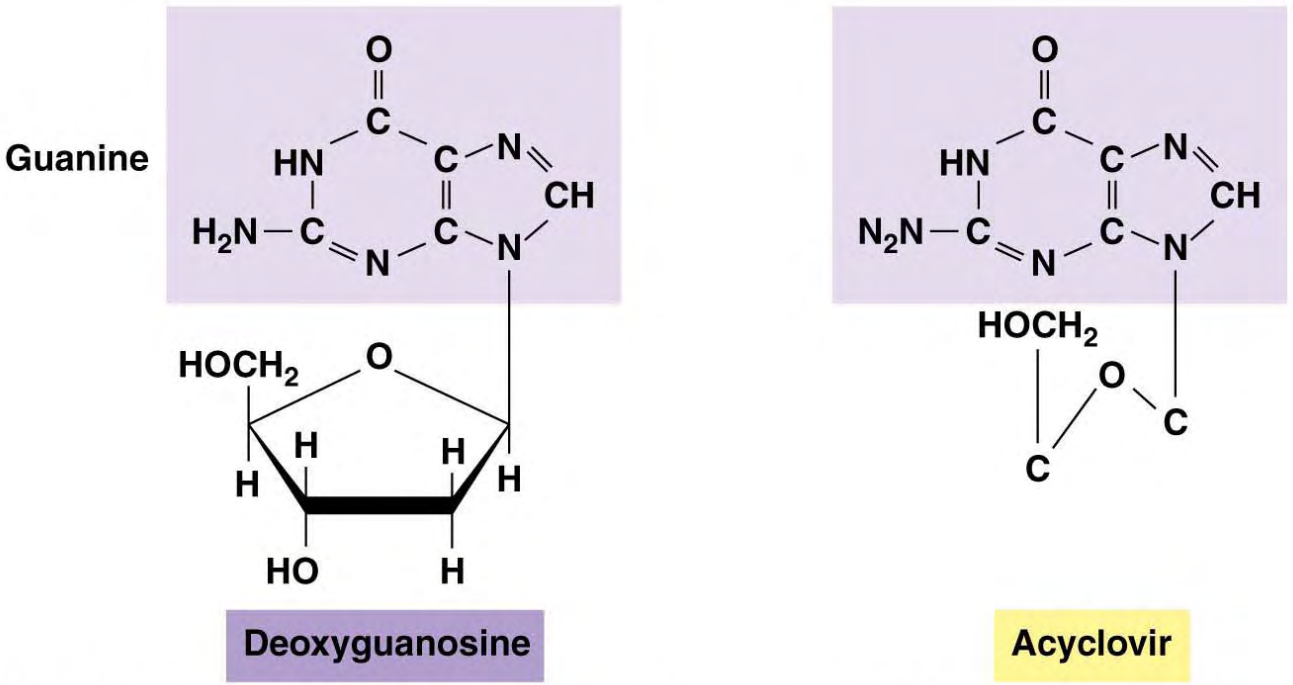
Fusion of enveloped viruses

- most enveloped viruses gain entry via fusion with the host membrane which can also be blocked

Nucleoside, Nucleotide Analogs

Many antiviral drugs are analogs of nucleosides (sugar + base) or nucleotides (sugar + base + phosphate):

- **incorporated into DNA or RNA**
- **function as "chain terminators", preventing elongation**

