CHAPTER-1
INTRODUCTION

The word drug is derived from the French word drogue, which means a dry herb. In a general way, a drug may be defined as a substance used in the prevention, diagnosis, treatment or cure of disease in man or other animals. According to WHO, a drug may be defined as any substance or product which is used or intended to be used for modifying or exploring physiological systems or pathological states for the benefit of the recipient and it is presumed that this refers to total benefit-physical, mental as well as economical. An ideal drug should satisfy the following requirements:

i) When administrated to the ailing individual or host, its action should be localized at the site where it is desired to act. In actual practice, there is no drug, which behaves in this way. It generally tends to distribute itself anywhere in the tissues of the host.

ii) It should act on a system with efficiency and safety.

iii) It should not have any toxicity.

iv) It should have minimum side effects.

v) It should not injure host tissues or physiological processes.

vi) The cells should not acquire tolerance or resistance to the drug after some time. In actual practice, the cells which were originally
susceptible to the action of a particular drug may after some time acquire tolerance or resistance to that drug.

Very few drugs satisfy all the above conditions. However, the search for ideal drug continues.
A). HISTORICAL EVOLUTION OF DRUGS

To understand science, one has to know its history and development. Since the dawn of civilization, mankind has been concerned about their protection from the evils of diseases and sufferings. Conquering these afflictions often determined their survival but the current state of knowledge did not permit rational use of drugs, additional help was sought from supernatural powers. This was especially true of ancient Greeks and Indians who believed that the Gods dispensed prosperity or pestilence. There was a recognition that a regularity prevailed in the natural world that was independent of supernatural whim or will. This was a giant step in the making and formation of scientific medicine.

Human beings began to believe that nature alone could provide the means to remove pain and disease and thus they sought remedies in nature, i.e., in plants, minerals and animals. A variety of medicinal agents were collected on the basis of their symbolic qualities as well as their astrological signs and portents, e.g. Since the sword symbolized strength and power, the early Greek Physicians attempted to use iron therapy against weakness and anemia. The observation that the horn of rhinoceros is powerful, led Chinese physicians to prescribe it as a potent aphrodisiac.
One should keep in mind that these practitioners brought forth their explanations in good faith. Many of their drugs were added to the therapeutic armamentarium only after considerable trial and error and application of clinical judgement. We should not automatically brand their explanations as silly and as having no basis for to-day's rational standards. These early drug users were just as intelligent as we are. In the light of the knowledge then available they had good reasons for what they said and did. The answer to the question, what did they consider good reasons, is not a simple one. It must take into consideration their entire intellectual, ethical and cultural background.

The earliest references about medicine preparations in writing come from India or Rigveda and from China in their Materia Medica 2500-3000 B.C. In India, later on, a large number of medicine preparations including Ayurveda were described by physicians such as Chark, Sushruta, Vaghbata and others. All the drugs used were of vegetable origin.

As a large number of drugs have been found to be listed on papyrus, and many clay tablets are discovered in Egypt, it is evident that the Western medicinal system comes from Egypt and from the kingdoms of Assyria and Babylonia.

It was the Greek physician, Hippo crates (450 B.C.) who laid the foundation of modern medicine. According to him, a disease is a pathological
process and its treatment with drugs is not a magic. The medicine system introduced by Hippocrates had a scientific basis, i.e.; it was based on observation, analysis and deductions. However, on the whole upto the nineteenth century it was believed that the treatment of diseases was mainly based on the combination of guess work and experience. This resulted quack doctors in many countries. These doctors used therapeutic preparations comprised of a limited number of substances extracted from herbs and animals or from the earth in the form of minerals. Some 500 years later the Roman, Galen of pergamon, besides conducting impressively detailed investigations of animal anatomy, was a convinced herbalist who also used certain metallic salts, copper and zinc ores, iron sulphate and cadmium oxide, and introduced the assaying of preparations in efforts to control the quantity and quality of his dosages. The next major advances were introduced by two Persians named Rhazes and Avrienna, who, in the tenth and eleventh century respectively, introduced opium pills for coughs and extracts of wild autumn crocus (colchicum) seeds to treat gout. Both of these remedies are still used in modern medicine. In Europe in the early sixteenth century theophrastus paracelsus extroled the virtues of antimony salts as cure-alls, and, for a period, metal therapy dominated herbal recipes.
Theophrastus paracelsus, originally named Bombastus von Hohenheim, was ironically frustrated by unsuccessful attempts during his lifetime to introduce the useful laudanum (morphine tincture) for relief of pain and tartar emetic, still a useful antimonial, for the dread schistosomiasis.

