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## Chapter 20

# Antimicrobial Drugs

**Chemotherapy** is the treatment of disease with chemicals (drugs) taken into the body. Drugs used for chemotherapy are **chemotherapeutic agents**. The class of chemotherapeutic agents used to treat infectious diseases is **antimicrobial drugs**; unlike disinfectants, they must act within the host where they kill the harmful organism without damaging the host, called **selective toxicity**. **Synthetic drugs** are synthesized in the laboratory; others, **antibiotics**, are produced by microorganisms.

## History of Chemotherapy

During the early part of the twentieth century, Dr. Paul Ehrlich of Germany speculated about a “magic bullet” that would destroy pathogens but not harm the host. Eventually, he found an arsenic derivative, *salvarsan*, that was useful against syphilis. Prior to this discovery, the only chemotherapeutic agent available was *quinine*, for the treatment of malaria. *Sulfa drugs* were discovered during the 1930s. *Penicillin*, an antibiotic, was first discovered in 1928 but was not available in a useful form until after 1940.

## Spectrum of Antimicrobial Activity

It is comparatively easy to find antimicrobials against prokaryotes (bacteria) because prokaryotes differ substantially from the eukaryotic cells of humans. Fungi, protozoa, and helminths are eukaryotic, which makes selective toxicity for the pathogen (without affecting the host) more difficult. It is difficult to find antimicrobials against viruses, which exist inside a host cell and interact with the host cell to synthesize new viruses.

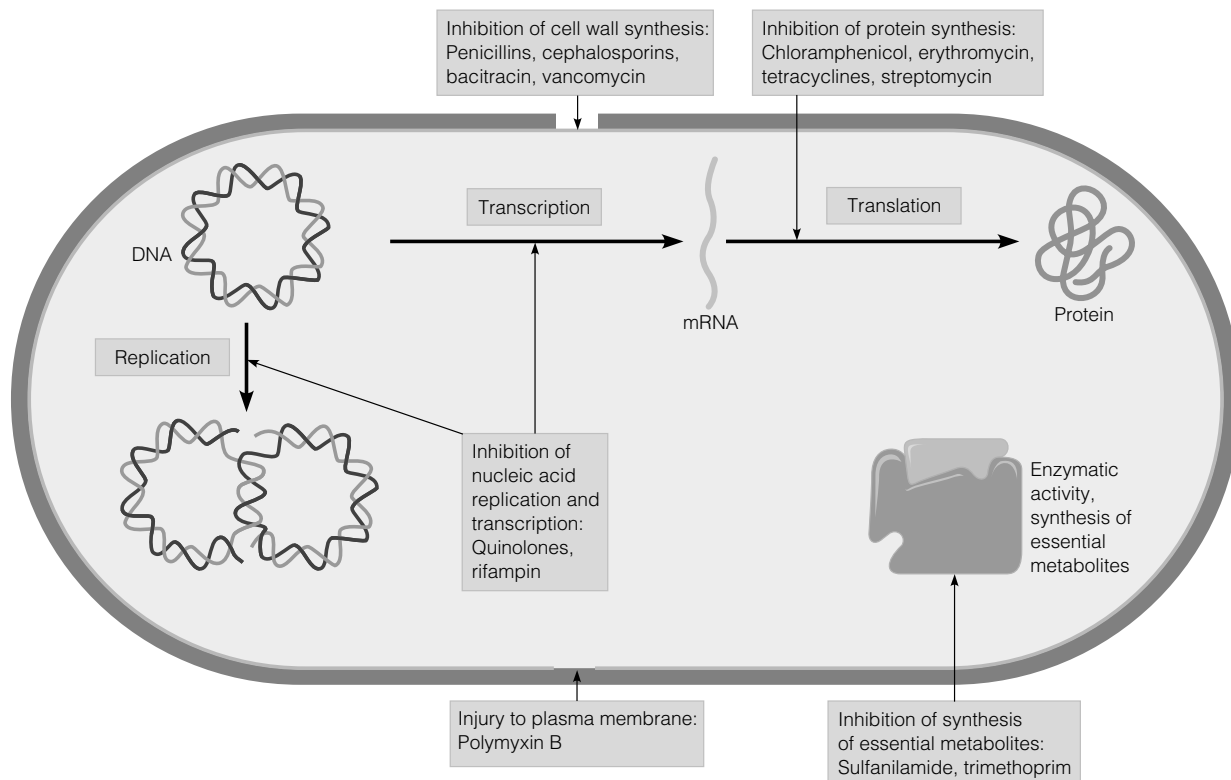
If an antimicrobial drug affects relatively few bacteria, it has a narrow **spectrum of microbial activity**, as opposed to **broad-spectrum antibiotics**. Antibiotics may eliminate normal microbiota and allow opportunistic pathogens to flourish (**superinfection**).

