SECTION
I

General Pharmacology

HISTORICAL OVERVIEW

Fighting disease with drugs is a timeless struggle and the scientific approach to this struggle is pharmacology. Pharmacology as a science is quite young as compared to other sciences but the knowledge of drugs and their application in disease is as old as man. Primitive pharmacologic ideas were not all of a theoretic nature and some were the result of observation and personal experience or were adopted after noticing that animals when ill, consumed certain herbs or berries.

The earliest civilization revealed by history so far is the Babylo-Assrian, and from the tablets discovered, 300 drugs have been found mentioned there. These drugs include plants, herbs, roots, seeds, juices, wood, mineral substances and stones.

The religion has always been the part in art of healing. The idea of disease has been conceived as an evil spirit sent by deity to harm a person physicaly or mentally. Hence gods and godesses have been brought in this art of healing. Among the earliest of mythical personages to whom the origin of healing art in Egypt has been attributed are Isis and Osiris. The mythical creator of Greek materia medica was Apollo. His son Aesculapius, a pupil of Chiron, is another prominent mythical personage to whom the emblem, a serpent on a staff has been attributed.

The knowledge of ancient Egyptian therapeutics is obtained from a scrol, the Ebers papyrus, discovered at Thebes in 1872 by Georg Moritz Ebers. It dates back about 1550 B.C. and consists of 110 Columns. More than 700 drugs are mentioned and majority of these have been identified and a few like opium, olive oil, saffron are still in use.

The terms pharmacology, pharmacy, pharmaceuticals, pharmacopoeia are derived from the Greek word "PHARMAKON' used for drugs. Greek contributed to knowledge of drugs to a great extent and Greek medicine has been a popular name even till now.

In the time of Hippocrates, a reaction has started against the more complicated temple medicine and more emphasis was being laid, in addition to drugs, on proper type of food. Hippocrates did not believe in magic remedis.

Theophratus, a successor of Aristotle had a good knowledge of plants and their use in the diseases. He described about 500 drugs.

With the founding of Alexandria in 331 B.C. and subsequent encouragement extended to scientists, pharmacology, like anatomy and physiology, started to take on the appearance of an experimental science.

In the ancient Hindu medical text called "SUSRUTA" seven hundred and sixty herbs have been described relating to the localities where particular herbs were found along with the opportune time to collect those.

In ancient Chinese medicine, the Emperor Shen Nung (2735 B.C.) is usually refered to as the father of Chinese materia medica. He has been described to be the author of "Pen Taao" which describes 265 drugs of which 240 are vegetable substances. The Chinese employed Iodine (in the form of Calcined Sea Weed), rhubarb, aconite, cannabis, iron, sulphur, mercury, alum, musk and numerous other drugs some of which contain ephedrine or camphor.

In early Roman period Celsus (25 B.C. to 50 A.D) wrote a book the fifth part of which was devoted to therapeutics and it consisted of 28 chapters. The most significant pharmacological treaties of the priod was the authoritative text of Dioscorides, "pedacius". Dioscorides has mentioned acacia, aconite, a variety of ammoniacal substances obtained from plants, dill, anisi, bitter almond, juniper, wild liquorice, gentian and a large number of other drugs which are still in practice. Dioscorides was the first to emphasize signs for the recognition of adultrated drugs. He was first to extol the soporific virtue of white poppy.

Pliny devoted seven of his books on remedies derived from plants and trees. Galen (130-200 A.D) wrote thirty books on drugs. One of these in which the items were discussed in alphabetical order enjoyed great popularity. He always emphasized the use of pure drugs and their careful handling. He introduced the methods of preparing pure drugs from their crude sources and such preparations like tinctures, fluid extracts etc., are still used and are called Galenicals.

The ultimate source of the medical knowledge of Arabs was Dioscorides. However they introduced new substances, one of these is castor oil. It was used as a cathartic. The Arabs also introduced musk and employed it for cerebral and ophthalmic diseases. The other drugs introduced by Arabs to the profession include ambergris in the treatment of cramps, heart diseases and brain disorders, camphor for fevers, cholera, haemorrhage and inflammation of the brain, senna as a cathartic, mace for cardiac diseases and indigestion, sandal wood for gout and headaches, picrotoxin for arthritis, nux vomica as emetic, borax gum and sandarac for dental complaints and tamarin, hops and spinach as laxatives.

Abu Baker Muhammad Ibn Zakria Al Razi (850-93) known in the West as Razes was one of the foremost physicians who wrote

numerous text books. The most important contribution attributed to him was the introduction of mercurical ointment.

Al Zahrawi (Abucasis or Abual Qazim Ibn Abbas Al Zahrawi, 936-1013) was a native of Cordova and author of Al-Tasrif. He pointed out that mercurical inunction produced gingivitis and glossitis.

Ali Ibn Al-Abbas almajusi (d.994), a persian Physician, is the author of an encyclopedic treatise entitled al-Kitab Al-Maliki which contained section on materia medica.

Abu-Ali Al-Hussain Ibn Sina (Avecena 980-1037) is the author of an important medical al-Qanun Fi Tibb and philosophical treatise, "Kitab Al-Shifa". The materia medica in Al-Qanun or Canon considered 760 drugs. This work served as a chief guide to the medical sciences in the West from the twelveth to sixteenth centuries. During Arab period great schools of learning had been established at Baghdad, Cordova, Seville and Toledo. A famous figure during the moorish period in medicine in Spain was Mamonoides or Al-Mamoon.

The medevial Europe was in close contact with Arabic influences and from the 10th century onwards Moslem culture slowly filtered into medeival Europe. The Islamic centres of learning at Cordova, Seville, Malaga and Granada which all date from the first half of the 10th century, were busily training men some of whom carried the pharmacologic and chemical knowledge to the courts and monastries of Europe. This pharmacologic and chemical literature filtered in to Europe, particularly through Salerno and the island of Sicily both of which were predominently muslim in culture.

A law for the regulation of the practice of medicine within the kingdom of two Sicilies which included drug control was promulgated in 1240 by the Emperor Frederic II. The copies of translations of Arabic writings were sent to Paris and the Engl sh students who later congregated at Oxford and Cambridge had become saturated with such Arabic culture at Paris: Travels in Spain and even prior to this period, Arabic influences were apparent in the Anglosaxan herbals of 11th & 12th century England.

Within the British Isles, pharmacology was extremely corrupt and complicated. English practitioners did not trouble themselves about the efficacy of their prescriptions. The published English herbal lacks a title and is simply known as "An herbal". The so called herbals did not confine themselves to herbs, but described the substances from each of the three natural kingdoms. Relatively chemical substances introduced by the Arab scholars, had played an increasingly important role from the 13th century onwards and during the next 2 centuries, the only important changes in pharmacology were the result of growing popularity of a alchemic experimentations. Towards the end of fifteenth or the beginning of 16th century, however, pharmacology received a [illegible] therapy in

the direction of treating diseases by means of herbs rather than chemical substances. This stimulus was the botanical and encountered in the discovery of America.

Although the main advances in 18th century pharmacology were due to the progress of chemistry, this century saw serious attempts to establish the physiological basis of action of all forms of drugs. Studies upon pharmacologic action were still hampered by the supposition that chemicals might not behave the same inside as outside the body. Another complication was the fact that individuals were still considered to be roughly divisible into certain types which reacted diversely towards drugs.

The contribution of 18th century colonial America to pharmacology were of little significance. With the growing unpopularity of England in the United States, there was an attempt to avoid the fashions of English pharmacy.

While the biologic or physiologic approach continued to yield important pharmacologic information, and sometimes was the only method which was found practical, the direction in which 19th century pharmacology tended was more closely correlated with the progress of chemistry.

Digitalis or Foxglove became popular in 18th century when William Withering published a treatise on it. The first pharmacopoeia of United States in 19th Century listed purple foxglove. Ether known as chemical agent from 19th century was used for toothache in 19th century. Nitrous oxide produced in 1776 by Joseph Prisetley was found having peculiar effects on inhalation by Humphry Davey (1778-1829). The use of ether as an anaesthetic had been a great controversial subject. Chloroform made in 1831 was used as general anaesthetic much later. An interesting example of the shift from a botanical to chemical materia medica is the history of the salicylicacid compounds. The poisonous effects of salicylic acid led to a search for compounds with lower toxicity and higher therapeutic efficacy. This resulted in introduction of aspirin and salol.

The great achievement in this century was the introduction of chemotherapeutic agents against the bacterial infection. The person responsible for much of this enthusiasm was Paul Ehrlich (1854-1915). From the research of Robert Koch and his own work, Ehrlich concluded that the staining of bacteria has its basis in a chemical union between the cell and the stain. He further imagined that it might be possible to discover dyestuff or other drugs whose chemical affinity for disease organism was so great that the organism might be killed without damage to the host. Ehrlich's early researches were not entirely satisfactory. The compounds capable of killing the microorganisms were also injurious to the host. However advances in

the subject brought in sulphonamide compounds and then the antibiotics which have made true the dreams of Ehrlich.

In early 19th century morphine was isolated from opium and was followed by isolation of quinine from cinchona bark and strychnine from nux vomica. The sites of action of strychnine and curare were also localized during this period.

A new phase of modern pharmacology was started by Oswald Schmied-Berg (1838-1921) with consideration of fate of drugs in the body.

The consideration of Prof. A.J. Clark, of the mode of action of drugs on cells did much to place pharmacology in the realm of science. Now in the 20th century the effect of drugs on subcellular level and molecular level has put pharmacology amongst the advanced sciences.

SUB-DIVISIONS OF PHARMACOLOGY

Pharmacology is the science that deals with drugs. The word is derived from Greek words *Pharmacon* (an active principle) and *loges* (a discourse or treaties)

The word drug is derived from the French word *drogue*, a dry herb. A drug is defined as any substance used for the purpose of diagnosis, prevention, relief or cure of a disease in man or animals.

Since a drug is any chemical substance that effects living processes, the subject of pharmacology is obviously quite extensive. In broad aspects, it includes 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. However, for the physician and the medical student the scope of pharmacology is rather limited to the study of action of drugs on living cells and the mechanism by which such effects are produced. The study of Pharmacology thus provides a sound basis for selection of drugs in therapeutics and allows for a better understanding of drug toxicity and of the interaction between drugs.

Following are the subdivisions of Pharmacology and allied fields:

Pharmacodynamics: It is the study of the biochemical and physiological effects of drugs as well as their mechanisms of action. It includes study of structure-activity relationship of drugs.

Pharmacokinetics: It deals with the absorption, distribution, biotransformation and excretion of drugs and their relationship to the onset, duration and intensity of drug effects.

Therapeutics: It is the art and science of treatment of disease. It includes drug treatment, *Pharmacotherapeutics*, which deals with the proper selection and use of drugs for the prevention and treatment of disease.

Chemotherapy: It deals with the effect of drugs upon microorganisms and parasites, living and multiplying in a living body, without damage to the host.

Clinical Pharmacology: It is the scientific study of drugs in man. It includes pharmacodynamic and pharmacokinetic investigations of drugs in man (young, adult, old, healthy or sick persons) and their therapeutic evaluations.

Toxicology: It deals with the adverse effects of drugs. It is concerned not only with drugs used in therapy but also with many other chemicals responsible for household, environmental or industrial poisonings.

Pharmacognosy: It is the science of identification of drugs.

Pharmacy: It is the science which deals with the preparation, compounding and dispensing of medicines.

Posology: It is the branch of Pharmacology which deals with doses of drugs.

SOURCES OF DRUGS

Since very old times vegetable drugs have been used by man for the relief of symptoms of disease. Initially these were prepared by grinding and mixing dried plants or parts of plants. Drugs from such natural sources are still being used to some extent. However, in modern times, most of the drugs are prepared synthetically.

Vegetable Sources (Plant Source): This is the oldest source of drugs which have been used emperically. All parts of the plants are used as drugs such as leaves, seeds, flowers, roots, bark, etc. Examples are: Belladonna leaves, Belladonna root, Cinchona bark, Digitalis leaves, Nux vomica seeds, Senna leaves, Sena fruit.

Action of crude drugs is due to *Active Principles* contained in them, e.g.:-

Belladonna contains atropine, opium contains morphine, cinchona contains quinine, digitalis contains digoxin.

With the advancement of organic chemistry, semisynthetic derivatives of active principles were produced e.g., Homatropine is semisynthetic derivative of Atropine.

Animal Sources: Various organs and tissues of animals wereused in the past without understanding their mechanism of action. Active principles of animal drugs are Proteins, Oil and Fats, Enzymes and Hormones. At present Insulin and Sex Hormones are obtained from animal source.

After isolating the active principles, their chemical structures were studied and many semisynthetic derivatives were produced and used in therapeutics.

Mineral Sources: Metals, metalloids, non-metal substances and their compounds have been used as drugs. Mercury was one of the earliest drugs to be used for treatment of syphilis. At present iron is used for treatment of anaemia and iodine for thyroid problems and as antiseptic.

Synthetic Sources: These days drugs are prepared in pharmaceutical laboratories. They may be organic or inorganic or a combination of organic and inorganic compounds. Chloroform, ether, nitrous oxide and chloral hydrate were the earliest synthetic drugs. Later on derivatives of active principles of crude drugs were prepared alongwith advancement in the knowledge of chemistry.

At present more than 90% of drugs used for treatment of patients are prepared synthetically. Antipyretics, sulphonamides, antihistamines, anticonvulsants, antianxiety agents are examples of such drugs.

Microbiological Sources: Antibiotic drugs which are very useful for treating infections have been prepared from bacteria and moulds. Some vitamins have also been prepared from such sources.

Penicillin was the first antibiotic to be discovered. Having known its chemical structure, many useful semisynthetic penicillins have been produced.

ACTIVE PRINCIPLES OF CRUDE DRUGS

Pharmacological actions of crude drugs are due to active principles contained in them. A description of important chemical constituents is given below:

1. Alkaloids: These are very active nitrogenous compounds with a very complex chemical structure. They are alkaline in reaction. They are intensely bitter. Most of them are insoluble in water and they form salts with acid e.g. Ephedrine Hydrochloride. Salts formed in this way are soluble in water. Most of the alkaloids are solids and only a few are liquids. Nicotine, lobeline and pilocarpine are the examples of liquid alkaloids.

More than one type of alkaloids may be present in the same plant and they may have similar pharmacological actions e.g., Belladonna contains Atropine and Hyoscine. Some plants may produce many alkaloids having different actions e.g. opium contains Morphine and Papavarine. Morphine has very powerful analgesic action and contracts smooth muscles. Papavarine is not analgesic and relaxes smooth muscles.

The names of alkaloids in English language end in letters "ine". Examples are Morphine, Atropine, Quinine, Ephedrine, Strychnine, Hyoscine and Pilocarpine.

2. Glycosides: These are very active and complex substances containing carbon, hydrogen and oxygen. These are hydrolyzed by acids or by certain enzymes in the presence of water and are split into two portions: (i) Sugar and (ii) Non Sugar component (Aglycone). Of these two, pharmacologically active portion is the non-sugar portion which is known as genin. When sugar portion is glucose then the glycoside is known as glucoside.

