Part 1

Section I

GENERAL PHARMACOLOGY

1. Introduction to Pharmacology
2. Routes of Drug Administration
3. Pharmacokinetics
4. Clinical Pharmacokinetics
5. Pharmacodynamics
6. Quantitative Aspects of Pharmacodynamics and Assay of Drugs
7. Drug Interactions
8. Adverse Drug Reactions
9. Development and Evaluation of New Drugs

This Page is Intentionally Left Blank

1 Introduction to Pharmacology

INTRODUCTION

Pharmacology is a branch of medical science which deals with drugs. It is derived from two Greek words, viz. *pharmacon* (means drug) and *logos* (means studies). It contains the knowledge of history, source, physical and chemical properties, compounding, biochemical and physiological effects, mechanism of action, absorption, distribution, biotransformation and excretion and therapeutic and other uses of drugs. The first book of pharmacology was written by Samuel Dale in 1693. Oswald Schmiedeberg (1838–1921) is known as the Father of Modern Pharmacology.

Drug and Medicine

A drug is a chemical substance that affects processes in living organism and used for the treatment, prophylaxis (prevention) or diagnosis of the disease. It is derived from a French word *Drogue* (means dry herb). According to WHO (World Health Organization), a drug is a chemical substance or biological product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient. A drug cannot create a new function but can modify (increase or decrease) an already existing function. When a drug is used in proper dosage form for safe administration in a recipient, then it is called a medicine. All medicines are drugs but all drugs are not medicines. There are thousands of drugs, but all drugs are not essential.

Essential Drug Concept

It was introduced by WHO in 1977 to avoid the complications of drug use faced by the physician. A list containing essential drugs is available for the physicians in clinical practice. Essential drugs are those drugs which satisfy the healthcare needs of the majority of the population and they should, therefore, be available at all times in adequate amounts, in appropriate dosage forms and at reasonable cost. Drugs which do not fulfill these criteria are not essential drugs. List of essential drugs is given in the last pages of this book.

- Orphan drugs are those drugs which are used for the treatment, prevention or diagnosis of rare diseases like kala-azar, cancers, viral diseases, etc. and in digoxin, heavy metal or other drug, e.g. digoxin specific fab antibodies, T_3, BAL, etc. poisoning. Though they may be life-saving for some patients, but they are less produced commercially due to high cost of manufacture and small number of patients requiring the drug.

Drug Nomenclature

A drug has more than one name, for example:

- **Acetylsalicylic acid (chemical name)**
  – Aspirin (official name)

- Dispirin (proprietary/brand name)
- Salicylate (generic name).

- **Chlorphenothiazine propyldiamine (chemical name)**
  - Chlorpromazine (official name)
  - Largactil (brand name/trade name)
  - Phenothiazine (generic name).

Drug Therapy

It is of three types:

1. **Rational therapy:** It is the logical treatment of diseases by drugs based on pharmacological effects of drugs correlated with pathological aspects of diseases, e.g. digoxin in congestive cardiac failure, ferrous sulphate in iron deficiency anaemia, antibiotics in bacterial infections, etc.
2. **Empirical therapy:** It is the treatment of diseases based on experience, belief or guess and without any pharmacological explanation, i.e. uses of homeopathic drugs for curing diseases.
3. **Accessory therapy (alternative medicine):** It is the treatment of diseases by other means besides drugs, e.g. use of physiotherapy in arthritis, administration of suitable foods in malnutrition, etc.

Branches of Pharmacology

These are described as follows:

1. **Pharmacokinetics (*Kinesia* meaning movement):** It deals with the absorption, distribution, metabolism and excretion of drugs. It is what the body does to the drug.
2. **Pharmacodynamics (*Dynamics* meaning power):** It deals with the biochemical and physiological effects of drugs and their mechanisms of action. It is what the drug does to the body.
3. **Pharmacotherapeutics (therapeutics):** It is the use of drugs in the prevention and treatment of diseases.
4. **Toxicology:** It deals with adverse reactions of drugs and their treatment.
5. **Clinical pharmacology:** It deals with the study of drug effects in human beings (normal and patients).
6. **Experimental pharmacology:** It deals with the study of drug effects in laboratory animals (rats, guinea pigs, rabbits, etc.).
7. **Pharmacy:** It is the collection, compounding and dispensing of drugs for use in man or animal.
8. **Posology:** It deals with the dosage of drugs.