## Action of Antimicrobial Drugs

See the summary in Figure 20.1.

### ***Inhibition of Cell Wall Synthesis***

The cell walls of bacteria consist of a layer of peptidoglycan, which is found only in bacterial cells. Therefore, interference with the synthesis of bacterial cell walls usually does not harm the host. Antibiotics using this mode of action include penicillins, cephalosporins, bacitracin, and vancomycin. Because the peptidoglycan layer of gram-positive bacteria is more accessible than that of gram-negative ones, these bacteria are the most susceptible to such agents.



**FIGURE 20.1 Summary of the major modes of action of antimicrobial drugs.** This illustration shows these actions as they might affect a highly diagrammatic representation of a bacterial cell.

### ***Inhibition of Protein Synthesis***

Ribosome structure differs greatly between prokaryotic and eukaryotic cells. Many antibiotics such as chloramphenicol, gentamicin, erythromycin, tetracyclines, and streptomycin interfere with protein synthesis by reacting with the ribosomes of bacteria.

### ***Injury to the Plasma Membrane***

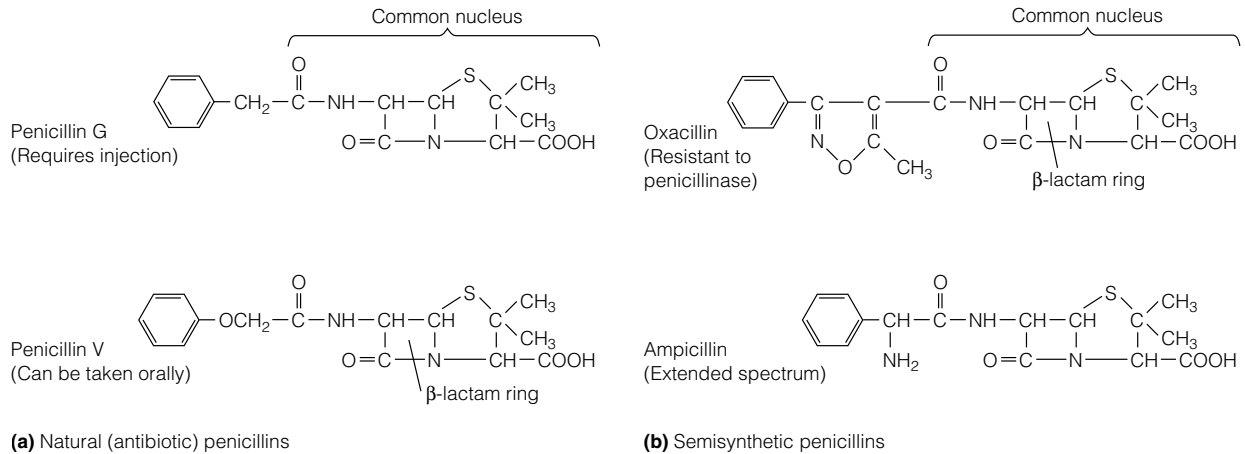
Antibiotics, especially such polypeptides as polymyxin B, can adversely affect the membrane permeability of microbial cells. Loss of important metabolites occurs from these changes in permeability. Similarly, the effectiveness of nystatin, miconazole, ketoconazole, and amphotericin B against fungi is based on their combining with sterols to disrupt fungal plasma membranes.

### ***Inhibition of Nucleic Acid Synthesis***

Similarities between microbial and host cell DNA and RNA are so close that drugs that act by interfering with the nucleic acid synthesis of microbial cells have only limited clinical application. Drugs acting on this principle are rifampin and the quinolones.