Important examples of glycosides are Cardiac Glycosides i.e. Digoxin, Digitoxin, Gitoxin, Gitalin and Strophanthin.

3. Saponins: These resemble glycosides. They are the compounds, which on shaking with water produce froth. They act as emulsifying agents. They are very toxic and may cause haemolysis e.g. Senega.

4. Fixed Oils: These are the oils which are obtained from various plants or from animals. They are called fixed oils, because they cannot be distilled without being decomposed.

These are esters of higher fatty acids, such as oleic acid, palmitic acid and stearic acid. They are bland and non-irritating. They

leave a greasy mark on paper. They form soaps with alkalies. Examples of fixed oils are: Castor Oil, Olive oil.

5. Volatile Oils: (Essential Oils, Ethereal Oils): These are the oils which are obtained from various parts of plants like flowers, fruit, leaves and seeds by distillation process. They are highly aromatic and are slightly soluble in water and give their smell and taste to water. They vary in composition. The majority contain liquid hydrocarbons which are monoterpenes. In addition, most contain oxidised hydrocarbons. They are usually crystalline solids such as menthol, thymol, camphor. They are called *stearoptenes*.

Volatile oils possess definite pharmacological activity and are used as carminatives, diuretics, antiseptics, counterirritants and expectorants.

6. Fats: A fat is a fixed oil which is solid at room temperature. Fats are natural esters of glycerol and fatty acids. All the three OH groups of glycerol are estrified in fats, therefore, they are known as Triglycerides. Fats used in Pharmacy are theobroma (Cocoa butter), lard, adeps lanolin (wool fat).

7. Waxes: Waxes are esters of fatty acid with monohydric alcohol. Waxes are complex mixtures. Waxes are used in the preparation of ointments and other drugs which are used locally on the skin. The wax used in pharmacy is white beeswax (cera alba).

8. Gums: These are exudations of plants. They contain carbohydrates e.g. starch and cellulose. Gums form a viscous solution with water known as *mucilage*. The gums and mucilages are used for the preparation of suspensions and emulsions. Thus they act as suspending and emulsifying agents e.g. Gum Acacia, Gum Tragacanth.

9. Resins: These are solid brittle substances which are produced by the oxidation of volatile oils. Resins form resin soaps with alkalies which are used in the preparation of emulsions and pills e.g. Colophony.

10. Oleoresins: These are formed when resins are dissolved in volatile oils e.g. Copaiba.

11. Gum Resins: These are combination of gums and resins and are used in Dentistry, e.g. Myrrh.

12. Balsams: These are combinations of resins with benzoic acid or cinnamic acid or both e.g. Benzoin, Tolu. Benzoin is used in the form of Tr. Benzoin Co which is applied on small superficial wounds and abrasions.

13. Tannins: These are non-nitrogenous substances possessing an astringent action on the mucous membrane. Some are hydrolysed to tannic acid. With iron salts they produce blue inky colour. They are precipitated by metallic salts and alkaloids.

14. Neutral Principles: These are active substances which do not conform to any special group e.g. Aloin, Santonin.

DIFFERENCES BETWEEN FIXED AND VOLATILE OILS

Fixed Oils	Volatile Oils
1. These are non-volatile.	1. These are volatile.
2. They are insoluble in water.	2. They are slightly soluble in water.
3. They give greasy mark on the paper.	3. They give no greasy mark on the paper.
4. They form soaps with alkalies.	4. They do not form soaps with alkalies.
5. They are bland and non-irritant.	5. They are mild irritant.
6. They cannot be distilled without being decomposed.	6. They can be transferred by the process of distillation.
7. They have usually few pharmacological actions.	7. They have many types of pharmacological actions.
8. They become decomposed and rancid when kept for long tme particularly during hot weather.	8. They do not decompose.
9. They give no smell or taste to water.	9. They impart smell and taste to water.

DRUG ADMINISTRATION

The route of administration of a drug depends upon (*i*) its physical and chemical properties, (*ii*) the site of desired action, (*iii*) seriousness and urgency of the disease, and (*iv*) condition of the patient. The route of administration influences the onset of action, duration of action and intensity of action of a drug. Whatever may be the route of administration, drugs may produce their pharmacological effects either (*a*) by acting locally, (*b*) reflexly or (*c*) by systemic effects.

Various routes through which drugs may be administered are described under the following main groups:

(a) ENTERAL (c) INHALATION
(b) PARENTERAL (d) TOPICAL

These are further subdivided into various channels discussed below:-

ENTERAL ROUTE OF ADMINISTRATION (Through Alimentary Tract): Drugs are usually given by mouth but may be placed under the tongue or may be given rectally.

(a) *Oral Route*: This is a natural route of administration. It is the most convenient, cheapest and most commonly used route. It has the advantage of ease and safety. Majority of drugs given orally are absorbed from small intestine. Few are absorbed from stomach and colon. As compared to injections, onset of action after oral administration is slow but effect is more prolonged. If given on empty stomach, absorption will be quick.

Disadvantages of Oral Route are:-

(*i*) Drugs may be destroyed by digestive enzymes. Examples: Adrenaline, Insulin, Oxytocin, Benzyl Penicillin.

(*ii*) Some drugs may not be absorbed at all e.g. Streptomycin, Neomycin.

(*iii*) Drug may be irritant to gastric mucosa to cause nausea and vomiting.

(iv) Some drugs may have objectionable taste or odour e.g. Quinine.

(v) Discoloration of teeth may occur e.g. Iron Mixture.

(vi) This route is unsuitable in emergency situations.

(vii) This route is not practicable in unconscious or uncooperatve patients.

(b) *Sublingual or Buccal Route*: Some drugs are given by this route. The tablet is placed under the tongue or placed between the

cheek and gingiva. Tablet is dissolved rapidly. Drug is absorbed rapidly and directly into the blood stream avoiding initial passage through the liver. The patient is asked to keep saliva in the mouth to facilitate drug absorption. Examples: Nitroglycerine (Angised), Isoprenaline, Oxytocin, Methyltestosterone.

(c) *Rectal Route*: Drugs are given sometimes per rectum. Drugs may be in solid form such as *suppositories* or in a liquid form such as *enema*. Drugs may have local action or systemic action after absorption. Drugs are given rectally when patient is either unconscious or cannot retain when administered orally. Drugs are absorbed more slowly from the rectum than from the small intestine. But the effect of digestive enzymes on the drug is avoided in this route.

Suppositories for local action (to relieve constipation) are: Glycerine Suppositories, Bisacodyl (Dulcolax) Suppositories.

Suppositories for systemic action are: Aminophylline, Indomethacin, Phenylbutazone.

PARENTERAL ADMINISTRATION (Through Injection): Administration of drugs by routes other than the alimentary tract is called parenteral administration. In practice it refers to administration of drugs by injection.

The advantages of injections are: (*i*) more rapid and predictable absorption than when drug is given by mouth (*ii*) parenteral therapy is useful if a patient is unconscious, unco-operative or unable to retain anything given by mouth. (*iii*) drug is not inactivated or destroyed as may happen in G.I. tract after oral administration (*iv*) Usually smaller doses are required.

On the other hand parenteral therapy is more painful requiring caution, skill and technique so that strict asepsis must be maintained in order to avoid infections. Moreover, it is difficult for the patient to take injections himself if self-medication is necessary. Injections are also more expensive and less safe than oral therapy.

Injections are classified according to the site of release of drugs from its needle. The most common injections are subcutaneous, intramuscular and intravenous injections. Less frequent methods are intradermal, intraperitoneal, intrapleural, intracardiac, intra-arterial, intrathecal and intra-articular.

The advantages and disadvantages of various kinds of injections will now be considered briefly. The techniques used are best learnt by practice in the laboratory and in the wards. Figure I-I shows length and bevel of the needle, angle of administration and point at which fluid would enter during subcutaneous, intramuscular and intravenous injections.

(i) *Subcutaneous (Hypodermic) Injection*: In this the drug is introduced into subcutaneous tissue. It is rapidly absorbed by the blood vessels and lymphatics. The possibility of the drug being destroyed in the stomach or having an irritant effect on gastro-intestinal tract as may occur after oral administration is avoided. The drug is thus surely absorbed. Volume of fluid to be injected should not be normally more than 2 ml. Generally forearm, arm and thigh are selected, but when a large amount of fluid is to be introduced, such as Normal Saline, the loose areolar tissue of subscapular region or the mammary region is selected. The fluid used must not contain solid particles, nor it should be irritating otherwise abcesses will result; it must be aseptic. Irritant drugs are more readily tolerated when injected intramuscularly and better still when given slowly intravaneously.

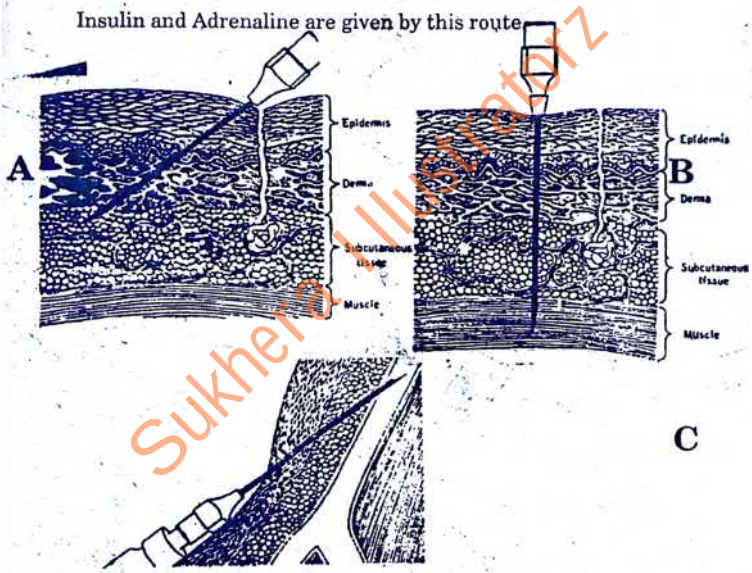


Figure 1-I. Note the length and bevel of the needle, angle of administration and point at which fluid containing the drug would enter during various types of injections.

A - Subcutaneous Injection: the drug is deposited in the subcutaneous layer of fat.

B - Intramuscular Injection: Needle passes through the skin, subcutaneous adipose tissue and fascia to enable the medication to enter the main body of the muscle.

C - Intravenous Injection: Point of needle should be free in the vein and the complete bevel should be inside the vein otherwise the fluid may partially pass into the tissue outside the vein or into the wall of the vein.

(*ii*) *Intramuscular Injection*: The drug is placed in the layers of the muscles. Drug in solution or suspension is injected deeply into a large muscle such as upper and outer quadrantof buttock, thigh and deltoid. The absorption of injected solution by this method is more rapid than when given subcutaneously. Mild irritants can be injected intramuscularly without causing intolerable pain. If intramuscular injection is not given carefully a nerve or vein may be injured. Nodules or abcesses may be formed.

To reduce pain during intramuscular injections the patient should be encouraged to relax the muscle selected for the injection site. Skin antiseptic should be allowed to dry on the applied surface before injection. New needle should be used before injecting into the patient. Needle should be inserted rapidly to minimise puncture pain. After injection, the needle should be withdrawn rapidly.

(*iii*) *Intravenous Injection*: The drug is injected directly into the lumen of a vein. Small or large quantities may be given by the method. This method is used for obtaining rapid results in emergencies or for the administration of drugs which are too irritating for introduction by alternate routes or for restoration of blood volume. The drug is injected into the lumen of a vein. There are many veins which could be used for injecting the drug. Generally the cubital vein is selected, although other convenient veins or even the superior longitudinal sinus, in case of children, may be selected; the median basilic vein should not be used because of the hazard of injecting the drug into the nearby brachial artery.

An intravenous injection should be given carefully and slowly. For a quantity of 10 ml at least one minute must be spent to inject intravenously. Drugs used by this route should be in solution and must not react with the proteins of the blood. Substances not soluble in water or oily solutions or suspensions cannot be used. Acids and metalic salts being incompatible with blood should not be used.

If large quantity of fluid is to be injected, the drug is given in form of intravaneous infusion slowly e.g. Dextrose solution in water or Normal saline.

The most frequent hazards with intravenous infusions are infilteration and phlebitis. To reduce the hazards of infilteration, placing intravenous needles near a movable joint should be avoided. Prominent veins with good blood flow and good elasticity should be used. Basilic and cephalic veins on the back of hand may be used. To reduce the hazards of phlebitis, infusion of high concentration of irritating drugs should be avoided by diluting drugs with compatible solutions of 50 to 100 ml. Infusion site should be checked if patient complains of pain or discomfort.

(*iv*) *Inra-arterial Injection*: The ijection is made into the lumen or an artery. In a few seconds the drug goes to its site of action and its

potency is not decreased by tissue enzymes. This method is used in special forms of therapy; for example, in the chemotherapy of malignant disease a very small dose of a drug may be injected into the lumen of the appropriate artery. This injection is also used for diagnostic purpose e.g. angiography.

(*v*) *Intracardiac Injection*: In sudden stoppage of the otherwise healthy heart drugs are introduced directly in the heart e.g. adrenaline.

(*vi*) *Intrathecal Injection*: Injection is made into the subarachnoid space by lumbar puncture or into the cisterna magna. Intrathecal injection is often used to produce regional anaesthesia. Much less frequently this route is chosen for the administration of the drug in proximity to the meninges and brain e.g. streptomycin in tuberculous meningitis.

(*vii*) *Injection into the bone marrow*: A wide bore needle is introduced into marrow cavity. In adults the sternum is usually chosen but in youngchildren the tibia is preferred. The effects are similar to those following intravenous injection. Bone marrow injections are used mainly when it is impossible to give the drug intravenously. This injection is mainly used for diagnostic purposes e.g. haematological disorders. Occasionally blood transfusion may be given by this route.

(*viii*) *Intrapleural Injection*: When the concentration of the drug given by mouth or by subcutaneous or intramuscular injection is not sufficient in pleural cavity, the drug is introduced into the cavity direct. An efficient concentration of the drug is maintained for a long period e.g. penicillin in saline is injected into the pleural cavity in empyema.

(*ix*) *Intraperitoneal Injection*: In some conditions involving peritoneal cavity, the drug may be given by intraperitoneal route. A large concentration of drug is achieved at the affected site. Also this is used for carrying out peritoneal dialysis for removal of poisons such as barbiturates.

(*x*) *Intra-articular Injection*: Certain drugs can be injected into the painful or inflammed joints to ensure a high concentration therein e.g. Corticosteroids.

(*xi*) *Intradermal (Intracutaneous Injection)*: This injection is used for introduction of drugs between the layers of skin. This is specially used for diagonostic purposes. e.g. Schick test for diphtheria, Dick test for scarlet fever, for production of infilteration anaesthesia and for sensitivity tests such as before giving penicillin injection.