Pharmacopoeia

It is an official book published by the authorised body in a country containing description of commonly used drugs with their sources, properties, uses, doses and tests of identity, purity and potency, e.g. Indian pharmacopoeia (I.P.), British Pharmacopoeia (B.P.), United States Pharmacopoeia (U.S.P.). Extra pharmacopoeia (Martindale), etc. It is revised every five years to contain newly developed and essential drugs. Harmful drugs that have better substitutes are omitted in the new edition. Drugs contained in pharmacopoeia are called official drugs.

Sources of Drugs

Drugs are obtained from various sources. According to sources they are as follows:

1. **Natural drugs:** These are obtained from:
   a. Plants, for example:
      - Morphine from poppy capsules
      - Atropine from belladonna leaves
      - Quinine from cinchona barks
      - Castor oil from castor seeds.
   b. Microorganisms, for example:
      - Penicillin from *Penicillium notatum* (a fungus).
      - Streptomycin from *Streptomyces griseus* (a soil dwelling organism)
      - Bacitracin from *Bacillus subtilis* (a bacteria)
      - Diastase from *Aspergillus oryzae* (a fungus)
   c. Animals, for example:
      - Insulin from pig or ox pancreas
      - Thyroxine from pig or ox thyroid gland

- Heparin from pig or ox liver
- Cod liver oil from cod fish liver.

d. Minerals, for example:

- Calcium, magnesium, aluminium, sodium, potassium and iron salts.
- Liquid paraffin from petroleum.

2. **Synthetic drugs:** These are prepared by chemical synthesis in pharmaceutical laboratories, e.g. sulphonamides, quinolones, salicylates, barbiturates, benzodiazepines, etc.
3. **Semisynthetic drugs:** These are prepared by chemical modification of natural drugs in pharmaceutical laboratories, e.g. ampicillin from penicillin-G, cephalexin from cephalosporin-C, dehydroemetine from emetine, dihydroergotamine from ergotamine.
4. **Biosynthetic drugs:** These are prepared by cloning of human DNA into the bacteria like *E. coli*. Cloning means production of identical subjects like the parent. The technique is called recombinant DNA technology or genetic engineering, for example:
   - Human insulins (insulin-S, insulin-I)
   - Human growth hormones (somatrem, somatropin)
   - Human interferons (interferon-α, interferon-β)
   - Tissue plasminogen activator (alteplase)
   - Human BCG vaccine
   - Human hepatitis B vaccine, etc.

Gene-based Therapy (Gene Therapy)

It is the introduction of functional genetic material (DNA) into the target cells to replace or supplement the defective genes. It can impart new functions to cells. By it many diseases which are now only palliated can be cured, e.g. cancers, Alzheimer's disease, Parkinson's disease, diabetes mellitus, hypertension, hyperlipidaemia, haemophilia, cystic fibrosis, muscular dystrophy, Gaucher's disease, sickle cell anaemia, dwarfism, multiple sclerosis, HIV infections, etc.

Chemical Natures of Drugs

Plant Products

The pharmacologically active substances (principles) of plants are as follows:

1. **Alkaloids:** These are organic nitrogenous substances containing cyclic nitrogen and also carbon, hydrogen and sometimes oxygen obtained from plants. These are basic substances (bases) which are insoluble in water but when combined with mineral acids, they form acidic salts, which are soluble in water. Their names end with "ine", e.g. atropine, morphine, nicotine, pilocarpine, emetine, caffeine, etc. Most alkaloids are solid and nonvolatile but some alkaloids are liquid and volatile, e.g. pilocarpine, nicotine, lobeline and amphetamine. Animal alkaloids are called amines, e.g. adrenaline, noradrenaline, dopamine, histamine and 5-hydroxytryptamine.
2. **Glycosides:** These are organic non-nitrogenous substances containing C, H, O and sometimes S obtained from plants. They are neutral or slightly acidic substances which are soluble in water. They do not combine with acids to form salts. When they are heated with mineral acids they hydrolyze and split up into two components, viz. sugar and non-sugar (aglycone or genin). Sugar component is responsible for water and lipid solubility, cell permeability, tissue fixation and potency, while non-sugar component is responsible for pharmacological actions, e.g. digoxin is obtained from leaves of digitalis lanata, sinigrin is obtained from mustard seeds, senna is obtained from senna leaves and picrotoxin is obtained from fish berries (*Anamirta cocculus*).
3. **Oils:** These may be fixed oils or volatile oils obtained from plants. Fixed oils are glycerides of oleic, palmitic and stearic acids. They are obtained from seeds of plants by expression. They are insoluble in water and cannot be distilled. Many of them are edible and have food (caloric) value. They are used for cooking, e.g.