### ***Inhibiting the Synthesis of Essential Metabolites***

Sulfa drugs, for example, competitively inhibit the synthesis of folic acid, which is a vitamin that is synthesized by bacteria but not humans. The drug resembles the metabolite **para-aminobenzoic acid** that is required to synthesize folic acid.



**FIGURE 20.2** Structure of penicillins, antibacterial antibiotics. The portion that all penicillins have in common—their nucleus, which contains the  $\beta$ -lactam ring—is shaded. The unshaded portions represent the side chains that distinguish one penicillin from another.

## Antibacterial Antibiotics

### Inhibitors of Cell Wall Synthesis

**Penicillins.** The term **penicillin** refers to a group of related antibiotics (see Figure 20.2). **Natural penicillins**, such as *penicillin G* or *V*, are products of *Penicillium* mold growth. *Procaine penicillin* and *benzathine penicillin* combine penicillin G with other drugs to prolong the antibiotic's retention in the body.

**Penicillinases ( $\beta$ -lactamases)** are enzymes that cleave the  $\beta$ -lactam ring of penicillins, causing resistance.

**Semisynthetic Penicillins.** A large number of **semisynthetic penicillins** have been developed to overcome the disadvantages of natural penicillins. Side chains of natural penicillins are removed and other side chains added to extend their spectrum or make them resistant to penicillinases.

**Penicillinase-Resistant Penicillins.** The first semisynthetic penicillin designed to evade the action of penicillinases was *methicillin*. Eventually, so many staphylococcal strains became resistant that it is now discontinued. Others still in use include *oxacillin* and *nafticillin*.

**Extended-Spectrum Penicillins.** Certain semisynthetic penicillins, such as *ampicillin*, *amoxicillin* (both **aminopenicillins**), *carbenicillin*, and *ticarcillin* (both **carboxypenicillins**), have a broader spectrum of activity than do natural penicillins. Semisynthetics such as the **ureidopenicillins**, which include *mezlocillin* and *azlocillin*, also have a broader spectrum of activity.

**Penicillins plus  $\beta$ -lactamase Inhibitors.** Another approach to penicillinase resistance is to combine penicillins with *potassium clavulanate* (*clavulanic acid*), which is a noncompetitive inhibitor of penicillinase. Augmentin is the trade name of such a combination.

**Carbapenems.** The carbapenems are a class of  $\beta$ -lactam antibiotics that have an extremely broad spectrum of activity. An example is Primaxin, a combination of *imipenem* and *cilastin*.

**Monobactams.** Another penicillin variant, the **monobactams**, has only a single-ring structure. One of these, *aztreonam*, affects only gram-negative bacteria.

**Cephalosporins.** The structural nucleus and mode of action of **cephalosporins** resemble those of penicillin. Cephalosporins, such as *cephalothin*, *cefamandole*, and *cefotaxime*, are often used as substitutes for penicillin.

**Bacitracin.** *Bacitracin* is a polypeptide antibiotic effective primarily against gram-positive bacteria. It inhibits synthesis of cell walls, and is used only topically.

**Vancomycin.** *Vancomycin* is a relatively toxic drug, a member of the small glycopeptide group, that inhibits peptidoglycan synthesis. It is used against penicillinase-producing staphylococci that cause life-threatening infections.

### **Antimycobacterial Antibiotics**

**Isoniazid (INH).** *Isoniazid*, used in the treatment of tuberculosis, is believed to inhibit synthesis of mycolic acids, which are part of the cell wall of mycobacteria.

**Ethambutol.** *Ethambutol* is effective only against mycobacteria and is used in chemotherapeutic treatment of tuberculosis. It inhibits the incorporation of mycolic acid into the cell wall.

### **Inhibitors of Protein Synthesis**

**Chloramphenicol.** *Chloramphenicol* is a broad-spectrum antibiotic that affects protein synthesis. Structurally simple, it is often synthesized chemically. It may cause a blood disorder, aplastic anemia. It is the drug of choice for typhoid fever and certain types of meningitis, for which the risk is considered justified.

**Aminoglycosides.** **Aminoglycosides** are a group of antibiotics with amino sugars and an aminocyclitol ring. Examples are *streptomycin* (used for tuberculosis treatment), *neomycin* (used in topical ointment with bacitracin and polymyxin B), and *gentamicin* (effective against most gram-negatives, especially *Pseudomonas*). *Tobramycin* is administered by aerosol to treat cystic fibrosis patients infected with pseudomonads. Aminoglycosides sometimes are toxic to the auditory nerve or the kidneys.