HYPOSPRAY (JET-INJECTION)

Recently a device of introducing a drug into the body through the skin under high pressure, is in practice. The drug solution is retained under pressure in a container. The container which is also called 'gun' is held with the nozzle against the skin. Pressure on the trigger allows a fine jet of solution to emerge with great force. The solution can penetrate the skin and subcutaneous tissues to a variable depth determined by the pressure in the gun. This method is very useful for mass inoculation. Though the patient's fear of prick can be avoided but needle-less injections are not without disadvantages. Equipment is expensive and sometimes cuts are resulted from improper use of the equipment. Moreover, skill of technique is required; also bleeding and ecchymoses are liable to be produced.

INHALATION:

Volatile liquids (ether, halothane) and gases (nitrous oxide) are administered by inhalation to produce general anaesthesia. Absorption takes place through the pulmonary epithelium which presents a large absorbing surface, thus attaining high blood level rapidly. Oxygen is given to prevent or relieve hypoxemia. Amyl nitrite is inhaled to produce vasodilatation.

Non-volatile fine particles of drugs prepared as nebulizers or aerosols are also administered by inhalation. *Sprays or nebulizers* are fine particles of a drug usually suspended or dissolved in water and inhaled. They are used for the nose, throat and lungs. They may be effective locally at the point of contact or systemically after absorption through the mucus membrane. *Aerosols* are suspensions of fine solids or liquid particles in air or gas. They may be drawn into the respiratory tract on air forced into the tract on a flow of oxygen from a tank. *Steam* is also used as a vehicle to carry drugs into the lungs. In this case it is the water vapour that is inhaled. The vapour may be the important substance or it may carry needed drugs e.g. Tr. Benzoin Co Inhalation.

TOPICAL APPLICATION:

This includes applications of drugs on external surfaces, the skin and also on mucosal surfaces of the internal organs.

1. Application to the skin: Application or introduction of a drug on or into the skin can be done by:-

(a) Enepidermic: Drugs are placed in contact with the unbroken skin without the application of massage, friction or rubbing; as for example application of pastes, poultices and plasters. Similarly, creams and ointments are also applied without being rubbed into the skin. The active principles contained in these preparations may act on the

superficial part of the skin. Fomentation is also performed on unbroken skin to increase extent of circulation at the painful sites of the body.

(b) Epidermic: This method is also called "Innunction". In this case the drugs are actually rubbed into the skin so as to promote the passage of the active principles contained in bases, into the epidermal cells of the skin. Cod-liver oil or olive oil massage in children or emaciated patients is a common example.

(c) Cataphoresis: This method is also called ionic medication. A constant current is passed through skin impregnated with medicine. The electric current, thus passed, splits the medicine into acid and basic radicals. Negative pole is attached to get the current passed if either acid or basic radicals are desired to be introduced into the tissues while positive pole remains attached to the neutral side accordingly. Ionization of salicylic acid from sodium salicylate is a common example.

2. Instillation: In this case, drugs in liquid forms are poured into the body cavities with the help of a dropper. The most common organs for drug instillation, are conjunctival sac, ear and nasal cavities, and open wound. Solid preparations in the form of ointments, powders, lamellae, and tablets are also applied to these organs.

3. Insufflation: In this case finally powdered preparations are blown into the body cavities or spaces such as nose, ear and wounds with the help of a special nebulizer. The drug is distributed on the tissue surface of these organs to obtain local effect. The method is however cumbersome, therefore, alternate routes are preferred.

4. Irrigation or douching: Body cavities like urinary bladder, uterus, vagina and urethra are irrigated. Douching is mostly done for cleansing the surfaces or for application of antiseptic drugs or to heat these organs. Open wounds are also cleaned and medicated locally.

5. Insertion: Preparations like suppositories containing fatty base, such as the oil of theobroma which melts at body temperature are introduced into the rectal cavity. Similar preparations which can fit into vagina and urethra are called pessaries and bougies respectively.

6. Painting or Swabbing: When drugs are simply applied in the form of lotions on cutaneous or mucous surfaces of buccal, nasal cavity and other internal organs, the methods are called either painting or swabbing.

TRANSPORT OF DRUGS ACROSS CELL MEMBRANE

In order to reach the site of action, the drug must pass across various cell membranes. Figure 1-5 depicts the general handling of a drug in the body. The absorption, distribution and excretion of a drug is determined by the natural barriers (intestinal epithelium, blood-brain barrier and kidney epithelium) which are composed of cells with remarkably similar membranes. Whether a drug is distributed in the extra-cellular pool only or in the total body (both extra and intracellular) space is determined by barriers of cell membranes. The passage and distribution of drugs across these barriers are governed by the principles of membrane transport.

Structure of cell membrane: It is approximately 80 A° thick. It is made up of a double layer of phospholipid and associated proteins. One portion (the phosphate) of the phospholipid molecules is hydrophilic or water soluble while the other portion (the fatty acid) is water insoluble or hydrophobic. In an aqueous environment these molecules orient themselves in pairs with the phosphate "heads" towards the water and the fatty acid "tails" towards each other forming the inner part of the membrane. (Figure 1-2).

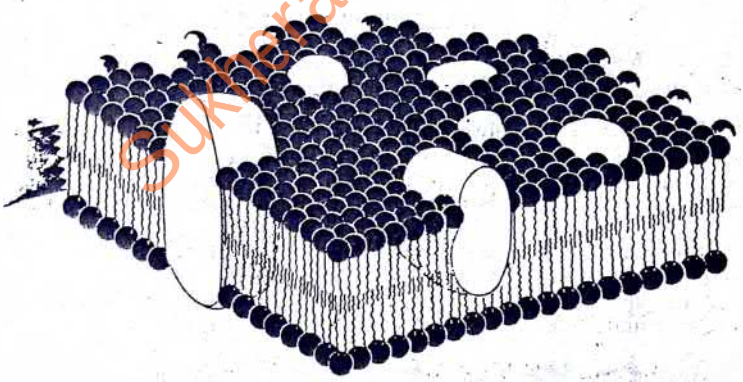


Figure 1-2. Schematic view of a cell membrane showing a lipid bilayer with protein molecules embedded in the matrix.

The protein is thought to be dispersed irregularly throughout the lipid bilayer and is capable of both lateral and vertical movement in the membrane. The proteins not only add structural strength but also act as enzyme, as carrier for transport of substances through the membrane and provide receptor sites. Because of its structure the cell membrane is highly permeable to lipid soluble substances. Cell membrane also contains minute water filled pores which allow for the passage of some water soluble and lipid insolulble substances.

TRANSPORT MECHANISMS: Drugs cross cell membranes by different mechanisms which are either passive processes or mechanisms involving the active participation of components of the membrane. Following are the mechanisms involved in transport of drugs:

1. Passive transfer:
   - (a) Simple diffusion
   - (b) Filtration
2. Spcialized transport:
   - (a) Active transport
   - (b) Facilitated diffusion
   - (c) Pinocytosis

Salient features of these transfer mechanisms are desscribed below:-

Simple Diffusion:- This is the most important transport mechanism for drugs. It is characterized by the directed movement of a solute (drug in solution) through the cell membrane from a phase of higher to a phase of lower concentration. The process requires no direct expenditure of energy by the biological system. The force which directs the movement of the solute is the concentration gradient i.e. the difference between concentrations on two sides of the membrane.

The activity of a drug to diffuse across a cell membrane is dependent on more than the concentration gradient. Other factors that influence the diffusion are as follows:

1. *Lipid solubility*: Drugs that are highly soluble in lipids have a high partition co-efficient (ratio of concentrations in the membranes and the plasma) and diffuse through cell membranes rapidly whereas drugs which are relatively lipid insoluble (low partition co-efficient) diffuse more slowly.

2. *Molecular size*: Relatively small water soluble molecules diffuse across cell membrane whether through pores or otherwise, at rates which are inversely proportional to their molecular size. The smaller the particle, the faster the rate of diffusion.

3. *Ionization*: The rate of diffusion of weak electrolytes is dependent on their degree of ionization. The greater the fraction that is non-ionized the greater is partition co-efficient and thus greater is the rate of diffusion.

Most drugs are weak acids or bases and are present in solution as both the non-ionized and ionized forms. The non-ionized molecules being lipid soluble diffuse across the cell membrane. But the ionized fraction being of low lipid solubility is usually unable to penetrate the lipid membrane.

The distribution of a weak electrolyte is usually determined by its pK_a (ionization constant) and pH gradient across the membrane. When the pK_a of a drug is equal to pH of the medium, then 50% of the drug will be ionized and 50% will be non-ionized.

Relationship between pH, pK_a and non-ionized/ionized fractions can be depicted from the Henderson-Hasselbalch equation.

For an acid:

$$pK_a = pH + \log \frac{\text{Molecular concentration of nonionized acid}}{\text{Molecular concentration of ionized acid}}$$

For a base:

$$pK_a = pH + \log \frac{\text{Molecular concentration of ionized base}}{\text{Molecular concentration of nonionized base}}$$

The ratio of nonionized and ionized fractions of a drug is thus influenced by pH of the medium thereby affecting its absorption and excretion through process of passive diffusion.

In the stomach weak acids e.g. aspirin, phenobarbitone will be mostly nonionized hence lipid soluble and would be better absorbed than from the alkaline medium of the intestine. On the other hand weak bases e.g. quinidine, ephedrine, would be highly ionized in the stomach and therefore, poorly absorbed from the stomach but would be better absorbed from the intestine with alkaline medium.

In the kidneys a weak acid is ionized by making the urine alkaline, therefore, its tubular reabsorption is decreased and its excretion in urine is increased. Similarly a weak base is ionized by making the urine acidic and its excretion is increased through decrease in tubular reabsorption.

Filtration: It is the passage of substances through pores in the cell membrane by means of their hydrostatic or osmotic pressure gradient. Water, ions and some polar and nonpolar molecules of low molecular weight diffuse through membranes indicating the existance of pores or channels. Transmembrane movement by filteration is of limited significance in the absorption and distribution of drugs. However, glomerular membrane of kidney is a good example of filter-

ing membrane. It pays an important role in urine formation and excretion of drugs and their degradation products.

Active Transport: In this mechanism the drug is transported across cell membrane against concentration gradient by an active energy requiring process, the energy being of cellular origin usually generated by the enzyme Na^+-K^+-ATP-ase. The drug forms a complex with a carrier at the outer surface of the membrane and is transported across the cell membrane to the inner surface when the drug is released from its carrier complex (Fig. 1-3)

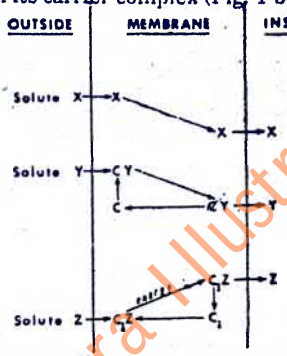


Figure 1-3. Passive diffusion, facilitated diffusion and active transport.

X is lipid soluble drug, freely diffusible in the membrane. Y is lipid insoluble drug which combines with carrier, C, at the outside surface of the membrane to form a complex CY which moves across the lipid membrane and is dissociated at the inner surface of the membrane to release Y into the intracellular space.

Both X and Y are transfered with the concentration gradient.

Z, a drug insoluble in the membrane, combines with carrier C_1. Z is actively transported against a concentration gradient.

The characteristics of active transport are selectivity, competitive antagonism by congeners, requirement for energy, saturability and movement against concentration gradient.

Active transport plays an important role in the absorption of 5-fluorouracil by the gut, and secrection of organic acids, penicillin and probenecid by the renal tubular cells and uptake of levodopa by the brain.

Facilitated diffusion: It is a special form of carrier-mediated transport in which the movement across cell membrane occurs with the concentration gradient. A carrier assists in the movement of the drug. The carrier makes the drug more soluble in the lipid membrane to allow this transport. It does not require energy.

Pinocytosis: The world pinocytosis is derived from the Greek word *pinein* (to drink). The process consists of formation of an invagination in the membrane towards the inside of the cell. This part of the membrane eventually becomes separated from the rest of the membrane and forms an intracellular vesicle. Finally the membrane of the vesicle is dissolved discharging its contents into the intracellular space. By pinocytosis very large molecules, such as proteins can be transported into or across cells. Pinocytosis requires the expenditure of energy derived from ATP.

PHARMACOKINETICS

Pharmacokinetics deals with the quantitative study of the absorption, distribution, biotransformation and excretion of drugs. Consideration of pharmacokinetic data of drugs is helpful in instituting rational dosage regimens and ensuring effective and safe drug therapy.

ABSORPTION OF DRUGS

Absorption is the process by which a drug is transferred from its site of entry to the volume of distribution.

The rate of absorption affects the onset, duration and intensity of drug action.

Factors Affecting Drug Absorption: Before considering factors which modify absorption of drugs through any specific route of administration, factors generally applicable to various routes of administration and sites of absorption are considered below:

(1) *Lipid-Water Partition Co-efficient*: Diffusion of a non-electrolyte drug across cell membrane is dependent on its lipid solubility. If drug is more lipid soluble and less water soluble i.e. it has high lipid-water partition coefficient, it will be absorbed rapidly.

(2) *Degree of Ionization*: In case of weak electrolytes absorption is dependent, in addition to lipid solubility, upon its degree of ionization which is influenced by pH. Weak acids become less ionized in an acid medium and weak bases become less ionized in an alkaline medium and vice versa. Unionized drug is lipid soluble and diffusible; ionized drug is less lipid soluble and less diffusible.

Quaternary compounds are highly ionized, lipid insoluble and are, therefore, poorly absorbed.

(3) *Drug Solubility*: Drugs given in aqueous solutions are more rapidly absorbed than when given in oily solution, suspension or solid form because they mix more readily with the aqueous phase at the absorptive surface.

(4) *Dosage Form (Preparation) of Drug*: For drugs administered in solid form such as tablets and capsules, rate of disintegration and dissolution is the limiting factor in their absorption. After dissolution, absorption depends on the particle size. The smaller the particle size, the more efficient is the absorption.

(5) *Concentration of the Drug*: Drugs ingested or injected in solutions of high concentration are absorbed more rapidly than drugs in solutions of low concentration.

(6) *Circulation at the Site of Absorption*: Increased blood flow brought about by massage or local application of heat increases absorption of drug. Decreased blood flow produced by vasoconstrictors, shock or other disease factors, slows absorption of drug.

(7) *Area of the Absorbing Surface*: Drugs are absorbed very rapidly from large surface areas such as pulmonary alveolar epithelium, intestinal mucosa etc. The area of the absorbing surface depends to a great extent on the route of administration.

Absorption of Drugs from Gastro-Intestinal Tract:

Most of the drugs are absorbted from the G.I. Tract by the transport mechanism of passive diffusion which depends upon their lipid-water partition coefficient, degree of ionization, pH of the medium and concentration gradient. These characteristics of passive diffusion and other factors which influence absorption of drugs from G.I. Tract are mentioned below:-

(1) *Area of Absorbing Surface:* Drugs are better absorbed from the small intestine than from the stomach because of the large area of absorbing surface of intestine.

