**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