**Tetracyclines.** **Tetracyclines** are broad-spectrum antibiotics that are also effective against chlamydias and rickettsias. They inhibit protein synthesis. They produce such side effects as tooth discoloration and liver damage. Commonly encountered are *tetracycline*, *oxytetracycline* (*Terramycin*), and *chlortetracycline* (*Aureomycin*). Some newer semisynthetic versions, such as *doxycycline* and *minocycline*, are retained in the body longer.

**Macrolides.** **Macrolides** are named for their macrocyclic lactone ring and are especially effective against gram-positive bacteria. *Erythromycin* inhibits protein synthesis and is used in treating infections resistant to penicillins, as well as legionellosis and mycoplasmal pneumonia. Other macrolides are *azithromycin* and *clarithromycin*; compared to erythromycin they have a broader spectrum and penetrate tissues better. **Ketolides** are new semisynthetic macrolides developed to combat microbial resistance. An example is *telithromycin* (*Ketek*).

**Streptogramins.** The **streptogramins** are a unique group of antibiotics developed to combat resistance to vancomycin. Synercid is a combination of two cyclic peptides *quinupristin* and *dalfopristin*, which are distantly related to macrolides.

**Oxazolidinones.** The **oxazolidinones** are a new class of totally synthetic antibiotics. They have a unique target, binding to the 50S ribosomal subunit close to the point where it interfaces with the 30S subunit. *Linezolid* (*Zyvox*), a member of the group, is used mainly to combat methicillin-resistant staphylococci.

### **Injury to the Plasma Membrane**

*Polymyxin B* is effective against gram-negative bacteria, even *Pseudomonas*. It is available for topical use in the antiseptic ointment that also contains *bacitracin* and *neomycin*.

## **Inhibitors of Nucleic Acid (DNA/RNA) Synthesis**

**Rifamycins.** *Rifampin*, the best known of the **rifamycin** family, is used in tuberculosis therapy. These drugs inhibit the synthesis of mRNA.

**Quinolones and Fluoroquinolones.** The first of the **quinolone group** was *nalidixic acid*, which selectively inhibits the enzyme DNA gyrase needed for DNA replication. This led to the development of the **fluoroquinolone group**. *Norfloxacin* and *ciprofloxacin* (*Cipro*) are used the most. Synthetic versions of the fluoroquinolones, such as *moxifloxacin* and *gatifloxacin*, are broader in spectrum and can be taken orally.

## **Competitive Inhibitors of the Synthesis of Essential Metabolites**

**Sulfonamides.** The **sulfonamides (sulfa drugs)** act by competitive inhibition of folic acid, a precursor to nucleic acids. *Silver sulfadiazine* is used on burn patients. The most widely used sulfa-containing preparation is the combination of *trimethoprim* and *sulfamethoxazole*. These are structural analogs that inhibit synthesis of DNA at different stages.

## **Antifungal Drugs**

**Agents Affecting Fungal Sterols.** In fungal membranes the principal sterol is ergosterol; in animal membranes it is cholesterol. This forms a basis for selective toxicity.

**Polyenes.** *Amphotericin B* is the most commonly used of the polyene antibiotics. Their activity is based on damage to fungal plasma membranes by combining with the membrane sterols. *Amphotericin B* is used for systemic fungal infections.

**Azoles.** **Imidazole** antifungals such as *miconazole* and *clotrimazole* are used topically against cutaneous fungal infections. *Ketoconazole*, taken orally, is a substitute for amphotericin B for many systemic fungal infections. **Triazoles** such as *fluconazole* and *itraconazole* are used for systemic fungal infections. *Voriconazole* is a new azole with a broad spectrum and the ability to penetrate the blood–brain barrier.

**Allylamines.** The **allylamines** are a recently developed class of antifungals that inhibit ergosterol synthesis in a different manner and are often used when resistance to azoles appears. *Terbinafine* and *naftifine* are examples.