One of the greatest herbal remedies of all was introduced into Europe in the seventeenth century by Jesuit missionaries who had accompanied the Spanish conquistadors on their exploration of central and South America. This was an extract of the cinchona bark obtained from South America. Indians who had long used it as an against chills and malarious in Europe.

In eighteenth century in England, Withering introduced the use of an extract of the foxglove plant for the treatment of dropsy, a heart condition characterised by excessive accumulation of liquid in the lower limbs of the afflicted. He used this extract on the personal recommendation of country folk who had been using the elixir for untold years, a fine example of an enquiring medical practitioner following up and developing a lead from folk culture. The active material digitalis is still used today for threatened heart failure and is even now obtained by extraction from the foxglove.

By the middle of the 19th century, modern medicine had brought to the fight against diseases only one effective weapon, i.e.; immunization against smallpox. In quick succession came surgical anesthesia and antisepsis. The last
quarter of the 19th century marked the identification of the causative organisms of few diseases like malaria, plague, cholera, typhoid and dysentery so that areas of the globe till then mastered by them changed hands to man. Insect vectors were identified. Vigilant students of preventive medicine contributed more than their mite. Organic and biochemistry gave a tremendous fill up to the study of hormones and vitamins. During the last decade intensive work in chemotherapy has given us such valuable aids as the sulpha drugs and antibiotics.

In the subsequent years, the knowledge of the chemistry of natural substances particularly of enzymes increased. This was made possible with the help of new physical, chemical and biological techniques. It is widely accepted that the enzymes play some role in drug action.

In the last fifty years, there had occurred more spectacular advances in medicinal chemistry, particularly with the discovery of sulpha drugs and antibiotics. Recent years have seen the creation of new therapeutic agents by medicinal chemists working usually as part of interdisciplinary terms. All their names and contributions are too numerous to mention here.

The systematic research in pharmaceutical laboratories has led to the introduction of more and more synthetic drugs in the modern times. The synthetic work is carried out more or less along the following lines.
i) Compounds are synthesised whose structures are more or less similar to naturally occurring substances. This sometimes produces drug whose price is much less than the naturally occurring one.

ii) Attempts are made to prepare the compounds with simplified structure based on the structures of natural drugs. For example, the structure of a compound having specific physiological activity is varied systematically. This work sometimes leads to the discovery of new drug with simplified structure.

iii) Attempts are made to synthesize new drugs, which have the properties of certain natural products but have no relation to them in structure.

iv) Attempts are made to synthesize new drugs, which are unrelated in structure and properties to natural products.

Sometimes it is found that a drug discovered poses certain serious problems. For example, phthalidomide was at one time considered to be an ideal hypnotic due to its low toxicity. Later on, this was found to be responsible for the birth of thousands of deformed children. Thus, this is not used at all. Certain drugs are known which are abused on the whole it is found that the...
beneficial effects of drugs are much more than the problems created. However, these problems could be overcome.

(B) SOURCES OF DRUGS

1. PLANTS

Medicinal plants have been used to treat various diseases from time immemorial. Crude medicinal preparations made from plants are called 'galenicals' because they were extensively used and popularized by Galen, the famous Greek physician. They owe their actions to biologically active ingredients contained in them. The important classes of active ingredients in plants and their characteristics are as follows.