(2) *pH of Gastrointestinal Fluid*: Acid drugs are rapidly absorbed from the stomach as they are in nonionized form in the acidic medium of stomach. Basic drugs are not absorbed until they reach the alkaline medium of small intestine where basic drugs being in nonionized form are rapidly absorbed.

(3) *Functional Integrity of Gastrointestinal Tract*: Increased peristaltic activity, as in diarrhoea, reduces the drug absorption. With anticholinergic drugs which delay emptying of stomach and reduce gut motility absorption is delayed. Metoclopramide which enhances gastric emptying increases the rate of absorption. Structural changes in the absorbing mucous membrane result in malabsorption syndrome. Gastrointestinal mucosal oedema (as in patients with congestive cardiac failure) depresses the absorption of drugs.

(4) *Presence of Other Agents*: Presence of some drugs in the G.I. tract may affect the absorption of other drugs. Examples are: (a) Vitamin C enhances the absorption of iron from the intestine while phytates retard it. (b) Absorption of fat soluble vitamins is reduced in

the presence of liquid paraffin. (c) Calcium present in milk and antacids containing calcium and aluminium form insoluble complexes with tetracyclines thus reducing their absorption. (d) Rapid absorption occurs if drug is given before meals. However, irritant drugs may cause nausea and vomiting if given on empty stomach and therefore they are deliberately given after food.

(5) *Lipid Solubility*: High lipid solubility of the non-ionized drugs favours its absorption from G.I. tract. Bile salts assist the absorption of fat soluble vitamins from the small intestine.

(6) *Physical State*: Liquids are better absorbed than solids and crystalloids are better absorbed than colloids.

(7) *Particle Size*: Smaller the particle size of sparingly soluble drug, better will be the absorption. Small particle size is important for absorption of corticosteroids, chloramphenicol and grisefulvin. Drugs given in dispersed or emulsified state are absorbed better e.g. vitamin A and D.

(8) *Dosage Form*: In case of tablets and capsules disintegration time which measures the rate of break up of the tablets or the capsules into the drug granules and dissolution rate are important factors affecting rate and extent of absorption.

(9) *Formulation*: Substances like lactose, sucrose, starch, calcium phosphate or lactate are commonly used as excipients in formulating powders or tablets. These substances may affect absorption as well as solubility of medicaments. Calcium and magnesium ions reduce absorption of tetracyclines.

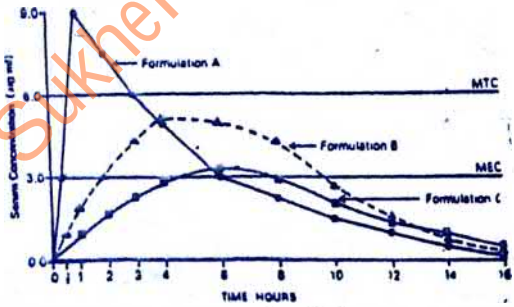


Fig. 1-4. Plasma drug level curves following administration of three different formulations of the same basic drug.

MTC = minimum toxic concentration.

MEC = minimum effective concentration.

Formulation A would produce quick onset and short duration of action compared to Formulation B whose effect would last much longer. Formulation C gives inadequate plasma levels and is, therefore, likely to be therapeutically ineffective.

Method of formulation can markedly influence drug absorption and thus determine its biological activity. A faulty formulation can render a useful drug totally useless therapeutically.
See Figure 1-4.

(10) *Chemical Nature of the Molecule*: Inorganic iron preparations are better absorbed from G.I. Tract than organic prepartions. Also ferrous salts are better absorbed than ferric salts.

(11) *Blood Flow*: In shock, blood flow to intestine is decreased and absorption from the intestine is reduced.

Absorption with Parenteral Administration:

Rate of absorption after subcutaneous or intramuscular injection depends on the following:

(1) *Solubility of the Preparation*: Suspensions or colloidal preparations are absorbed more slowly than aqueous solutions. When protamine is added to insulin to form a suspension the rate of absorption is decreased.

(2) *Blood Flow*: Massage of site of injection or application of heat increases blood flow. It speeds up absorption of the drug. Cooling the area of injection slows the absorption. In the presence of circulatory failure, absorption may be very slow. This has been observed in the subcutaneous administration of morphine to patients in shock.

Absorption is more rapid and complete after intramuscular injection than subcutaneous injection due to greater blood supply in the skeletal muscles.

When drug is injected intravenously absorption into blood is immediate and complete. The drug is rapidly distributed in the various compartments of the body.

DISTRIBUTION OF DRUGS

Once a drug has been absorbed in to the blood, it is taken to various parts of the body, its sites of action, biotransformation, and elimination (Figure 1-5). The rate, extent and pattern of distribution are determined by the drug characteritics and regional blood flow.

Ability of Drug to Cross Membranes:- Principles involving the movement of drugs across cell membranes which have already been discussed are applicable during distribution of drugs in the body. Lipid soluble drugs cross cell membranes readily and are distributed through all fluid compartments e.g. alcohol, salicylates. Drugs that are ionized at physiological pH are nondiffussible. They remain mainly in the extracellular fluid e.g. quaternary ammonium compounds, aminoglycosides.

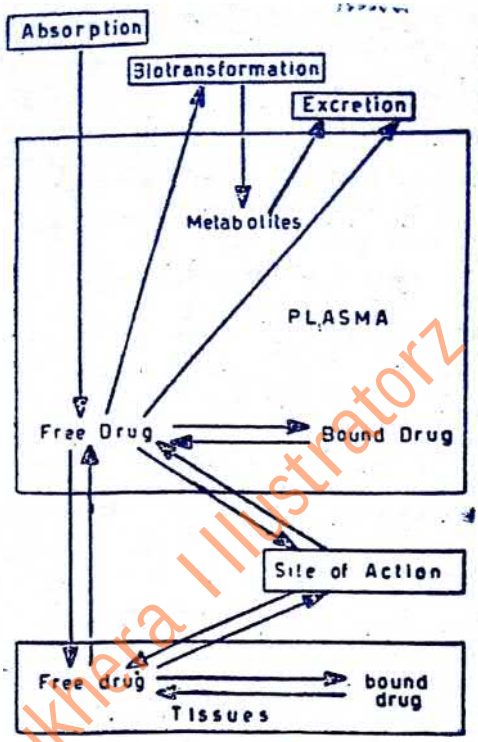


Fig. 1-5. Schematic representation of the interrelationship of the absorption, distribution, binding, biotransformation and excretion of a drug and its concentration at its site of action.

Regional Blood Flow: Initially heart, liver, kidney, brain and other highly perfused organs receive most of the drug during first few minutes after absorption. There is *redistribution* of drug upon its release from those sites as the drug reenters the circulation and is delivered to muscles, most viscera, skin and fat. Delivery to some tissues is slow and they take much longer time before equilibrium is attained.

Plasma Protein Binding: On entering the blood a portion of the drug is bound to plasma proteins (chiefly albumin) and a portion is free or unbound in solution. Protein binding is reversible. There is equilibrium between bound and free drug.

The protein bound fraction is inactive pharmacologically. It cannot leave the vascular space and is not metabolized or eliminated. Only the unbound drug is available for pharmacological action at receptors.

Protein binding becomes clinically important when it involves a high proportion i.e. more than 90% of drug in the blood. Following drugs are highly protein bound:

Phenytoin	Tolbutamide	Diazoxide
Propranolol	Prazosin	Frusemide
Warfarin	Phenylbutazone	Chlorpromazine
Tricyclic antidepressants		

Protein binding acts as temporary 'store' of a drug and tends to prevent large fluctuations in concentrations of free drug in the body fluids. It delays the metabolic breakdown and excretion of drug because only the unbound drug can be metabolised and excreted.

The extent of protein binding of drugs may be altered under following conditions leading to increased drug effects which may be of clinical significance.

Disease: Plasma proteins are altered both in quantity and chemical characteristics in renal and hepatic disease. There is decrease in drug binding and the concentration of free drug increases resulting in increased drug effects.

Drugs Competing for Protein Binding Sites:- Sometimes two drugs compete for the same plasma protein binding sites. One drug may displace another, the freed drug then diffusing into tissues and possibly causing toxic effects when potent drugs are involved. An example of this occurs when phenylbutazone is started on a patient who has been stabilized on the oral anticoagulant, warfarin. Phenylbutazone replaces warfarin from the plasma binding sites and toxic blood level leading to haemorrage can occur. When such drug must be used at the same time dosage adjustment must be made to avoid adverse effects.

Storage of Drugs in Tissues: Apart from plasma proteins some drugs have selective preference for certain tissues and they are concentrated in these tissues e.g. mepacrine is stored in liver, chloroquine in liver and retina, arsenic in keratinous tissue, calcium in bones and lipid soluble substances in body fat depots. These depots are in equilibrium with free circulating drugs.

Some areas of the body are not readily accessible to drugs due to anatomic barriers such as brain.

Distribution to the Brain:- To enter the brain, drugs must pass through a biologic membrane called *Blood Brain Barrier*. This

barrier separates the blood and cerebrospinal fluid. It is composed of connective tissue called glia. The membrane favours the passage of lipid soluble, nonionized substances and prevents the entrance of strongly ionized and non-lipid soluble drug. Examples: (1) Thiopentone sodium being highly lipid soluble immediately enters brain after intravenous administration and is used for induction of general anaesthesia. (2) Physostigmine, a tertiary amine and lipid soluble drug, can enter the brain and antagonizes central toxic effects of atropine whereas neost-igmine, a quaternary ammonium compound, highly ionized and of low lipid solubility cannot enter the brain and is not effective for the treatment of acute atropine toxicity. (3) Levodopa crosses blood brain barrier but dopamine cannot do so, therefore levodopa is administered and not dopamine for treatment of Parkinsonism. (4) After intramuscular administration adequate concentration of penicillin in cerebrospinal fluid is not achieved on account of its low lipid solubility.

Distribution Across the Placenta: Drugs may pass into the foetal circulation across the placenta mainly by the process of simple diffusion. Generally nonionized lipid soluble drugs move readily across the placenta whereas water soluble drugs move more slowly and in inverse proportion to their molecular size. The rate and direction of this exchange is dependent on concentration gradients and the rate of blood delivery. The unborn infant thus can be exposed to the pharmacological effects of drugs taken by the mother at time when its ability to respond and to metabolize drugs is not fully developed.

All the commonly used hypnotics, narcotics, anaesthetics, cardiac glycosides, adrenal corticosteroids, hypotensive agents, sympathomimetics, sulphonamides and many of antimicrobial drugs cross the placental barriers.

Drugs and Pregnancy:- Drugs may prove toxic to the developing foetus, when administered during the first trimester of pregnancy. As this is the period of organogenesis the drugs may produce congenital malformations. Development of seal limbs (phocomelia) following thalidomide administration is well documented tragedy. Androgens administered during pregnancy can produce masculinization of the female foetus. Vigorous tetracycline therapy of the pregnant mother may result in deposition of the drug in the foetal bones and this may interfere with their development.

Drugs administered during the last trimester of pregnancy may interfere with the vital fuctions of the foetus. For example (1) Morphine administered to the mother during labour may produce foetal asphyxia. (2) Anticoagulants may initiate haemorrhage in the newborn. (3) Administration of diazepam to the mother may sometimes cause hypothermia and hypotonia in neonates. (4) Antithyroid drug, carbimazole, produces neonatal goitre.

Drugs liable to cause congenital abnormalities are known as *teratogens*. It is important for the physician to be aware of teratogens since birth defects can be minimized by avoidance of these agents. Drugs should be given during pregnancy only after the potential risks to the foetus have been carefully considered.

For the treatment of various diseases which occur during pregnancy selection of the drug should be made carefully. For urinary tract infection, which is common during pregnancy, penicillins are the preferred treatment. They are not teratogenics. Tetracyclines are contraindicated. Co-trimoxazole should be avoided during pregnancy. There is no evidence of foetal damage from cephalosporins and metronidazole. Chloramphenical should not be used at the end of pregnancy. Aminoglycosides can cause foetal eighth nerve damage.

For the management of hypertension methyldopa and beta blockers are often used. They are not teratogenics. Diuertics should not be used. For the treatment of bronchial asthma, aminophylline, salbutamol by inhalation and steroids have been used safely in all stages of pregnancy.

BIOTRANSFORMATION

(DRUG METABOLISM)

Chemical alteration which a drug undergoes within a living organism is called Biotransformation.

Almost all drugs undergo biotransformation, which however varies greatly in different species and in individuals of the same species.

Drug metabolism mostly takes place in the liver but it also occurs in the gut, blood, skin, kidneys, lungs and adrenal glands. Intestinal bacteria may also be involved in drug metabolism.

The metabolism of drugs usually makes them transformed into less lipid soluble and more water soluble compounds so as to facilitate their excretion by kidney, by preventing their tubular reabsorption. Occasionally a drug is metabolised to a product which may be less water soluble e.g. conversion of diazepam to desmethyldiazepam.

Effect of Biotransformation on Pharmacological Activity:

Biotransformation of drugs may result in their inactivation, activation or modification. Usually there is inactivation of drugs but not always.

Some inactive drugs are activated by metabolism. The inactive precursors are called *Prodrugs*. Examples are (i) 6-Mercaptopurine is

converted to 6-Mercaptopurine ribonucleotide. (ii) Chloral hydrate itself inactive is converted to trichloroethanol which acts as hypnotic. (iii) Phenacetine is metabolised and converted to Paracetamol which acts as analgesic.

Sometimes an active drug is converted into another product which retains pharmacological activity and may be even more potent than the parent drug e.g. conversion of diazepam into oxazepam.

Drug-Metabolism Enzymes: Biotransformation is usually brought about by various enzyme systems of the body. Some drugs may undergo spontaneous changes without involvement of enzymatic reactions e.g. alkylating agent mustine.

Enzymes in biotransformation may be described under the following two groups:

Microsomal Enzymes: They play a predominant role in biotransformation. These enzymes are located in microsomes, the subcellular components of the smooth endoplasmic reticulum of cells in many organs, especially the liver. Cytochrome P-450 reductase and cytochrome P-450 are the primary components of the enzyme system. The microsomal enzymes represent a mixed-function oxidase system. In the presence of nicotinamide adenine dinucleotide phosphate (NADPH) and oxygen the enzyme system transfers one atom of oxygen to the drug while another atom of oxygen is reduced to form water.

Nonmicrosomal Enzymes: Soluble enzymes found in mitochondria of cells are responsible for the metabolism of a relatively few compounds which are, however, of clinical significance.

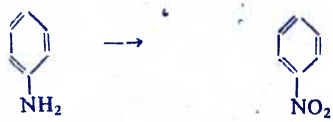
Chemical Reactions: Reactions involved in biotransformation are classified into two groups:

(a) *Nonsynthetic Reactions*:	Oxidation, Reduction, Hydrolysis.
(b) *Synthetic Reactions:*	Acetylation, Alkylation, Glucuronide Conjugation etc.