**Agents Affecting Fungal Cell Walls.** A primary target for selective toxicity is the  $\beta$ -glucans that are unique to fungal cell walls. A new class of antifungals, **echinocandins**, interfere with synthesis of glucans. An example is *caspofungin* (*Cancidas*).

**Agents Inhibiting Nucleic Acids.** *Flucytosine*, an analog of cytosine, interferes with synthesis of RNA, and therefore protein synthesis.

**Other Antifungal Drugs.** *Griseofulvin* is a fungistatic drug that interferes with mitosis. Although taken orally, this drug binds selectively to keratin in skin, hair, and nails, preventing fungal growth at these sites. *Tolnaftate* is a topical agent used as an alternative to miconazole for athlete's foot infections. *Undecylenic acid* is a fatty acid with antifungal activity. *Pentamidine isethionate* is used in the treatment of *Pneumocystis pneumonia*.

## **Antiviral Drugs**

The number of antiviral drugs, compared to that of antibacterial drugs, is very limited. A drug used to treat influenza, *amantadine*, was the first to be licensed, though its mode of action is unknown. Most new antivirals are directed at control of HIV, and many of them are listed in Table 20.5 in the text.

**Nucleoside and Nucleotide Analogs.** *Acyclovir* is one of the most widely used antivirals, especially against genital herpes. Derivatives of acyclovir are *famciclovir* and *ganciclovir*. Other antivirals are *ribovirin* and *lamivudine*.

**Antiretrovirals.** RNA viruses depend upon the enzyme reverse transcriptase, which is an enzyme humans do not have. HIV is an RNA virus and the antiretroviral group is largely directed at it; in fact, the term antiretroviral implies that it is used to treat HIV. Most antiretrovirals are nucleoside analogs such as *zidovudine (AZT)*, which is an analog of thymidine. Another example is *cidofovir*, which is used to treat cytomegalovirus eye infections and is considered a possible treatment for smallpox. The only example of a nucleotide analog is *tenovir*. An antiretroviral that is a non-nucleoside agent is *nevirapine*.

**Other Enzyme Inhibitors.** The inhibitors of the enzyme neuraminidase, *zanamivir (Relenza)* and *oseltamivir phosphate (Tamiflu)*, are used for treatment of influenza. Another approach to control of HIV is inhibition of enzymes that control the last stage of viral reproduction, which requires protease enzymes. The protease inhibitors *indinavir* and *saquinavir* are examples.

**Interferons.** Cells infected with a virus often produce interferon, which inhibits further spread of the infection. Interferons are cytokines; *alpha-interferon* is used for viral hepatitis infections. A new drug, *imiquimod*, stimulates the production of interferons.

## Antiprotozoan and Antihelminthic Drugs

**Antiprotozoan Drugs.** *Quinine* still has limited use against malaria, but it has generally been replaced with synthetic derivatives, such as *chloroquine* and *mefloquine*. *Quinacrine*, used against giardiasis, functions similarly. *Diiodohydroxyquin (iodoquinol)* is an amoebicide. *Metronidazole* is used for treatment of many protozoan diseases and also is effective against certain anaerobic bacteria. It probably causes disruption of DNA under anaerobic conditions.

**Antihelminthic Drugs.** *Niclosamide* inhibits ATP production in tapeworms. *Praziquantel* also is effective against tapeworms and several fluke-caused diseases. *Mebendazole* and *albendazole* are used to treat ascariasis. *Ivermectin* is widely used in the livestock industry for helminth control.

## Tests to Guide Chemotherapy

### Diffusion Methods

The **disk-diffusion method (Kirby–Bauer test)** uses a dish of agar medium seeded uniformly with a test organism. Filter paper disks impregnated with known concentrations of chemotherapeutic agents are placed on the agar surface. If the chemotherapeutic agent is effective, a zone of inhibition (no growth) is observed around the disk. The diameter of the zone can be used to calculate the susceptibility of the organisms to the agent.

A more advanced diffusion method, the **E test**, includes an estimate of the **minimum inhibitory concentration (MIC)**.

### Broth Dilution Tests

A series of dilutions of an antibiotic can be placed in tubes (shallow wells in a plastic plate usually are used in practice) and inoculated with test bacteria. After incubation they are examined for turbidity. The minimum inhibitory concentration (MIC) of the antimicrobial is defined as the lowest concentration that prevents growth. Subculturing from the tubes that show no growth will determine if the bacteria have been killed or only inhibited. The lethal concentration that actually kills the bacteria is called the **minimum bactericidal concentration (MBC)**. Many of these tests are highly automated and use light scattering to determine bacterial growth.

