**Chapter 10**

**The History of Antimicrobial Agents**

* Chemicals that affect physiology in any manner
* Chemotherapeutic agents – drugs that act against diseases
* Antimicrobial agents – drugs that treat infections
* Paul Ehrlich
  + “Magic bullets”
  + Arsenic compound that killed trypanosomes and another that worked against treponemes
* Alexander Fleming
  + Penicillin released from *Penicillium*
  + Antibiotics – antimicrobial agents produced naturally by organisms
* Gerhard Domagk
  + Discovered sulfanilamide in 1932
    - First antimicrobial agent used to treat wide array of infections
* Semi-synthetics
  + Chemically altered antibiotics that are more effective than naturally occurring ones
* Synthetics
  + Antimicrobials that are completely synthesized in a lab

**Mechanisms of Antimicrobial Action**

* Key is selective toxicity
* Antibacterial drugs constitute largest number and diversity of antimicrobial agents
* Fewer drugs to treat eukaryotic infections
* Even fewer antiviral drugs
* **Inhibition of Cell Wall Synthesis**
  + Inhibition of synthesis of bacterial walls
    - Most common agents act by preventing cross-linkage of NAM subunits
    - Beta-lactams are most prominent in this group; functional groups are beta-lactam rings
    - Beta-lactams bind to enzymes that cross-link NAM subunits
    - Bacteria have weakened cell walls and eventually lyse
    - Semi-synthetic derivatives of beta-lactams
      * More stable in acidic environments
      * More readily absorbed
      * Less susceptible to deactivation
      * More active against more types of bacteria
    - Simplest beta-lactams – effective only against aerobic Gram-negatives
    - Vancomycin and cycloserine interfere with particular alanine-alanine bridges that link NAM subunits in many Gram-positives
    - Bacitracin blocks secretion of NAG and NAM from cytoplasm
    - Isoniazid and ethambutol disrupt formation of arabinogalactan-mycolic acid in mycobacterial species
    - Prevent bacteria from increasing amount of peptidoglycan
    - Have no effect on existing peptidoglycan layer
    - **Effective only for growing cells**
    - No effect on plant or animal cells; no peptidoglycan
* **Inhibition of Protein Synthesis**
  + Prokaryotic ribosomes are 70S (30S and 50S)
  + Eukaryotic ribosomes are 80S (40S and 60S)
  + Drugs can selectively target translation
  + Mitochondria of animals and humans contain 70S ribosomes; can be harmful
* **Disruption of Cytoplasmic Membranes**
  + Some drugs become incorporated into cytoplasmic membrane and damage its integrity
  + Amphotericin B attaches to ergosterol in fungal membranes
    - Humans somewhat susceptible because cholesterol similar to ergosterol
    - Bacteria lack sterols; not susceptible
  + Azoles and allyamines inhibit ergosterol synthesis
  + Polymyxin disrupts cytoplasmic membranes of Gram-negatives; toxic to human kidneys
  + Some parasitic drugs act against cytoplasmic membranes
* **Inhibition of Metabolic Pathways**
  + When differences exist between metabolic processes of pathogen and host, anti-metabolic agents can be effective
  + Quinolones interfere with the metabolism of malaria parasites
  + Heavy metals inactivate enzymes
  + Agents that disrupt tubulin polymerization and glucose uptake by many protozoa and parasitic worms
  + Drugs block activation of viruses
  + Metabolic antagonists
  + Trimethoprim binds to enzyme involved in conversion of dihydrofolic acid to THF
  + Humans obtain folic acid from diet; metabolism unaffected
  + Antiviral agents can target unique aspects of viral metabolism
    - Amantadine, rimantadine, and weak organic bases neutralize acidity of phagolysosome and prevent viral uncoating
  + Protease inhibitors interfere with an enzyme (protease) that HIV needs in its replication cycle
* **Inhibition of Nucleic Acid Synthesis**
  + Several drugs function by blocking DNA replication or mRNA transcription
  + Only slight differences between prokaryotic and eukaryotic DNA; drugs often affect both types of cells
  + Not normally used to treat infections; used in research and perhaps to slow cancer cell replication
  + Compounds can interfere with function of nucleic acids (nucleotide analogs)
  + Nucleotide Analogs can distort shapes of nucleic acid molecules and prevent further replication, transcription, or translation
  + Most often used against viruses; viral DNA polymerases more likely to incorporate and viral nucleic acid synthesis more rapid than that in host cells
  + Also effective against rapidly dividing cancer cells
  + Quinolones and fluoroquinolones act against prokaryotic DNA gyrase; little effect on eukaryotes or viruses
  + Other drugs, including rifampin, bind to and inhibit action of RNA polymerase during transcription
  + Reverse transcriptase inhibitors act against the enzyme, reverse transcriptase, an enzyme HIV uses in its replication cycle
    - Inhibitor does not harm people because humans lack reverse transcriptase
* **Prevention of Virus Attachment**
  + Attachment can be blocked by peptide and sugar analogs of attachment or receptor proteins (attachment antagonists)
  + New area of antimicrobial drug development

