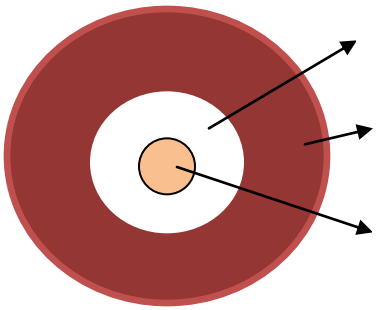
Unit I – Problem 6,7 – Pharmacology: Principles of Antimicrobial Chemotherapy

- **Chemotherapeutic drugs work against:**
  1- Disease-causing agents.
  2- Your own cells (in case of malignancy: cancer).
- **Antibiotic**: this word means (something against life). They are also known as antimicrobials and aim to kill microorganisms.
- **Selective toxicity of drugs:** drugs work against disease-causing agents without harming the host. For example, they recognize cell walls –which are found in bacterial cells but not human cells- and destroy them. Penicillins are very safe in our bodies, because their target is the cell wall of the microorganism.
- **Spectrum**:
  - **Narrow-spectrum***:* the drug works against only one type of microorganism (usually gram-positive).
  - **Extended-spectrum***:* the drug works on both gram-positive and gram-negative microorganisms.
  - **Broad-spectrum***:* the drug works on gram-positive, gram-negative and other microorganisms.
    If there is an infection and you know what it is and its origin then you are going to use the narrow-spectrum to reduce toxicity and adverse effects. If the origin is unknown, then broad-spectrum drugs are going to be used.
- **There are many mechanisms by which antimicrobials kill the microorganism such as:**
  - Inhibiting the cell wall synthesis.
  - Interacting with protein synthesis.
    If you aim to combine drugs, you must combine those which have different mechanisms.
- **Bacteriostatic drugs:** are those which inhibit the organism and its growth. These drugs will not be effective if the immune system of the host is weak.
- **Bactericidal drugs**: are those which will kill the bacteria (more effective).
  - **Combining bacteriostatic and bactericidal drugs will reduce the efficacy and lead to (antagonism).**
- **Susceptibility:**
  - **Sensitivity***:* the drug is able to inhibit or kill the microorganism.
  - **MIC***:* minimum inhibitory concentration.
  - **MBC**: minimum bactericidal concentration.
- **Sensitivity testing:**



- **Resistance:**
  - **Primary resistance***:* the microorganism was never sensitive to the drug.
  - **Secondary resistance***:* the microorganism was once sensitive to the drug but it became resistant later (due to prolonged exposure to the drug).
  - **Resistance can be applied by two mechanisms:**
    - ✓ Drug adaptation: the microorganism changes its cell wall or cell membrane.
    - ✓ Drug destruction: by enzymes.

- **Adverse drug reactions:**
  - **Dose-dependent***:* depends on the concentration.
  - **Dose-independent**: does not depend on the concentration but time. Allergy is an example.
    Some antibiotic which are transmitted through breast-milk may cause diarrhea to the baby.
- **Interactions:**
  - **Pharmacokinetics interactions***:* they include (absorption – distribution – metabolism and elimination).
  - **Pharmacodynamics interactions.**
  - **Rifampicin** is a drug which is used to treat patients with tuberculosis (TB).
  - The liver conjugates estrogen. Then, this will be secreted in the bile which will finally end in the intestines. Normal flora will break this conjugation and estrogen will be reabsorbed. If antibiotics are given, the reabsorption of estrogen will be inhibited; therefore, it will be eliminated from the body.
- **Prophylaxis:** aims to prevent infection in healthy people (protecting them from the disease).
- **Pre-emptive:** there is an evidence of infection but the person is still asymptomatic.
- **Empiric:** infection is present (there are symptoms) but the origin of the microorganism is still unknown. Treatment is initiated immediately but before that samples must be taken and sent to the lab. Broad-spectrum drugs will be used.
- **Definitive:** once lab results are available, treatment must be changed to narrow-spectrum.
- **Suppressive:** the infection is controlled but not yet eliminated because the underlying cause is still there.
- **Drug combinations results in:**
  - **Synergism***:* sulfonamide & trimethoprim.
  - **Antagonism.**
    Combination can help in reducing the frequency of the given dose and toxicity.
- **Postantibiotic Effect (PAE):**
  - Microorganism continue to be inhibited even when the level of the drug becomes low or it is eliminated from the body.
  - This reduces the frequency of the given drug.
- **Sulfonamides:**
  - **Mechanism of action**: they bind and competitively inhibit dihydropteroate synthetase, the enzyme responsible for combining para-aminobenzoic acid (PABA) and pteridine. **Subsequently, folic acid synthesis is terminated.**
  - Sulfonamides are bacteriostatic with extended spectrum (against gram-positive and gram-negative microorganisms).
  - Sulfonamides can be administered orally or intravenously.
  - They can easily penetrate the central nervous system (CNS) even in the absence of inflammation.
  - **Toxicities include the following:**
    - ✓ Hypersensitivity.
    - ✓ Stevens-Johnson syndrome.
    - ✓ GI disturbance (nausea, vomiting and diarrhea).
    - ✓ Hematotoxicity (hemolytic anemia).
  - They are contraindicated in pregnant and nursing women because they can cross into the placenta and breast milk.
  - **When does resistance to sulfonamides occur?**
    - ✓ Decreased intracellular accumulation of the drug.
    - ✓ Increased production of PABA.
    - ✓ A change in the sensitivity of dihydropteroate synthetase to the sulfonamides.

- **Trimethoprim**:
  - **Mechanism of action:** stops the conversion of dihydrofolate to tetrahydrofolate by inhibiting the enzyme dihydrofolate reductase.
  - It is administered orally and most often combined with sulfonamides.
  - **Adverse effects of trimethoprim/sulfonamide combination:**
    - ✓ Dermatologic effects**.**
    - ✓ Stevens-Johnson syndrome.
    - ✓ GI disturbance (nausea, vomiting, glossitis and stomatitis).
    - ✓ Hematological effects.
    - ✓ Headache.
    - ✓ Depression.
  - **Resistance to sulfonamide/trimethoprim:**
    - ✓ Decreased uptake of the drug.
    - ✓ Increased concentrations of dihydropholate reductase.
    - ✓ Altering the structure of dihydrofolate reductase to reduce its affinity for the drug.