## Effectiveness of Chemotherapeutic Agents

### Drug Resistance

Resistance to drugs may be based on production of an enzyme such as penicillinase. Another serious threat to chemotherapy is drug resistance of various kinds that is carried on **plasmids**, called **resistance (R) factors**. Plasmids may transfer genes for resistance to several antibiotics at a time and to closely related bacterial species. Bacteria that drugs are unable to control are called **superbugs**.

### Effects of Combinations of Drugs

Two drugs given simultaneously may be more effective than either given alone; this is called **synergism**. Other combinations can show **antagonism**, in which the effect of the two drugs is less than when either is used alone.

### The Future of Chemotherapeutic Agents

The most pressing concern currently is the spread of resistance to antibiotics.

**Antimicrobial Peptides.** Plants, insects, and many animals defend themselves against microbes with broad-spectrum **antimicrobial peptides** (sometimes called *cationic peptides*). Examples are *magainin* (from the skin of certain frogs), *squalamine* (found in the tissue of the spiny dogfish shark), and *protegrins* (isolated from pigs). Several such peptides are in clinical trials. *Nisin*, used as a food preservative, resembles magainin in its mode of action. A certain moth defends itself with *cecropin*.

**Antisense Agents.** Another approach to microbial control is short strands of synthetic agents, called **antisense agents**. The principle is to identify sites on DNA or RNA of the pathogen that are responsible for its pathogenic effects. Segments of DNA are then synthesized that will selectively bind to and neutralize this site. An antiviral based on this principle, *fomivirsen*, has been approved for treatment of cytomegalovirus retinitis.

## Self-Tests

In the matching section, there is only one answer to each question; however, the lettered options (a, b, c, etc.) may be used more than once or not at all.

### I. Matching

- |   |                     |
|---|---------------------|
| ___ 1. Plasmids that carry antibiotic resistance.   | a. Antibiotics      |
| ___ 2. Chemotherapeutic agents produced by microorganisms.                                  | b. E test           |
| ___ 3. Disk-diffusion test for antibiotic sensitivity.                                      | c. Chemotherapy     |
| ___ 4. Diffusion test that also measures minimum inhibitory concentration of an antibiotic. | d. Kirby–Bauer test |
|   | e. R factors        |

### II. Matching

- |   |                    |
|---|--------------------|
| ___ 1. Activity based on damage to the sterols in plasma membrane of fungi. | a. Cephalosporins  |
| ___ 2. Inhibition of protein synthesis.                                     | b. Chloramphenicol |
| ___ 3. Inhibition of RNA synthesis.   | c. Amphotericin B  |
| ___ 4. Inhibition of synthesis of cell wall peptidoglycans.                 | d. Isoniazid       |
| ___ 5. Inhibition of DNA synthesis.   | e. Sulfonamides    |
| ___ 6. Inhibition of synthesis of cell wall mycolic acids.                  | f. Rifampin        |

### III. Matching

- |  |                  |
|--|------------------|
| ___ 1. Similar structurally to penicillin.                                 | a. Cephalosporin |
| ___ 2. A synthetic drug used in tuberculosis chemotherapy.                 | b. Polymyxin B   |
| ___ 3. Antifungal, a polyene.  | c. Ethambutol    |
| ___ 4. Causes plasma membrane leakage; useful against <i>Pseudomonas</i> . | d. Idoxuridine   |
| ___ 5. An antiviral drug; a nucleoside analog.                             | e. Voriconazole  |
| ___ 6. Antifungal; an allylamine.  | f. Terbinafine   |

**IV. Matching**

- |  |                   |
|--|-------------------|
| ___ 1. Used in treating diseases caused by protozoa.                 | a. Erythromycin   |
| ___ 2. An antifungal drug taken orally that concentrates in keratin. | b. Griseofulvin   |
| ___ 3. Useful against tapeworms.                                     | c. Amphotericin B |
| ___ 4. A drug that is useful against symptoms of genital herpes.     | d. Niclosamide    |
| ___ 5. An antifungal drug of the polyene type.                       | e. Metronidazole  |
| ___ 6. A macrolide antibiotic.                                       | f. Acyclovir      |
| ___ 7. A streptogramin-type antibiotic.                              | g. Synercid       |