Drug metabolism involving such reactions generally occurs in two phases.

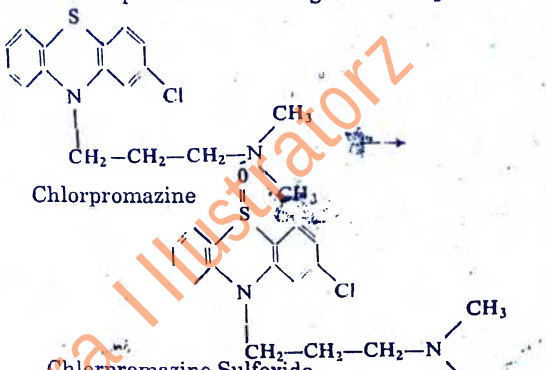
Phase I Metabolism: Drugs are converted to more polar (water soluble) compounds. This occurs through *non-synthetic reactions*. Mainly it is oxidation but sometimes there is reduction or hydrolysis. The reactions occur mainly with assistance of microsomal enzymes. These metabolites usually have only minor structural differences from the parent drug but may exhibit different pharmacological actions. For example the aromatic hydroxylation of phenobarbitone abolishes its hypnotic activity, while metabolism of azathioprine produces the powerful antimetabolite 6-mercaptopurine.

(5) *N-oxidation*: Aniline is changed to nitrosobenzene. Trimethylamine is changed to trimethylamine oxide.



Aniline Nitrosobenzene

(6) *Sulfoxidation:* Chlorpromazine is changed to chlorpromazine sulfoxide.



Chlorpromazine

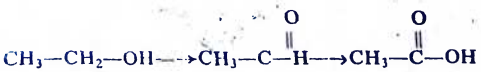
Chlorpromazine Sulfoxide

(7) *Deamination*: Amphetamine is changed to phenylacetone.

(8) *Desulfuration*: Parathion is changed to paraoxon which is more toxic.

Following are examples of *nonmicrosomal oxidations*:

(1) Alcohol dehydrogenase oxidizes ethylacohol to acetaldehyde which is changed to acetate by aldehyde dehydrogenase.



Ethanol Acetaldehyde Acetic acid

(2) Xanthine oxidase converts hypoxanthine to xanthine and xanthine to uric acid.

(3) Tyrosine hydroxylase converts tyrosine to dopa.

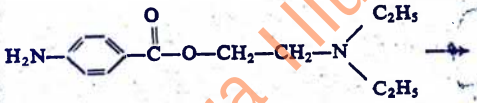
(4) Monoamine oxidase is important for the metabolism of catecholamines and serotonin.

Reduction: It occurs in both the microsomal and non-microsomal metabolizing systems. It is less common than oxidation. Examples are: reduction of chloramphenicol to the arylamine, prontosil to sulfanilamide, progesterone to pregnanediol, and chloral hydrate to trichloroethanol.

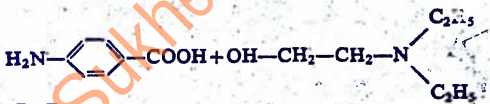
Chloral Hydrate Trichloroethanol

Hydrolysis: Acetylcholine, suxamethonium, procaine and other drugs which contain ester linkage are readily hydrolysed in the body.

Procaine is rapidly hydrolysed by pseudocholinesterase in the blood to paraaminobenzoic acid (PABA) and diethylaminoethanol.



Procaine



PABA Diethylaminoethanol

Conjugation: It involves the coupling of a drug or its metabolite with an endogenous substrate.

Following are important conjugation reactions:-

(1) *Glucuronide Conjugation*: It is the most common conjugation reaction. It occurs frequently with phenols, alcohols, carboxylic acids and compounds containing amino or sulphydryl groups.

The mechanisms of reaction is as follows:

Uridine diphosphoglucuronide + ROH ------>

RO glucuronide + Uridine diphosphate

Where ROH is the drug or its metabolite.

Glucuronides are generally without pharmacological activity. They are highly water soluble at the usual pH of the urine, consequently they are rapidly eliminated through the kidney.

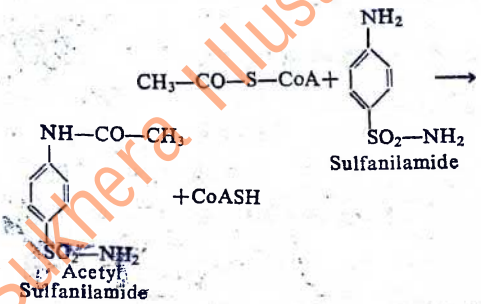
Also they may be secreted into the bile by an active transport process. It can be split up by the intestinal bacteria and free drug can be reabsorbed. This *enterohepatic circulation* of the drug can greatly prolong the action of the drug.

(2) *Glycine Conjugation*: It converts benzoic acid to hippuric acid. Salicylic acid is metabolized by glycine conjugation.

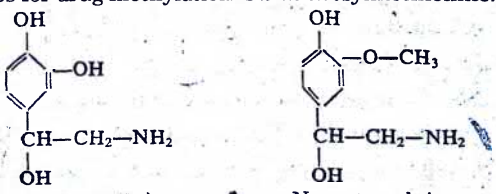
(3) *Sulfate Conjugation*: Phenols, alcohols or aromatic amines undergo sulfate conjugation. The sulfate is 3-phospho-adenosine-5-phosphosulfate (PAPS).

(4) *Acetylation*: Sulphonamides, isoniazid, aminopyrine and PAS are transformed by this mechanism. Acetyl coenzyme is the acetyl donor.

The acetylating ability of different patients may vary considerably. They may be rapid acetylators or slow acetylators. This is genetically determined. In case of isoniazid a low degree of acetylation shows correlation with incidence of toxic reactions such as peripheral neuritis.



(5) *Methylation*: Adrenaline and noradrenaline are metabolized in part to metanephrine and normetanephrine respectively by a process of O-methylation. Nicotinic acid is metabolized to N-methylnicotinic acid, an example of N-methylation. The source of methyl groups for drug methylation is S-adenosylmethionine.



Factors Affecting Drug Metabolism:

1. *Age*: Drug metabolism is usually feeble in the new-born infant. In the foetus microsomal enzyme system may be completely absent. For this reason, the new born, particularly the premature baby, requires special consideration when drugs are administered, e.g. Chloramphenicol may cause grey syndrome (cyanosis and circulatory collapse) in neonates. In old age the ability to metabolize drugs decreases due to decreased hepatic functioning.

2. *Pathological Conditions*: Liver being the prominent site of drug metabolism, frequently there is depression of drug metabolism in hepatic disease. Jaundice depresses the glucuronic acid conjugation and the oxidative function of the liver microsomes.

3. *Nutrition*: Starvation and malnutrition depress drug metabolism due to decreased amount of proteins. Glycine stores are depleted in starvatian and glycine conjugation is altered.

4. *Species Difference:* The rate of metabolism of drugs may vary considerably in different species. Generally drugs are metabolized faster in laboratory animals than in man. Examples are phenylbutazone, pethidine and barbiturates. Experimental data regarding drug metabolism obtained in animals should not be accepted as such in human beings.

5. *Genetic Differences*: Within the same species there are great individual variations in drug metabolism. It has been shown that the variation is under genetic control. (This has been discussed in detail under Pharmacogenetics). Examples are acetylation of isoniazid. hydrolysis of suxamethonium by pseudocholinesterase.

6. *Sex*: Difference in rates of metabolism of certain drugs e.g. hexobarbitone, among males and females are known in certain animals. This is due to increased hepatic microsomal enzyme activity in male. The sex differences in drug metabolism are under the influence of the sex hormones.

7. *Route of Administration*: The oral route can result in extensive hepatic metabolism of some drugs (*first-pass effect*) before the drug reaches its sites of action. Propranolol is about 80% metabolised before it reaches the systemic circulation. Lignocaine and glyceryl trinitrate may be completely metabolised so that bioavailability following oral administration is almost zero. Passage through the liver and thus extensive initial metabolism is avoided by the subligual route.

8. *Circadian Rhythm*: The rate of hepatic metabolism of some drugs follows a diurnal rhythm in rats and mice. This may be true in humans as well.

Effects of Drugs on Drug Metabolism:

Some drugs may either stimulate or inhibit drug metabolism.

Stimulation: The activity of the microsomal oxidative enzyme is stimulated by a number of drugs, e.g. phenobarbitone, phenytoin, phenylbutazone, carbamazepine, meprobamate, rifampicin. All these drugs are lipophilic at physiological pH. The increased activity is mainly due to *Enzyme Induction*. There is increased rate of synthesis of new enzyme molecules. This is accompaied by hypertrophy of the endoplasmic reticulum of the liver cells.

As a variety of drugs is normally metabolized by the microsomal oxidative enzymes, the induction of this enzyme system can alter the quantitive action and toxicity of drugs. Enzyme induction can thus lead to drug interaction. This is illustrated by the following example.

The dose of oral anticoagulant, warfarin, is individually adjusted under the control of the patient's clotting time. If the patient is simultaneously treated with another drug, such as phenobarbitone, which induces the microsomal enzyme formation, it increases the rate of metabolic disposal of warfarin so that more drug has to be given to achieve the desired effect, so that more drug has to be given to achieve the desired effect. But if the administration of phenobarbitone is discontinued, the microsomal enzyme level again falls towards normal and what was previously the therapeutic dose of warfarin now suddenly becomes toxic. Severe, even fatal bleedig may occur because of failure to adjust the dose of warfarin.

Inhibition: Concurrently administered drugs can also lead to an inhibition of enzyme acivity. Sulphonamides decrease the metabolism of phenytoin so that phenytoin blood levels becomes toxic. Similarly, cimetidine decreases the metabolism of propranolol leading to enhanced bradycardia.

The metabolism of tolbutamide is inhibited by drugs such as phenylbutazone or coumarins. The inhibition is manifested as exaggerated action of tolbutamide leading to prolonged hypoglycaemia.

EXCRETION OF DRUGS

Kidney is the most important excretory organ for drugs. Excretion of drugs and their metabolites into the urine involves three processes:

(*i*) Glomerular filtration: This is the more common route of renal elimination. The free drug is cleared by filteration and the protein bound drug remains in the circulation.

(*ii*) Active tubular secretion: Both weak acids and weak bases have specific secretory sites in proximal tubular cells. Penicillins are eliminated by this route as well as about 60% of Procainamide. Probenecid inhibits tubular secretion of penicillin.

(*iii*) Passive tubular reabsorption: Only the nonionized lipid soluble drugs are reabsorbed. Ionized drugs are not reabsorbed and are, therefore, excreted in urine. Ionization of weak acids and bases depends on urine pH. This fact is utilized in enhancing the renal elimination of salicylates and barbiturates following overdosage.

If renal function is impaired as in case of disease or old age, then there is a decrease in the elimination rate of drugs that usually undergo renal excretion e.g. streptomycin, gentamicin. These drugs are liable to accumulate in the body to produce toxic effects in patients with impaired renal function. In these patients, doses of such drugs must be appropriately reduced.

Bile: Some drugs which are metabolized in the liver are excreted through bile. In general minimum molecular weight of substances eliminated in the bile is 300 to 600. Novobiocin and erythromycin appear in high concentration in the bile. Phenolphthalein is excreted in bile and is repeatedly reabsobed from the jejunum and reexcreted in bile thereby exerting a prolonged action. (*Enterophepatic circulation*).

Intestines: Anthracene purgatives which act mainly on the large bowel are partly excreted into that area from the blood stream after their absorption from the small intestine.Heavy metals are also excreted through intestines and can produce intestinal ulceration.

Lungs: Volatile general anaesthetics are excreted unchanged through lungs. Paraldehyde and alcohol are partially excreted by the lungs and impart their odour to breath.

Skin: Arsenic and mercury are excreted in small quantities through the skin. Arsenic gets incorporated in the hair follicles on prolonged administration.

Saliva: Iodides and metallic salts are excreted in the saliva. Lead compounds deposited as lead sulfide produce blue line on the gums.

Breast Milk: Nearly all drugs taken by the mother are likely to be found in milk though not necessarily in the concentration that can affect the infant. Milk being slightly more acidic (pH 7.0) than plasma, weak bases become more ionized with decrease in pH will have equal or higher concentration in milk than plasma. Non-electrolytes like ethyl alcohol and urea readily enter into the milk independent of pH.

Following drugs given to mother appear in milk in amounts sufficient to affect the infant adversely.

Penicillin (allergy), ampicillin (diarrhoea), chloramphenicol (grey syndrome), metronidazole, isoniazid, antithyroid drugs, iodides, ergotamine, anticancer drugs, anthracene purgatives and high dose corticosteroids.

BIOAVAILABILITY

Bioavailability of a drug (availability of biologically active drug) is defined as the proportion of the active drug that reaches the systemic circulation in unchanged form after administration of the pharmaceutical preparation containing such active drug.

In the case of intravenous administration bioavailability will be 100% but most drugs are given orally and numerous factors can interfere with absorption and decrease bioavailability.

The bioavailability of a drug may vary from one dosage form to another and for the same dosage form it may vary according to the pharmaceutical formulation. Thus dosage forms that satisfy the chemical and physical standards laid down in pharmacopoeia (*chemically equivalent*) may not necessarily yield similar concentrations of the drug in the blood or the tissues (*biologically non-equivalent*) and thus may not provide equal therapeutic benefits (*therapeutic non-equivalent*).

The bioavailability from dosage forms is of great importance in therapeutics especially in the case of life saving drugs, antibiotics and drugs with a narrow margin of safety e.g. chloramphenicol, digoxin, anticonvulsants and anticoagulants. Differences in the rate of absorption of the active drug of pharmaceutical products from different manufacturers or from different production batches may cause patients to be overmedicated or undermedicated. As a result adverse effects or therapeutic failure may be the outcome especially with potent drugs with low therapeutic index. Indiscriminate change from one preparation to another must be avoided to prevent serious consequences.

Figure 1-4 illustrates a study of the comparative biological availability of three preparations containing the same pure chemical entity in different pharmaceutical formulations. The biologic availability varies considerably. The three preparations although chemically identical, are therapeutically not equivalent.

Factors Affecting Bioavailability: A large number of factors are involved in determining the bioavailability of drugs.

(1) *Quality Control in Manufacturing and Formulation*: If the drug is administered in a solid form (tablet, pill, capsule) it has to be dissolved before the active drug is released and absorbed from the G.I. tract. The disintegration and dissolution time depends on many factors, such as (a) compression pressure applied during manufacture of tablets (b) moisture content (c) nature of additives e.g. excipients, lubricants, disintegrants (d) particle size of the active drug (e) polymorphism i.e. variations in the arrangemnt of molecules or ions to form a crystal. Various polymorphism forms are chemically indistinguishable. However, they differ significantly in physical properties such as

solubility and dissolution rates. (f) nature of diluent or vehicle which although may be pharmacologically inert yet it may interfere with drug absorption by physicochemical means e.g. adsorption of active principles or complex formation with them.

