**Chemotherapeutic Agents**

Chemotherapeutic agents are chemical substances used for the treatment of infectious diseases or diseases caused by the proliferation of malignant cells. These substances are prepared in the chemical laboratory or obtained from microorganisms and some plants and animals. To be useful as a chemotherapeutic agent a substance must have selective toxicity for the parasite, which means low toxicity for host cells and high toxicity for the parasites. In other words, the substance must damage the parasite and cause little or no damage to the host cells. Most of these agents are **antibiotics** (Greek *anti*, against, and *bios*, life), microbial products or their derivative that can kill susceptible microorganisms or inhibit their growth. Drugs such as the sulfonamides are sometimes called antibiotics although they are synthetic chemotherapeutic agents, not microbially synthesized. **A satisfactory chemotherapeutic agent must follow:**

1. Destroy or prevent the activity of a parasite without injuring the cells of the host or with only minor injury to its cells
2. Be able to come in contact with the parasite by penetrating the cells and tissues of the host in effective concentrations.
3. Leave unaltered the host’s natural defense mechanisms, such as phagocytosis and the production of antibodies.

**General characteristics of Antimicrobial Drugs**

As Ehrlich so clearly saw, to be successful a chemotherapeutic agent must have **selective toxicity:** it must kill or inhibit the microbial pathogen while damaging the host as little as possible.

The degree of selective toxicity may be expressed in terms of

(1) the therapeutic dose, the drug level required for clinical treatment

of a particular infection, and

(2) the toxic dose, the drug level at which the agent becomes too toxic for the host.

The **therapeutic** **index** is the ratio of the toxic dose to the therapeutic dose. The larger the therapeutic index, the better the chemotherapeutic agent (all other things being equal).

The undesirable effects on the host, called **side effects,** are of many kinds and may involve almost any organ system. Because side effects can be severe, chemotherapeutic agents should be administered with great care.

Drugs vary considerably in their range of effectiveness. Many are **narrow-spectrum drugs**—that is, they are effective only against a limited variety of pathogens. Others are **broad spectrum** **drugs** and attack many different kinds of pathogens.

**Mechanisms of action of important chemotherapeutic agents**

The mechanisms of action of specific chemotherapeutic agents are important to know as such knowledge helps to explain the nature and degree of selective toxicity of individual drugs and sometimes aid in the design of new chemotherapeutic agents. Chemotherapeutic agents can be synthesized by microorganisms or manufactured by chemical procedures independent of microbial activity. A number of the most commonly employed antibiotics are natural—that is, totally synthesized by one of a few bacteria or fungi. In contrast, several important chemotherapeutic agents are completely synthetic. The synthetic antibacterial drugs are the **sulfonamides, trimethoprim, chloramphenicol, ciprofloxacin, isoniazid, and dapsone**. Semisynthetic antibiotics are natural antibiotics that have been chemically modified by the addition of extra chemical groups to make them less susceptible to inactivation by pathogens. Ampicillin, carbenicillin, and methicillin are good examples.

The most selective antibiotics are those that **interfere with the synthesis of bacterial cell walls** **(e.g., penicillins, cephalosporins, vancomycin, and bacitracin)**. **These drugs have a high therapeutic index because bacterial cell walls have a unique structure not found in eukaryotic cells.**

**Streptomycin, gentamicin, spectinomycin, clindamycin, chloramphenicol, tetracyclines, erythromycin, and many other antibiotics inhibit protein synthesis by binding with the prokaryotic ribosome.** Because these drugs discriminate between prokaryotic and eukaryotic ribosomes, their therapeutic index is fairly high but not as favorable as that of cell wall synthesis inhibitors. **Some drugs bind to the 30S (small) subunit, while others attach to the 50S (large) ribosomal subunit. Several different steps in the protein synthesis mechanism can be affected: aminoacyl-tRNA binding, peptide bond formation, mRNA reading, and translocation.**

The antibacterial drugs that inhibit nucleic acid synthesis or damage cell membranes often are not as selectively toxic as other antibiotics. This is because prokaryotes and eukaryotes do not differ greatly concerning nucleic acid synthetic mechanisms or cell membrane structure. **Good examples of drugs that affect nucleic acid synthesis or membrane structure are quinolones and polymyxins.**

**Quinolones inhibit the DNA gyrase and thus interfere with DNA replication, repair, and transcription. Polymyxins act as detergents or surfactants and disrupt the bacterial plasma membrane.**

Several valuable drugs act as **antimetabolites:** they block the functioning of metabolic pathways by competitively inhibiting the use of metabolites by key enzymes. Sulfonamides and several other drugs inhibit folic acid metabolism. Sulfonamides (e.g., sulfanilamide, sulfamethoxazole, and sulfacetamide) have a high therapeutic index because humans cannot synthesize folic acid and must obtain it in their diet. Most bacterial pathogens synthesize their folic acid and are therefore susceptible to inhibitors of folate metabolism.