mustard oil, sunflower oil, peanut oil and coconut oil. Some are used for pharmacological actions, e.g. castor oil is used as purgative and olive oil is used as emollient and cholagogue (to cause evacuation of gallbladder by contraction). Fixed oils of animal origin are cod liver oil, shark liver oil, halibut liver oil, butter, lard (animal fats), etc. Fats are fixed oils which remain solid due to presence of more stearin (solid) than palmitin (semi-solid) and olein (liquid). Oils contain more olein than others. Volatile oils are obtained from flowers, leaves, fruits and seeds of plants by distillation. They contain the hydrocarbon "terpene" or some polymers of it, which serves as a diluent or solvent of the active compound. They are soluble in water and impart to it their taste and smell. They are volatalized by heat and possess aromas (smell). They have no food (caloric) value. They are used as carminative, flavouring agent, antiseptic, anodyne or counter-irritant, e.g. cardamom oil, peppermint oil, thymol, clove oil or turpentine oil respectively. Some volatile oils remain solid at ordinary temperature. They are called stearoptenes, e.g. camphor, menthol and thymol. Mineral oils are mixture of hydrocarbons of the methane and related substances obtained from petroleum by fractional distillation, e.g. liquid paraffin, soft paraffin and hard paraffin. Liquid paraffin is used as emollient laxative, while soft and hard paraffins are used as ointment bases.

4. **Tannins:** These are organic non-nitrogenous substances obtained from plants. They have astringent action upon the mucous membrane and thus exert a protective action. They are soluble in water and have astringent taste. They are used as tincture, e.g. tincture of catechu is used as anti-diarrhoeal agent (releases tannic acid in intestine) and tincture of Kalmegh is bitter and is used as appetizer in hepatic dysfunction.
5. **Resins:** These are solid nonvolatile substances formed by oxidation or polymerization of volatile oils in plants. They are insoluble in water but soluble in alcohol, e.g. jalap and colocynth (previously used as drastic purgatives). Podophyllum resins (20% suspension in liquid paraffin) is used as cauterising agent in venereal warts. Oleoresin is a mixture of resin with volatile oil, e.g. male fern extract (previously used to remove tapeworms from the intestine).
6. **Antibiotics:** These are antibacterial substances derived from fungi, actinomycetes and bacteria, e.g. penicillin, streptomycin and bacitracin respectively.
7. **Vitamins:** Majority of vitamins are obtained from plants, e.g. vitamins B complex, C, E, K, etc.

The pharmacologically inert (inactive) substances of plants are:

- **Gums:** These are secretory products of plants. These are colloidal carbohydrates (polysaccharides). These are dispersible in water and form thick mucilaginous colloids, e.g. gum acacia and gum tragacanth are used as emulsifying or suspending agents for preparation of emulsions or suspensions in pharmacy.
- **Waxes:** These are waxy or plastic substances obtained from various plants (vegetable wax) or from animals, e.g. sheep wool (wool wax/lanolin) and honeycomb deposited by bees (beeswax). These are esters of long chain fatty acids with higher, usually monohydroxy alcohols. Beeswax is yellow. It is converted to white wax by bleaching with chlorine. Waxes are used in pharmacy for preparing ointments, creams, suppositories, etc.

Animal Products

These are hormones, enzymes, fixed oils, vitamins and waxes. These have been discussed in respective chapters.