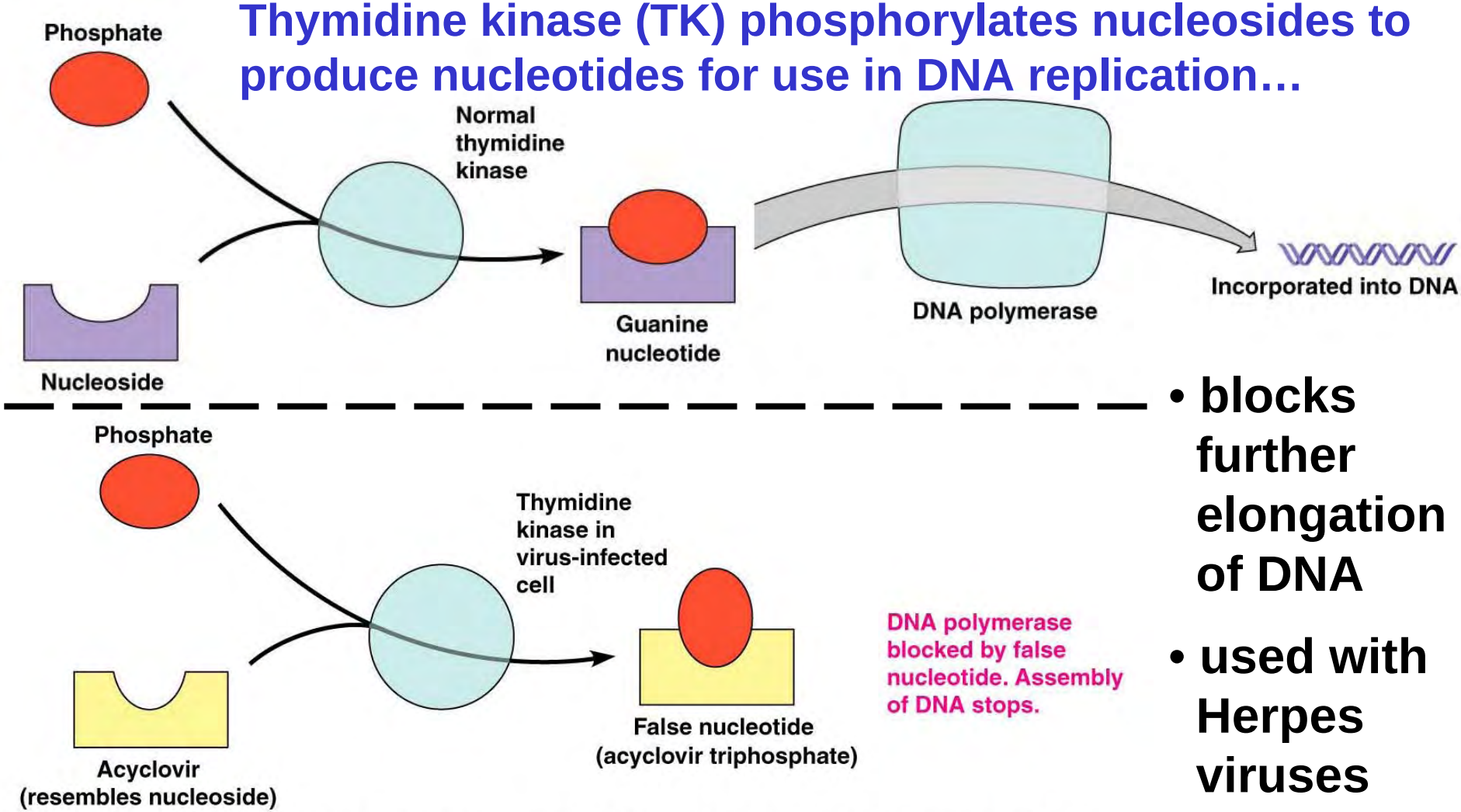


- **acyclovir is a common antiviral drug that is an analogue of the nucleoside guanosine**

(a) Acyclovir structurally resembles the nucleoside deoxyguanosine.

Acyclovir: Mechanism of Action

Thymidine kinase (TK) phosphorylates nucleosides to produce nucleotides for use in DNA replication…



- **blocks further elongation of DNA**
- **used with Herpes viruses**

- **viral TK will phosphorylate acyclovir which is incorporated into DNA by viral DNA polymerase**

Enzyme Inhibitors

Some antiviral drugs bind directly to viral enzymes and inhibit their activity:

Protease inhibitors

- **for many viral proteins to assemble into new viral particles, they must be cleaved by specific viral proteases**
- **protease inhibitors therefore can prevent viral maturation**

Reverse transcriptase inhibitors

- **unlike “chain terminators”like the nucleotide analogs, some drugs directly inhibit reverse transcriptase activity**
- **prevents conversion of RNA to DNA, only effective against retroviruses such as HIV**

Problems with Antiviral Drugs

Toxicity

- although antiviral preferentially inhibit viral factors, they can also inhibit host cell enzymes
    - e.g., nucleotide analogs are ~100 times more likely to be used by viral polymerase than host polymerase, but this can still adversely affect host cells

Selection for “resistant” viruses

- due to viral “evolution” via mutation
    - the use of antiviral drugs in combination can minimize this problem, though viruses tend to mutate rapidly

4. Drugs for Eukaryotic Pathogens

Challenges of Eukaryotic Pathogens

Unlike bacteria, eukaryotic pathogens have less features that differ from host cells and thus less targets to work with:

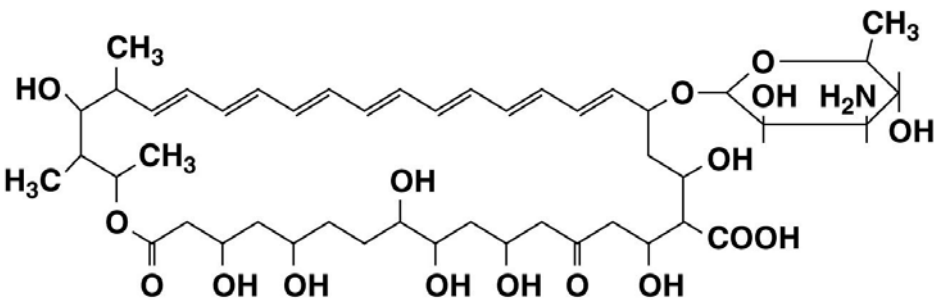
- **e.g., ribosomes and other metabolic processes are basically the same as ours**

For this reason there are fewer drugs to turn to in order to treat eukaryotic infections, however there are some unique features with which to target many eukaryotic pathogens…

Targets of Antifungal Drugs

Fungal cells differ from animal cells like ours in the following ways thus providing targets for drug treatment:

- **cell walls made of chitin**
  - **targeted by the <u>echinocandin</u> class of drugs**
- **fungal membranes have <u>ergosterol</u> as opposed to cholesterol**



amphotericin B (a polyene)

- **<u>polyenes</u>: a class of drugs that are somewhat toxic**
- **<u>azoles</u>: a class of drugs used topically in many antifungal creams**

Drugs that Target Protists & Helminths

Quinine

- obtained from the cinchona tree in Peru
- used for centuries to treat malaria (*Plasmodium vivax*)

Metronidazole (Flagyl)

- used for *Trichomonas vaginalis*, *Giardia intestinalis*
- inhibits anaerobic metabolism

Ivermectin

- produced by *Streptomyces avermectinius*
- paralyzes and kills many nematodes

Niclosamide

- inhibits ATP production in tapeworms

Key Terms for Chapter 20

- **broad vs narrow spectrum of activity**
- **natural vs semisynthetic antibiotics**
- **penicillinase**
- **nucleoside & nucleotide analogs**
- **chain terminators**
- **ergosterol**
- ***all the various classes of antimicrobial drugs***

Relevant Chapter Questions

rvw: 1-10 **MC: 1, 4-6, 9-12**