**Clinical Considerations in Prescribing Antimicrobial Drugs**

* **Ideal Antimicrobial Agent**
  + Readily available
  + Inexpensive
  + Chemically stable
  + Easily administered
  + Nontoxic and nonallergenic
  + Selectively toxic against wide range of pathogens
* **Spectrum of Action**
  + Broad-spectrum antimicrobials may allow for secondary or superinfections to develop
  + Killing of normal flora reduces microbial antagonism
* **Efficacy**
  + Ascertained by
    - Diffusion susceptibility tests
    - Minimum inhibitory concentration test
    - Minimum bactericidal concentration test
* **Routes of Administration**
  + Topical application of drug if infection is external
  + Oral – simplest; lower drug concentrations; no reliance on health care provider; patients do not always follow prescribing information
  + Intramuscular – requires needle; concentration never as high as IV administration
  + Intravenous – requires needle or catheter; drug concentration diminishes as liver and kidneys remove drug from circulation
  + Must know how antimicrobial agent will be distributed to infected tissues
* **Safety and Side Effects**
  + Toxicity
    - Exact cause of many adverse reactions poorly understood
    - Drugs may be toxic to kidneys, liver, or nerves
    - Considerations needed when prescribing drugs to pregnant women
  + Allergies
    - Although allergic reactions are rare, they may be life threatening
  + Disruption of normal microbiota
    - May result in secondary infections
    - Overgrowth of normal flora – superinfections
    - Of greatest concern for hospitalized patients

**Resistance to Antimicrobial Drugs**

* **Mechanisms of Resistance**
  + At least six mechanisms of resistance
    - Resistant cells may produce an enzyme that destroys or deactivates the drug
    - Microbes may slow or prevent the entry of the drug into the cell
    - Alter the target of the drug so it cannot attach or binds less effectively
    - Alter their metabolic chemistry
    - Pump the antimicrobial out of the cell before it can act
    - *Mycobacterium tuberculosis* produces MfpA protein, which binds to DNA gyrase preventing the binding of fluoroquinolone drugs
* **Multiple Resistance and Cross Resistance**
  + Pathogen can acquire resistance to more than one drug at a time
  + Common when R-plasmids exchanged
  + Develop in hospitals and nursing homes; constant use of drugs eliminates sensitive cells
  + Superbugs
  + Cross resistance
* **Retarding Resistance** 
  + High concentration of drug maintained in patient long enough to kill all sensitive cells and inhibit others so immune system can destroy
  + Use antimicrobial agents in combination; synergism vs. antagonism
  + Limit use of antimicrobials to necessary cases
  + Develop new variations of existing drugs
    - Second-generation drugs
    - Third-generation drugs
  + Search for new antibiotics, semi-synthetics, and synthetics
    - Bacteriocins
    - Design drugs complementary to the shape of microbial proteins to inhibit them