Antibiotics (Chapter 20)

Paul Erlich (1910): wanted to find magic bullet for syphilis; proposed idea of blood brain barrier; first with idea of "selective toxicity"; 1908 Nobel Prize
Alexander Fleming (1928): studied bacterial action of blood and antisepsis; discovered lysozyme; discovered mold (Penicillium notatum), that inhibited Staph aureus; 1945 Nobel Prize
Chain and Florey (1940): developed system for growing and purifying Penicillium; tested drug in mice; 1945 Nobel Prize

Selective toxicity: easier to find agents toxic to prokaryotic cells (bacteria) that do not harm eukaryotic hosts than to find agents toxic to eukaryotic pathogens (fungi, protozoans, helmiths)

Theraputic index: toxicity; lowest dose toxic to patient divided by dose used for therapy (if high→less toxic to patient)

Antibiotics: substance produced by a microorganism that inhibits or kills other microbes

Bacteriostatic: inhibit growth/host immune system destroys bacteria
Bacteriocidal: kills bacterial

Synergistic: two different antibiotics work together to enhance action
Antagonistic: one antibiotic would interfere with action of another

Spectrum of Activity:
- Narrow spectrum: targets one group of microbes (eg. Gram positives)
- Broad spectrum: targets wide range of microbes
  - may also destroy normal flora leading to superinfection
    - Yeast
    - "Antibiotic Associated Colitis" from Clostridia difficile (produces life threatening toxin; cannot establish growth unless normal flora destroyed)

Targets of Antibiotics:

I. Inhibition of Cell Wall Synthesis: peptidoglycan (only in prokaryotic cells)
   Penicillin prevents synthesis of cell wall of actively growing bacteria
II. Inhibition of Protein Synthesis: difference in ribosomes; prokaryotics=70S/eukaryotics=80S
   Chloramphenicol and Erythromycin: bind to 50S
   Streptomycin and Gentamicin: change shape of 30S
   Tetracylcine: interferes with binding of tRNA to mRNA
III. Injures Plasma Membrane: changes permeability of membrane and valuable compounds lost
IV. Inhibits Nucleic Acid synthesis: interferes with replication and transcription (but also toxic to animal cells)

V. Inhibits synthesis of Essential Metabolites: competitively inhibited by similar substance
Sulfanilamides; competes with PABA (para aminobenzoic acid) that is necessary for folic acid synthesis

MIC minimum inhibitory concentration: lowest dose that will inhibit growth of bacterial
MBC minimum bacteriocidal concentration: lowest dose that will kill bacteria

Tests for microbial sensitivity:
Kirby-Bauer
E-test for MIC
Dilution tests for MIC

Development of antibiotic resistant bacteria:
1. Destruction or inactivation of drug (beta-lactamase)
2. Prevention of penetration to target site
3. Alteration of target site (mutation)
4. Rapid ejection of drug from cell

Examples: Neisseria gonorrhoea
Enterococcus: VRE-vancomycin resistant enterococci
Staphylococcus aureus: MRSA-methicillin resistant Staph aureus
VISA-vancomycin intermediate Staph aureus
Streptococcus pneumoniae
Mycobacterium tuberculosis