These factors affect disintegration of the dosage form and dissolution of the drug and hence rate and extent of drug absorption.

Proper quality control during manufacturing and formulations of pharmaceutical products is essential to ensure uniform bioavailability.

(2) *First Pass Metabolism*: It is the presystemic metabolism i.e. metabolism of drug that occurs en route from the gut lumen to the systemic circulation.

Some drugs e.g. levodopa and chlorpromazine are metabolized in the gut wall. However in most cases first pass metabolism occurs in the liver. This is so complete with glyceryl trinitrate and lignocaine that bioavailability following oral administration is zero. Bioavailability of orally administered drugs with a high first pass metabolism is relatively low. Examples of such drugs are: Propranolol, labetalol, metoprolol, nortriptyline, paracetamol, pentazocine, prazosin and propxyphene.

In patients with severe liver disease a greater proportion of drugs that normally undergo extensive first pass metabolism is absorbed unchanged and consequently bioavailability of these drugs in such patients is increased and the usual therapeutic dose in them will lead to toxic effects.

(3) *Factors Affecting Absorption of Drugs from G.I. Tract*, such as, pH of gastrointestinal fluids, area of absorbing surface, functional integrity of G.I. tract, presence of food and other substances in the stomach, blood flow and physicochemical properties of the drug have already ben discussed under absorption of drugs. All these factors are applicable to bioavailability as the rate and extent of absorption depends on them.

PLASMA CONCENTRATION OF DRUGS

The level of drug found in the plasma at any time *after* administration is determined by (*i*) the rate of absorption, (*ii*) the rate of distribution to the tissues, and (*iii*) the rate of removal from the tissues and plasma by metabolism and excretion.

After intravenous administration, peak level of the drug in plasma is achieved immediately (Figure 1-6). However after oral administration, peak level of the drug is achieved gradually in accordance with the rate and extent of absorption.

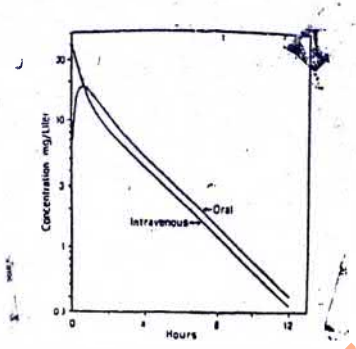


Figure 1-6. Curves of plasma concentration of a drug following I.V. and oral administration

The onset, intensity and duration of action of the drug is determined by the rate and extent of absorption, distribution and elimination by metabolism and excretion. The onset of action of an orally administered drug occurs after suffi-cient absorption and distribution takes place and the minimm effective concentration is achieved. The plasma level gradually increases until the peak plasma level is reached at which time the maximal drug resp-onse occurs. After this peak level elimination occurs more rapidly than absorption. The drug effects are terminated when the plasma concentr-ation falls below the minimum effective concentration (Figure 1-7).

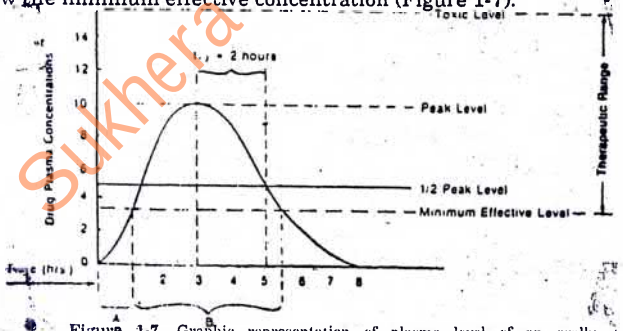


Figure 1-7. Graphic representation of plasma level of an orally administered drug. A indicates period of onset of time before onset of action. B indicates the priod of time for duration of action.

Plasma half-Life ($t_{1/2}$) is a useful parameter. It is defined as the time required for the concentration of drug in the plasma to decrease to one half of its initial value. For example if the initial plasma concentration of a drug is 100 mg and if the half life is one hour only 50 mg will remain in the plasma at the end of one hour.

Time (Hour)	0	1	2	3	4
Plasma concentration (mg)	100	50	25	12.5	6.25

It should be noted from the above mentioned figures that after each hour the concentration is decreased to one-half of the concentration in the previous hour.

Plasma half-lives vary greatly between drugs as is evident from half-lives of various drugs mentioned below:

Penicillin G	0.5 (Hours)	Tetracycline	8.7	(Hours)
Amoxycillin	1.0	Doxycycline	12.0	
Ampicillin	1.2	Digoxin	36.0	
Cephaloridine	1.7	Diazepam	55.0	
Morphine	2.0	Phenylbutazone	84.00	
Gentamicin	2.3	Digitoxin	198.0	

Plasma half-life denotes how quickly a drug is removed from the plasma by biotransformation or excretion. Since drugs require a minimum concentration in the plasma to produce pharmacological action a drug which is eliminated quickly requires more frequent dosing than a drug with a long half-life.

Plasma half-life thus indicates the duration of action of the drug and, therefore, it determines the frequency of administration of the dose of the drug for therapeutic effectiveness. Drugs with a short t 1/2 of 2 to 3 hours will need to be administered more frequently, whereas those with a long t 1/2 may only need to be administered once daily.

Simple calculations show that 93.75% of drug is eliminated after four half-lives. For complete elimination, more time is required. Drugs that are administered repeatedly at intervals shorter than the elimination time show increasing peak and minimum plasma concentrations. The level will eventually reach a "plateau" of constant peak and minimum values which can be maintained over a long priod by repeated doses (Figure 1-8).

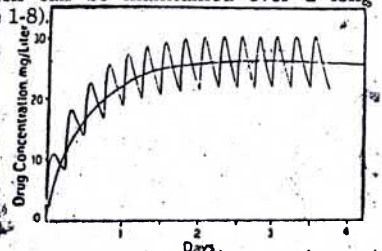


Figure 1-8. Rise of drug concentration to a plateau (steady state) level during repeated oral administration of a constant dose.

PHARMACODYNAMICS

Pharmacodynamics is the study of biochemical and physiological effects of drugs and their mechanism of action. It deals with what the drug does to the body, as well as, where the drug acts and how the drug acts.

Action of drug can be either local or systemic. When it occurs within the immediate vicinity of the site of application and it generally does not affect tissues in other areas, it is called *local action*. The action of drug which occurs after its absorption and distribution is called *systemic action*. It occurs in tissues away from the site of administration.

Drug action may increase or decrease normal function of tissues or organs but cannot confer any new function on them. Thus the drug produces only a quantitative and not a qualitative change in the function of the target organ.

No drug produces a single effect. The desired or therapeutic effect is called the *primary effect*. The other effects that occur as a result of drug action are called *secondary effects*. These effects may be desirable or undesirable. Undesirable effects are called *adverse effects*. Example: ganglion blocking drug, Mecamylamine, lowers blood pressure and is used for treatment of hypertension. This is primary effect. But it causes dryness of mouth and constipation. These are secondary effects and being undesirable, they are the adverse effects.

MECHANISM OF DRUG ACTION: Drugs bring about their effects as a result of complex chemical and physical interactions with the molecules of living systems.

Drugs may act through one or more of the following mechanisms:

I. Action on Specific Receptors: Vast majority of drugs shows a remarkably high structure activity specificity. Drugs exert their action by selectively combining with receptors which are macromolecular components of the cell. The macromolecule thereby becomes excited and undergoes configurational change, (Configuration =arrangement of atoms or groups in a molecule) which alone or through eliciting a chain reaction of conformational changes may manifest itself as effect. (Conformation=a particular shape of molecule that arises through the normal rotation of its atoms or groups about single bonds). An effect can be the contraction of a muscle, the increase of secretion, a change in membrane permeability etc.

To occupy the receptor, a sufficient number of drug molecules must be present in the immediate vicinity of the receptor i.e. in the *biophase*. The drug concentration in the biophase is dependentupon the physicochemical nature of the drug and the tissue barriers in the body.

DRUG-RECEPTOR INTERACTIONS:

Drugs could combine with receptors reversibly or irreversibly.

(a) *Reversible Combination*: Most drugs combine reversibly with a receptor site, within a cell or on its surface to form a drug-receptor complex.

$$D + R \underset{K_2}{\overset{K_1}{\rightleftharpoons}} DR$$

Where D = Drug, R = receptor and DR = drug receptor complex and K_1 and K_2 are the association and dissociation constants respectively.

This reaction obeys the mass law. Consequently the concentration of the free receptors (R), the concentration of the occupied receptors (DR) and the concentration of the free, un-bound drug in a biophase (D) will be in equilibrium.

Binding between drugs and the receptor is weak, and probably involves electrostatic and hydrogen bonds, and van der Waals forces.

(*b*) *Irreversible Combiation*: Some drugs combine with receptors irreversibly. This is usually seen with alkylating agents which produce highly reactive carbonium ions which bind covalently with receptors. These include cytotoxic drugs and irreversible alpha blockers (e.g. phenoxybenzamine) which produce noncompetitive antagonism, their effects are not overcome by increasing the concentration of the agonist.

AFFINITY AND INTRINSIC ACTIVITY:

The two important parameters of drug action are affinity and intrinsic activity.

Affinity is the tendency of a drug to form a combination with the receptor. It is expressed by the reciprocal of the dissociation constant.

The fraction of receptors occupied at any given time is proportional to the affinity of the drug for receptor and its concentration. In general, drug with high affinity will occupy more receptors at any given concentration than drug with low affinity. However if the concentration of drug with low affinity is increased there will be increase in the number of receptors occupied by it as compared to drug with high affinity with unchanged concentration. This forms the basis of competition for receptor sites.

As stated above, action of drug depends not only upon its affinity to form a combination with receptor but also on its capacity to initiate chain reaction resulting in its effect. This capacity is called

Intrinsic activity or efficacy. It is defined as the capacity to stimulate for a given receptor occupancy. It is determined by the molecular properties of the drug.

The configurational pecularities that determine the intrinsic activity are different from those which determine the affinity to the receptor.

For the characterization of a given drug, both the affinity and the intrinsic activity are to be considered.

Figure 1-9 illustrates two dose-response curves for drugs (I) and (II) which have equal intrinsic activities (judged by having similar magnitude of response) but the drug (II) has lower affinity as it is required in greater concentration to elicit similar response.

Figure 1-9. Log dose-response curves of drugs with equal intrinsic activities but different affinities.

Figure 1-10 shows nearly equal affinities of drugs III, and IV but different intrinsic activities.

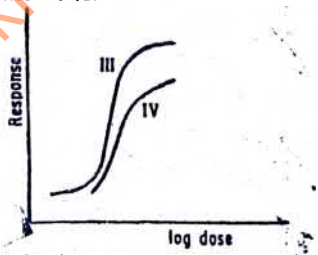


Figure 1-10. Log dose-response curves of drugs with nearly equal affinities but different intrinsic activities.

An *agonist* is a drug that produces a pharmacological effect when it combines with a receptor. It has affinity as well as intrinsic activity. Examples: Acetylcholine, noradrenaline.

An *antagonist* is a drug that has affinity but no intrinsic activity. It has no effect of its own but it reduces or abolishes effect of an agonist. Examples: Atropine, Propranolol.

Antagonism is either competitive if the drug-receptor interaction is reversible or non-competitive if the drug-receptor complex is irrevisible. Blockade by a competitive antagoist can be overcome by higher concentration of the agonist (Figure 1-11).

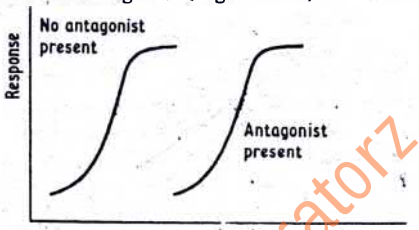


Figure 1-11. Log dose-response curves of a drug showing the effect of an antagonist. (Competitive antagonism)

Partial agonist has affinity and some intrinsic activity. It may antagonize the action of other drugs which have higher intrinsic activity. Drug (IV) in figure 1-10 is a partial agonist.

II. Action on Specific Enzymes:

Enzymes, like receptors, are protein macromolecules with which substrates interact to activate or inhibit enzymatic activity.

Inhibition of enzyme activity may be competitive (reversible) and relatively short lasting. Examples are allopurinol which inhibits the enzyme xanthine oxidase; neostigmine which inhibits the enzyme cholinesterase.

Alternatively the inhibition of enzyme activity may be non-competitive (irreversible) and long lasting, persisting until new enzyme protein has been synthesized. For example Organo phosphorus compounds which irreversibly phosphorylate the active site of the enzyme cholinesterase.

Given below are few examples of drug actions through enzyme inhibition:

1. Anticholinesterases: Hydrolysis of acetylcholine is inhibited so as to prolong duration of action of acetylcholine. They are of two types:

(a) Reversible: Physostigmine, Neostigmine.
(b) Irreversible: Organophosphorus compounds.

2. Carbonic Anhydrase Inhibitors: They inhibit the enzyme carbonic anhydrase so as to decrease formation of H^+ and HCO^-_3 ions e.g. Acetazolamide.

3. Monoamine Oxidase Inhibitors: Oxidation of amines such as Catecholamines, Serotonin and Tyramine is inhibited by these drugs e.g. Iproniazid, Nialamide.

4. Aldehyde Oxidase Inhibitors: Oxidation of acetaldehyde is inhibited e.g. disulfiram.

5. Dopa Decarboxylase Inhibitors: Conversion of dopa to dopamine is inhibited. e.g. Methyldopa.

6. Xanthine Oxidase Inhibitors: Conversion of hypoxanthine and xanthine to Uric acid is reduced e.g. Allopurinol.

7. Antimetabolites: Analogues (Compounds structurally similar to a natural substrate) combine with enzymes but fail to undergo the enzyme-catalyzed reactions and thus inhibit entire chain of metabolic processes, e.g. methotrexate, 5-Fluorourasil, 6-mercaptopurine.

III Non Specific Interactions:

A variety of drugs which differ widely in their chemical structure exerts common pharmacological action. It would be difficult to assume that they all produce similar action by combining with a receptor of high degree of structural specificity.

Volatile general anaesthetics interact with membranes to depress excitability. Their diversity of structure suggests a relatively nonspecific biophysical mechanism of action and their individual potencies correlate well with the physical property of their oil-water partition coefficients.

DOSE-RESPONSE RELATIONSHIP

A given dose or concentration of drug produces in a biological system a measurable degree of action. The biological system may be a piece of smooth muscle suspended in solution in organ bath (*in vitro*) or it may be a whole animal (*in vivo*). Usually larger doses produce a greater action while smaller doses produce smaller action. The study of relationship between dose and response is of great importance in the science of pharmacology. There are two types of dose-response relationship: (*i*) the graded type, and (*ii*) the quantal type.

Graded Dose-Response Curve: It is defined as a quantitative curve in which increasing doses of a drug produce varying changes in effects. The dose which produces the first noticable effect is called 'threshold dose'. Further increases in dose result in larger effects

until a maximum, a 'Ceiling effect' is reached and further increase of the dose does not elicit further increase of the effects.