(a)ALKALOIDS: These are plant bases containing nitrogen which form salts with acids they are insoluble in water. Acid salts of alkaloids are freely soluble in water. To day hundreds of synthetic alkaloids are being produced. Examples are as follows:

Morphine (narcotic analgesic) from unripe capsule of papaver somniferum.
Ephedrine (bronchodilator) from plant Ephedra vulgaris.
Atropine (anticholinergic) from leaves of Atropa belladonna.
Quinine (antimalarial) from bark of cinchona.
Reserpine (antihypertensive) from root of Rauwolfia serpentina.
(b) GLYCOSIDES: They are ether-like combination of sugars and non-sugar moiety (cyclopentane-phenanthrene steroid nucleus). If a glycoside is boiled with mineral acid, it is hydrolysed and it splits off the sugar. The non-sugar residual part of the glycoside is called aglycone. Examples of glycoside are digoxin, a cardiac stimulant obtained from the leaves of Digitalis Lanata.

(c) OILS: They are immiscible with water but dissolve readily in solvents like ether chloroform and alcohol. Oils of medicinal value can be divided into three classes.

i) Fixed oils: Chemically these are esters of fatty acids and glycerol. Most of them are edible oils e.g., ground nut oil, coconut oil, mustard oil, olive oil. Some have pharmacological actions e.g., castor oil (purgative) and cod liver oil (rich source of vitamin A and D).

ii) Volatile oils: These are terpenes or their polymers. They are also called essential or flavouring oils. Most of them are liquids. For example, clove oil (anodyne-relieves pain when applied locally specially in toothache), eucalyptus oil, coriander oil, dill oil, ginger oil (carminative, for expulsion of gas from the stomach), methyl salicylate (oil of wintergreen) and terpentine oil (counter irritant, applied locally to relieve pain in arthralgia). Few volatile oils exist in
a solid form and they are known as stearoptenes e.g. camphor and menthol.

iii) Mineral oils: They are hydrocarbon by chemical nature and are obtained from petroleum e.g. liquid paraffin (lubricant and laxative).

(d) RESINS: They are formed by oxidation or polymerization of volatile oils, e.g. podophyllum, colocynth, jalap. They are more of toxicological importance than pharmacological.

(e) GUMS: They are secretory products of plants chemically they are related to polysaccharides. They form thick mucilage when mixed with water. Some gums are pharmacologically inert and are mainly used as emulsifying agents e.g. gum acacia, gum tragacanth; while other gums are active e.g. agar (bulk purgative), gum guggul (hypolipidemic).

(f) TANNINS: They are non-nitrogenous compounds characterized by their astringent action on the mucous membrane, i.e. they precipitate proteins from the cells of the mucous membrane and have a protective action.

2. ANIMALS

Some drugs are obtained from animals. Examples are as follows: Insulin (hypoglycemic) from pancreas of sheep, oxen and pigs.

Thyroid extract (for hypothyroidism) from thyroid gland of oxen.

Gonadotropins (sex hormone) from serum of pregnant mares.
Pepsin (enzyme) from stomach of oxen and pigs.

3. HUMAN:
Some drugs are available from human source. Examples are as follows:
Immunoglobulins from blood.
Growth hormone from anterior pituitary.
Chorionic gonadotropin from urine of pregnant women.

4. MICROBES
They are mainly the source of antibiotics, i.e. chemical substances produced by one type of microorganism and lethal to others. Apart from antibiotics, certain other drugs have also been derived from microorganisms e.g. the enzyme streptokinase (fibrinolytic) as obtained from streptococcus.
Examples of antibiotics are as follows:
Penicillin from the fungus penicillium chrysogenum.. Streptomycin, neomycin and actinomycin from Actinomycetaceae.. Griseofulvin from penicillium griseofulvum. Nystatin from streptomyces noursei.

5. MINERALS
Some elementary substances like iron, iodine and sulphur are used in the treatment of diseases. Some metallic compounds like antimony salts for kalaazar and bismuth salts for peptic ulcer are valuable drugs. Similarly
magnesium and aluminium salts are widely used in antacid preparations. Some
important examples are as follows:

- Sulphur in sulphur ointment for scabies.
- Iron in hematinic preparations for anemia.
- Magnesium sulphate (epsom salts) as a purgative.
- Iodine in Lugol’s iodine for thyrotoxicosis and tincture iodine as antiseptic.
- Aluminium hydroxide in antacid preparations.
- Radioactive isotopes ($^{131}\text{I}$) in diagnosis and treatment of thyroid disorders
  and ($^{32}\text{P}$) in polycythemia vera.