**V. Matching**

- |  |                            |
|--|----------------------------|
| ___ 1. Inhibits ATP production in tapeworms.                   | a. Chloroquine             |
| ___ 2. Used in the treatment of malaria.                       | b. Niclosamide             |
| ___ 3. Used in the treatment of <i>Pneumocystis</i> pneumonia. | c. Pentamidine isethionate |
| ___ 4. Stimulates production of interferons.                   | d. Imiquimod               |

**VI. Matching**

- |  |                        |
|--|------------------------|
| ___ 1. Used in the treatment of HIV infections, a nucleoside analog.                               | a. Zidovudine          |
| ___ 2. Acts by competitive inhibition of folic acid, usually in combination with sulfamethoxazole. | b. Diiodohydroxyquin   |
| ___ 3. A derivative of penicillin G designed to be retained for a longer time in the body.         | c. Methicillin         |
| ___ 4. A penicillin designed to be resistant to penicillinase; no longer in use.                   | d. Ampicillin          |
| ___ 5. A synthetic fluoroquinolone that acts against the gyrase enzyme.                            | e. Procaine penicillin |
| ___ 6. An amoebicide.  | f. Trimethoprim        |
| ___ 7. Very broad spectrum; carbapenem group.  | g. Norfloxacin         |
|  | h. Primaxin            |

**VII. Matching**

- |  |                   |
|--|-------------------|
| ___ 1. Zidovudine, an analog of thymidine.   | a. Nalidixic acid |
| ___ 2. Inhibits DNA synthesis of bacteria.   | b. Flucytosine    |
| ___ 3. An arsenic derivative used against syphilis before the development of modern antibiotics. | c. Salvarsan      |
| ___ 4. A rifamycin-type drug used for therapy of tuberculosis; inhibits synthesis of mRNA.       | d. Rifampin       |
| ___ 5. An antifungal drug; interferes with synthesis of RNA.                                     | e. AZT            |
| ___ 6. A possibility for use against smallpox.   | f. Cidofovir      |

**VIII. Matching**

- |  |                    |
|--|--------------------|
| ___ 1. Inhibitor of protein synthesis; inexpensive; may cause aplastic anemia.                           | a. Chloramphenicol |
| ___ 2. An aminoglycoside antibiotic used in tuberculosis treatment; may cause deafness or kidney damage. | b. Vancomycin      |
| ___ 3. A cytokine.   | c. Streptomycin    |
| ___ 4. An antiviral protease inhibitor.  | d. Indinavir       |
| ___ 5. Used mainly against life-threatening staphylococcal infections resistant to penicillin.           | e. Interferon      |

**Fill in the Blanks**

- Cell walls of most bacteria contain \_\_\_\_\_, the target of activity by penicillins.
- The treatment of disease with chemicals taken into the body by injection or ingestion is called \_\_\_\_\_.
- Many bacteria develop resistance to penicillin by producing the enzyme \_\_\_\_\_.
- The usual principle of antibiotic activity is \_\_\_\_\_, meaning it kills the harmful organism without damaging the host.
- The term *penicillin* is applied to a group of antibiotics that all have a \_\_\_\_\_ in their structure.





3. Advantages:

- Broad-spectrum activity means that the identity of the pathogen need not necessarily be known; this saves valuable time.
- Many important pathogens and opportunistic organisms are eliminated by broad-spectrum antibiotics.

Disadvantages:

- Normal microbiota are killed, allowing opportunistic microbiota (for example, yeasts) to proliferate.
- Resistant strains of bacteria develop with the indiscriminant use of broad-spectrum drugs.

4. Synergism refers to the use of two or more antimicrobial drugs simultaneously. It has been found that their combined effect is greater than the effect of either given alone.

Combinations of antimicrobial drugs should be given for the following purposes:

- a. To prevent or minimize development of resistant strains.
- b. To take advantage of the synergistic effect.
- c. To provide optimal therapy in life-threatening, time-critical situations.
- d. To lessen drug toxicity by reducing the necessary drug concentration.