Figure 1-12 shows the graded responses to varying doses of acetylcholine on the contractions of isolated piece of small intestine recorded on kymograph. Anything between no contraction at all to the full contraction is possible, depending upon the concentration of drug applied to the tissue.

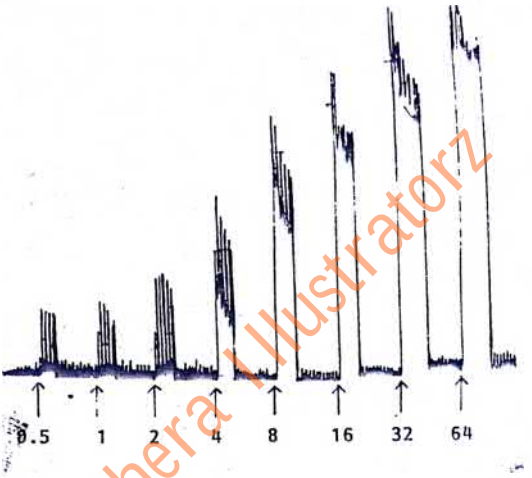


Figure 1-12. Effect of varying concentrations of acetylcholine on isolated small intestine of rabbit showing graded responses. Arrows and figures underneath denote micrograms of ACH added to the fluid bathing the tissue.

When drug concentrations and their responses are plotted on arithmatic scale, the dose-response curve is a hyperbola. If drug concentrations are plotted on logarithmic scale on the abscissa, but responses on arithmatic scale on the ordinate then the dose-response curve is sigmoid (S shaped). There are advantages of such a semilog dose-response curve. The middle part of the sigmoid curve is linear. Drugs with the same action at a receptor but with different potencies usually show parallel dose-response curves. Their potencies can be compared by easily determining the doses showing 50% maximal responses. On account of these advantages the graded dose-response curve is usually plotted on semilog scale.

Figure 1-13 shows dose response curves for two drugs (A and B). The curves are hyperbola when doses are plotted on arithmatic scale

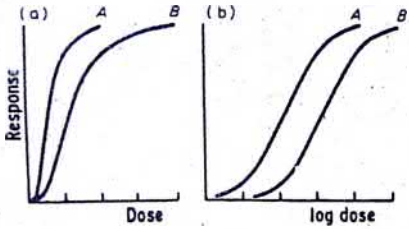


Figure 1-13. (a) Dose-response curves of two drugs A and B. Plotted on arithmatic scale. Curves are hyperbola.

(b) Log dose-response curves of the same two drugs A and B Curves are sigmoid shaped. Middle parts of the curves are linear and parallel.

(Panel a) and sigmoid when doses are plotted on logarithmic scale (Panel b). The sigmoid curves are parallel. Both drugs produce the same maximum response but potency of drug B is less than that of drug A as higher doses of drug B are required to produce response similar to drug A.

Quantal Dose-Response Curve: A quantal response is an all-or-none response to a drug. This can be studied in whole animals (*in vivo*). Each animal is categorized as responding or non-responding according to the priorly decided criterion of response, such as dead or alive, cured or not cured.

Specified doses of a drug are administered to a number of test animals and the frequency with which a certain drug evokes a stated, fixed, all or none effect (e.g. death) is determined. The results of this type of experiment can be plotted as log dose-percentage curve.

The quantal curve is essentially a curve that describes the distribution of minimum doses that produce a given effect in a population of test animals. Some animals in a population being sensitive respond to smaller doses of a drug while some animals being resistant need very large doses.

Usually the sensitivity of animals to different doses of a drug is distributed normally with respect to the logarithm of the dose. Thus, for a given drug, if log dose is plotted on the horizontal axis and percent responding (dead) to the various dose levels is plotted on the vertical axis, a Gaussian (normal) distribution is obtained. A graphic representation of this Gaussian distribution curve is shown in Fig. 1-14. The quantal dose response curve is a cummulative graph of the frequency distribution curve. It has sigmoid shape. It can be used to determine LD_{50} and ED_{50} values of a drug.

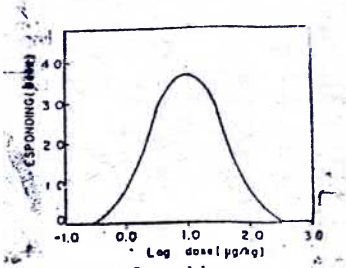


Figure 1-14. Quantal dose-response curve.

Median Effective Dose: It is the dose of a drug required to produce a specified intensity of effect in 50% of individuals. It is abbreviated as ED_{50}.

Median Lethal Dose: It is the dose of a drug required to kill 50% of experimental animals. It is abbreviated as LD_{50}. It is the measure of toxicity of a drug.

Therapeutic Index: It is the ratio of the median lethal dose to the median effective dose.

$$\text{Therapeutic Index (TI)} = \frac{LD_{50}}{ED_{50}}$$

It is an approximate assessment of the safety of the drug. The larger the therapeutic index, the safer is the drug. Some drugs such as Digitalis, have low therapeutic index. They are liable to cause serious toxicity with slight increase in dose.

Margin of Safety: Therapeutic Index is based on median doses. These doses tell nothing about slopes of the dose-response curves for therapeutic and toxic effects, that is, to what extent the two curves may overlap. Hence therapeutic index is only an approximate assessment of the relative safety of the drug. To overcome this deficiency, a more useful expression, margin of safety, is applied. It is the ratio

$$\frac{LD_{0.1}}{ED_{99.0}}$$

Where $LD_{0.1}$ is the minimum lethal dose for 0.1 percent of the population and $ED_{99.9}$ is the minimum effective dose for 99.9 percent of the population.

STRUCTURE ACTIVITY RELATIONSHIP

The activity of a drug is intimately related to its chemical structure. The structure activity relationship is quite specific and minor modifications in the drug molecules may result in major changes

in the pharmacological action. The levo-isomer of adrenaline is ten times more potent than its dextroisomer.

Structure activity relationship has been utilised to develop valuable therapeutic agents from parent compounds so as to attain better therapeutic efficiency and to act as competitive antagonists and to be helpful in understanding the mechanism of action.

I-Synthesis of New Compounds with More Specific Actions and Fewer Adverse Effects:

(a) Chlorpromazine used as antipsychotic drug has many other actions such as antihistaminic, anticholinergic and hypotensive effects. By structural modification of chlorpromazine molecule compounds like trifluoperazine have been synthesized having more potent antipsychotic effect and negligible antihistaminic and hypotensive effects.

(b) Cardiac action of procaine is too transient for therapeutic use on account of its rapid hydrolysis by pseudocholinesterase. Procainamide, structurally related to procaine, is resistant to hydrolysis hence it is a valuable drug for cardiac arrhythmias.

(c) Benzyl penicillin, being inactivated by HCl in the stomach cannot be administered orally and has to be injected. New penicillins, phenoxymethyl penicillin, ampicillin, amoxycillin are not inactivated by HCl and are given orally.

(d) Thiazide diuretics like polythiazide and bendrofl-umethiazide are more potent than the parent compound, cholor-othiazide. Smaller doses of these drugs are needed to cause effective diuresis.

(e) Mydriatic and cycloplegic action of atropine has the disadvantage of lasting for about a week. Its substitute, homatropine, has such actions only for a day.

(f) Nicotinic acid used in treatment of pellegra produces itching and flushing of skin. A related compound nicotinamide has the same efficacy against pellegra without itching and flushing of skin.

II-Synthesis of Structurally Related Competitive Antagonists:

(a) Para-amino benzoic acid (PABA) is an essential growth factor for several micro-organisms. Para-amino salicylic acid which shows structural similarity to PABA acts by competing with PABA for the uptake by certain bacteria. Absence of PABA ultimately arrests the multiplication of bacteria.

(b) Nalorphine is structurally related to morphine and is used to antagonize respiratory depression due to acute morphine poisoning.

III-Understanding the Mechanism of Drug Action:

(a) Adrenaline stimulates both alpha and beta adrenergic receptors. A related drug Isopropylarterenol (Isoprenaline) selectively stimulates beta receptors while a very closely similar compound, dichloroisopropylarterenol (DCI) blocks beta receptors.

(b) Chlorpromazine is antipsychotic drug. A structurally similar compound imipramine is an antidepressant.

These examples emphasize the importance of certain chemical groups for the drug action and also give some idea about their mechanism of action.

COMPLEX DRUG ACTIONS

Whereas action of drugs at molecular level due to interactions with receptors and enzymes is usually specific and discrete, it is quite complex in the various organ systems and in the intact animals. Some important complexities are discussed below.

COMBINATION OF DRUGS

In clinical practice frequently more than one drug is administered at the same time. Two drugs given at the same time may:

1. act entirely independently on two separate sites.
2. produce similar actions on the same organ (synergism)
3. oppose each other's action (antagonism)

SYNERGISM

The word synergism is derived from two Greek words, *Syn* (together) and *ergo* (work) and indicates a pharmacologic co-operation. This usually results in enhancement of drug effects. There are various ways for two drugs to act in concert.

I. Summation: Two drugs with the same effect, when given together produce an effect that is equal in magnitude to the sum of effects when the drugs are given individually i.e. drug effects are additive. Example: general anaesthetics.

II. Potentiation: One drug enhances the action of the other drug. Two drugs may have similar action but the combined effect is greater than the simple algebric sum of the action of two drugs. Examples are: ammonium chloride itself a weak diuretic potentiates diuretic effect of organic mercurials. Antibacterials, trimethoprim and sulphamethoxazole potentiate and the combination is bacteriocidal with wide range of activity.

Sometimes a drug potentiates action of the other drug without having similar pharmacological actions itself. Examples are: Anticholinesterases potentiate the action of endogenous acetylcholine by inhibiting the enzyme cholinesterase and thus protecting acetylcholine.

ANTAGONISM

The phenomenon of opposing action of two drugs on the same biological system is known as drug antagonism. The word antagonism is derived from Greek words, *anti* (against) and *ago* (act).

An antagonist is a drug which reduces or abolishes the effect of an agonist. Whereas agonist possesses both affinity and intrinsic

activity, a pure antagonist possesses only affinity but no intrinsic activity. Examples of pure antagonists are atropine, tubocurarine. Some drugs are agonist-antagonists. Example is succinylcholine which is agonist itself; it produces muscle fasiculations but is antagonist for acetylcholine, preventing its access to the receptor so that paralysis ultimately occurs.

Antagonism is of three types:

I. Chemical Antagonism: There is simple chemical reaction between agonist and antagonist whereby the former loses its activity. Examples: antacids (sodium bicarbonate, aluminium hydroxide) neutralize HCI by chemical reaction.

II. Physiological Antagonism: The two drugs act independently on different receptors. They have opposite actions. A typical example is histamine-adrenaline antagonism. Histamine causes capillary vasodilation, fall in blood pressure and bronchoconstriction by acting on histaminergic receptors. Adrenaline causes arteriolar constriction, rise in blood pressure and bronchodilatation by acting on adrenergic receptors. Both histamine and adrenaline are normally present in the body.

III. Pharmacological Antagonism: This occurs when an antagonist prevents an agonist from acting upon its receptors to produce an effect.

Pharmacological antagonism is of two types:

(a) *Competitive Antagonism*: Antagonist competes with agonist in a reversible fashion for the same receptor site. The antagonism can be overcome by increasing the concentration of the agonist at the receptor site. Example: acetylcholine and atropine antagonism at muscarinic receptors. In the presence of antagonist the log dose-response curve of the agonist is shifted to the right indicating that a higher concentration of agonist is necessary to achieve the same response as when the antagonist is absent. Also maximum height of the curve can be achieved indicating that the action of the antagonist has been overcome. This results in parallel shift of the log dose-response curve towards right side (Fig. 1-11).

(b) *Noncompetitive Antagonism*: The antagonist binds irreversibly to the receptor site or to another site that inhibits the response to the agonist. This antagonism cannot be overcome no matter how much concentration of the agonist is increased. Although log dose-response curve shifts to the right the slope will be reduced and the maximum response will diminish. This results in nonparallel shift of the log dose-response curve. (Fig 1-15) Example: Phenoxybenzamine and [illegible] receptors.

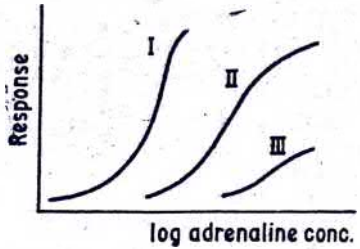


Figure 1-15. Log dose-response curves of a drug showing the effects of increasing concentrations (I, II, III) of the antagonist (non-competitive antagonism).

TOLERANCE

Tolerance is an acquired resistance to drug which develops on its repeated administration over prolonged period. It is manifested by the fact that more drug is required to produce the same pharmacologic effect.

Tolerance mostly develops with drugs which affect the C.N.S. (narcotic analgesics, barbiturates, alcohol) and seldom with drugs which act mainly on other parts of the body.

Chemically related substances may induce *cross-tolerance* for each other. Frequently chemically unrelated compounds (morphine, methadone) produce similar gross pharmacological actions and produce cross tolerance.

Tolerance is frequently but not always accompanied by *physical dependence*. When this occurs, abrupt termination of the drug produces a serious condition called *abstinence syndrome*, which can be promptly reversed if the drug is readministered. *Psychic dependence* is a craving to take the drug for pleasure or for relief of discomfort.

Present knowledge about the mechanism of tolerance can be expressed only in general terms. Attempts to find a more tangible explanation at the cellular or molecular levels has led to many speculations.

Change in Receptor Sensitivity: Continued administration of narcotic analgesics leads to a gradual decrease of the sensitivity of opioid receptors. More drug has to be administered to produce an effect. As opioids by combining with the specific receptors restrict the release of neurotransmitters, their withdrawal results in a loss of synaptic inhibition. Withdrawal syndrome is thus a manifestation of the loss of synaptic inhibition.

Enzyme Induction: Some drugs induce adaptive degrading enzyme formation. There is increased metabolism of the drug and

there is decreased duration and intensity of action. It has been observed that chronic alcoholics develop lower blood levels even if the drug is administered intravenously; thus they must eliminate alcohol from the body more readily.

Decreased Intestinal Absorption: Chronic administration of same drug orally for many years leads to decreased intestinal absorption. Examples; regular ingestion of arsenic trioxide by the natives in some parts of Austria. Similar resistance to arsenic can be developed in experimental animals on chronic feeding. Chronic alcoholics absorb less alcohol from the G.I. tract than non-alcoholics.

TACHYPHYLAXIS

Certain drugs when given repeatedly at short intervals usually in experimental animals produce each time smaller magnitude of response to the same doses. This phenomenon is called tachyphylaxis.

It differs markedly from tolerance. Whereas tolerance develops slowly, tachyphylaxis is a rapidly developing phenomenon. In case of tolerance, increase in dose manifests initial response but in tachyphylaxis, increase in dose does not manifest increase in response.

Tachyphylaxis is usually seen with drugs which act by depleting the stores of endogenous active substances; for example, indirectly acting sympathomimetics, ephedrine, amphetamine. If such a drug is repeatedly administered before the stores are replenished, there will be progressivly less action. Directly acting sympathomimetics, adrenaline, phenylephrine do not show tachyphylaxis. (Figure 1-16).

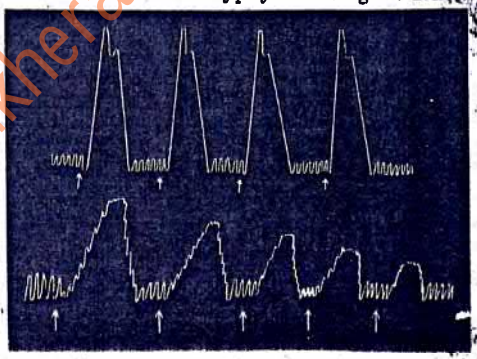


Figure 1-16 Effect of repeated doses of adrenaline (upper graph) and ephedrine (lower graph) on blood pressure in anaesthetised dog. Arrows denote administration of the same doses.

Effect of repeated doses of adrenaline is similar. It does not show tachyphylaxis. Exphedrine, an indirectly acting drug, shows tachyphylaxis as effect of repeated doses is progressively decreased.

Another mechanism of tachyphylaxis is seen with drugs which combine with the receptors and dissociate slowly. When the second dose is given some of the drug administered previously is still occupying the receptors thus a new receptor drug combination is inhibited, no stimulus is generated and no action is produced. An example is suxamethonium.

CUMULATION

Drugs which are slowly metabolized or strongly bound to plasma proteins are eliminated from the body slowly. Such drugs are liable to accumulate in the body especially if they are administered frequently so that intake exceeds elimination. The amount of drug in the body increases until a new equilibrium is reached between intake and output. In other words the drug accumulates in the body. For example Digitoxin is strongly bound to plasma proteins and, therefore, eliminated slowly. It readily accumulates and if not administered with caution it may cause toxicity. On the other hand Ouabain is almost unbound to proteins thus clearing the body rapidly. The danger of cumulative toxicity with ouabain is practically nonexistent.

Highly lipid soluble drugs are stored in the body's fat depots. In the stored form they are completely inert. If fat depots are rapidly depleted as in starvation the drug is released and can cause toxicity. The halogenated hydrocarbon type insecticides (e.g. DDT) are typical examples.

In some instances appropriate body concentration of a drug cannot be obtained in any way but by cumulation. The bromide anion is typical example. It is eliminated by the kidney which does not distinguish between chloride and bromide. To achieve therapeutic concentration, the drug has to be administered in frequent doses for several days. A low salt diet increases the accumulation. Conversely, if toxic amounts of bromide have been accumulated in the body, elimination is hastened by feeding large amounts of sodium chloride.

Sometimes the drug itself is not cumulative but its effect is. Monoamine oxidase inhibitors if repeated frequently the enzyme has no time to regenerate leading to serious inhibition of the metabolism of amines. This results in a cumulative pharmacological effect without effective cumulation of the causative agent.

Metallic silver may be permanently deposited in the skin giving it a bluish discoloration. Iron after prolonged therapeutic use may be deposited in various organs, causing siderosis while lead, thorium, radium and strontium are deposited in the bones.

PHARMACOGENETICS

Pharmacogenetics is the branch of pharmacology devoted to the study of genetic factors in the individual response to drugs.

Not all persons respond to drugs in exactly the same manner. Considerable individual variations occur in response to drugs not only quantitatively but even qualitatively.

Response of the individual to a drug is under genetic control. Inherited characteristics that are controlled by many genes (multifactorial inheritance) show a continuous trait and normally distributed. A typical example is the distribution of height in human population. It is depicted by a *unimodal*, bell-shaped normal (Gaussian) distribution curve. If the characteristic is detrmined by one single gene, an individual either has it or lacks it. Consequently the trait in the population will be discontinuous. It is described statistically by a *bimodal* or polymodal distribution.

Polymorphism is the state in which, in the same population, two or more discontinuous forms of species occur.

Genetic control over a pharmacologic response occurs on the level of synthesis of specific proteins. Two specific protein structures which play an outstanding role in the action of drug are the receptor and the drug metabolising enzyme. As the study of receptors is more complex, practically all pharmacogenetic studies at present are concentrated on the effect of genetic control on the drug metabolizing enzymes.

The interindividual variation in the rate of drug metabolsim for most of drugs shows normal distribution. Hence, approximately two percent of the normal population will have a rate of metabolism more than two standard deviations from the mean while another two percent will have a rate that is less than two standard deviations from the mean (Figre 1-17). Drugs showing discontinuous variation in the rate of metabolism are much less common. However, they are of great clinical significance on account of unusual drug response which may occasionally be dangerous.

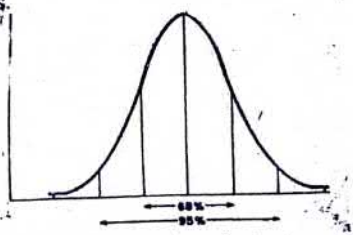


Figure 1-17. Normal (Gaussian) distribution curve depicting interindividual variation in the rate of drug metabolism in the population.

While prescribing drugs genetic differencs must be considered in selecting the best drugs and the doses most approximate for each individual patient. Furthermore when unexpected drug reaction occurs the possibility of an inherited genetic anamoly should be considered and detailed family history should be taken.

Given below are few examples which illustrate possible genetic involvements responsible for variation in rate of drug metabolism and hereditory disorders leading to variation in drug responses.

1. *Acetylator Status*: The population is divided into fast and slow acetylators, the proportion varying between ethnic groups. The characteristics are controlled by a single pair of genes, fast being dominant over slow. This is best exemplified by Isoniazid which undergoes conjugation with acetyl coenzyme A in the liver to form acetylated isoniazid. The *bimodal* distribution shows that after administration of a 9.8 mg/kg dose, one group of individuals will show plasma concentration of about 1 mcg/ml and the other group will show concentration of 4.5 mcg/ml. The populations are thus termed either slow inactivators or fast inactivators.

Slow acetylators are likely to show drug accumulation and toxicity such as peripheral neuropathy while fast acetylators are likely to demonstrate a failure to respond.

Hydralazine, procainamide, phenelzine and some sulphonamides are also acetylated before excretion. Serious toxic effects may occur with these drugs in slow acetylators.

2. *Pseudocholinesterase Deficiency*: Suxamethonium (succinylcholine) is used as skeletal muscle relaxant in anaesthesia and in shock therapy. Its duration of action is very short as it is rapidly destroyed by plasma pseudocholinesterase. The presence of pseudocholinesterase is determined by a gene the lack of which is recessively inherited. If suxamethonium is given to a person who lacks the enzyme, the drug causes unusually prolonged muscular paralysis, including apnoea. Incidence of this deficiency is one patient in 3000.

3. *Acatalasia*: Hydrogen peroxide, which is used as antiseptic is rapidly converted to oxygen and water by the enzyme catalase which is present in most tissues and blood. The production of catalase is under control of a single gene the lack of which causes a condition called acatalasia. Hydrogen peroxide will be ineffective in patients lacking such a gene.

4. *Glucose-6-Phosphate Dehydrogenase (G-6-PD) Deficiency*: This deficiency predisposes erythrocytes to haemolysis as a result of the oxidative stress imposed by some commonly used drugs.

The mechanism responsible for haemolysis is complex but it seems to involve initially a shortage of NADPH; the reduced form of the cofactor nicotinamide adenine dinucleotide phosphate. NADPH is

produced alongwith conversion of glucose-6-phosphate to 6-phosphogluconate catalysed by the enzyme glucose 6-phosphate dehydrogenase. NADPH itself then serves as a cofactor for glutathione reductase, an enzyme that converts glutathione to the reduced form. In normal individuals the red cell membrane is maintained in a functional state by adequate supply of reduced gluthathione which keeps membrane proteins in a reduced and operative condition and thereby protecting them from oxidation by highly reactive drug metabolites. A genetically induced glucose-6-phosphate dehydrogenase enzyme deficiency results in decreased reduced glutathione leading to altered cell membrane and thereby causing haemolysis.

Glucose-6-Phosphate dehydrogenase deficiency is most common in persons who belong to ethnic groups originating in the Mediterranean basin and negroes. The defect is determined by a sex-linked gene carried on X-chromosomes. Males are more likely to show drug related haemolysis than females.

Following drugs are liable to cause haemolysis in G-6-PD deficient subjects:

(*a*) Antimalarials: Primaquine, pamaquine, chloroquine, quinine.

(*b*) Sulphonamides: Sulphapyridine, sulphanilamide, sulphamethox-pyridazine.

(*c*) Analgesics: Aspirin, phenacetine, acetanilide, phenazone.

(*d*) Nitrofurons: Nitrofurantoin, nitrofurazone, furazolidine.

(*e*) Sulphones: Dapsone, sulfoxone.

(*f*) Miscellaneous: Dimercaprol, chloramphenicol, nalidixic acid, quinidine.

5. *Acute Intermittent Porphyria*: Acute porphyria can be precipitated in susceptible individuals by barbiturates and other enzyme inducing drugs due to increased acivity of the enzyme delta-aminolaevulinic acid synthetase which enhances porphyrin sythesis. Other drugs responsible for porphyria are sulphonamides, pentazocine, meprobamate, glutethimide, tolbutamide, methyldopa, alcohol, griseofulvin and oral contraceptives.

6. *Malignant Hyperpyrexia*: This is a rare but potentially fatal condition. Rapid increase in body temperature with or without muscle rigidity occurs in the sensitive individuals given general anaesthetic halothane and/or suxamethonium. The condition is familial and appear to be inherited as an autosomal dominant trait. Patients are often young, healthy individuals who unexpectedly develop these symptoms. There appears to be disturbance with the intracellular distribution of calcium.

Dantrolene, a directly acting skeletal muscle relaxant, is used for the treatment of malignant hyperpyrexia. It acts by decreasing the amount of calcium released from the sarcoplasmic reticulum.

7. *Methaemoglobinaemia*: Haemoglobin is converted to methaemoglobin by oxidation of the iron content to the ferric form. This is normally prevented by the enzyme methaemoglobin reductase. Some individuals lack this enzyme. In such individuals, drugs such as sulphonamides, phenacetine, nitrates, quinones which act as oxidising agents produce methaemoglobinaemia.

8. *Warfarin Resistance*: This is very rare. Affected patients show resistance to all coumarin anticoagulants although they are absorbed and metabolized normally. The resistance is hereditary. Such patients require nearly 20 times as much drug to produce the expected increase in prothrombin time, an amount that could cause a fatal haemorrhage in the usual patient.

9. *Vitamin D Resistance*: Patients with this trait fail to metabolize vitamin D to the active form and develop vitamin D resistant rickets.

10. *Atropinesterase*: Some strains of rabbits are resistant to the toxic effects of atropine due to an atropine hydrolyzing enzyme in their liver. The presence or absence of this enzyme is genetically controlled.

DOSES OF DRUGS

The study of the dosage of drugs is called *Posology*.

Dose is the quantity of drug given to the patient at one time. The quantity should be adequate to produce certain therapeutic effects. It should not be too small or too large. If too large, undesirable effects will appear. However there are individual variations and the same drug in the same doses may show marked differences in response. Some persons may be highly sensitive and respond to a very small dose, while others are more resistant and fail to respond except in very large doses. This is known as normal *biological variation*.

The British Pharmacopoeia gives two doses, one a minimum and the other a maximum dose. By *minimum* dose is meant the minimum amount which is expected to produce some therapeutic effect. By *maximum dose* is meant the largest amount which one can use without risk of producing toxic effects. These doses are meant for oral administration unless otherwise stated, and are for adults i.e. for persons between 18 and 60 years. When a drug is meant for administration by any other route, the dose to be used as well as the route of administration is specifically mentioned.

The United States Pharmacopoeia gives only an *average dose*. It is for the prescriber to adjust the dose according to the requirements of the patient.

Daily dose is the total amount of the drug which can be given in the day either as a single dose, as with emetine hydrochloride, or the total amount is to be divided into three or four doses. The total daily dose of sodium aminosalicylate is 10 to 15 G and this should be given in divided doses.

Total dose is the total amount of the drug to be given to the patient during the full course of treatment. It should not be exceeded on account of toxicity. Thus the dose of colchicine is 1/2 to 1 mg. Total dose is 8 mg.

Single dose means that only one dose should be given during the day. Single dose of Emetine is 30 to 60 mg.

For the treatment of certain diseases it is necessary to use a large dose initially to produce an effective concentration as quickly as possible and then to use small dose to maintain the effect. The former is known as initial or *loading dose* and the latter as *maintenance dose*. The initial dose of sulphadiazine is 3 G and subsequent dose is I G. Initial dose of digoxin is 1 to 1.5 mg and the maintenance dose is 0.25 mg once or twice daily.

For certain drugs the British Pharmacopoeia does not prescribe any dose and expects the physician to select the dose according to the requirements of the patients; for example, no dose is given for insulin and some of the antibiotics.

Median Lethal Dose (LD_{50}) is the amount of drug which is fatal to 50 percent of experimental animals. It is the measure of acute toxicity of the drugs.

Median Effective Dose (ED_{50}) is the amount of the drug which produces the desired therapeutic effect in 50 percent of experimental animals. It is the measure of effectiveness of the drug.

Therapeutic Index (Therapeutic Ratio) is the ratio of median lethal dose to the median effective dose. The higher is the ratio the safer is the drug.

Toxic Dose is the amount of drug which produces undesirable harmful effects of serious nature and liable to endanger the life of the patient.

Fatal Dose is the amount of drug which is liable to cause death due to toxic effect of the drug in a normal person.

FACTORS WHICH MODIFY ACTIONS AND DOSES OF DRUGS

Many factors influence the dosage and actions of drug. The dose should be adequate to produce the desired action. If it is too small, the drug will not produce the desired action. If it is too large it will produce toxic effects which are not desirable e.g. small dose of morphine produces euphoria, large dose produces analgesia and very large dose produces unconsciousness and causes death due to respiratory failure.

Dose and action of a drug are interdependent to a great extent. Therefore important factors which influence these two aspects of drugs will be considered together.

1. Age:- Adult dose is for a person between the age of eighteen and sixty years. Children are given small dose. For children dose may be calculated as a fraction of adult dose in accordance with the age of the child. Various rules followed for calculating the dose are given below:-

1. Young's:- $\frac{\text{Age}}{\text{Age} + 12} \times$ adult dose

e.g. for a child 3 years old $\frac{3}{3+12} = \frac{3}{15} = \frac{1}{5}$ th adult dose

2. Dilling's:- $\frac{\text{Age}}{20} \times$ adult dose

e.g. For a child 5 years old $\frac{5}{20} = \frac{1}{4}$ th adult dose

There are exceptions to these rules for individual drugs e.g. Children take iron' belladonna, sulphonamides and chloral hydrate very well but they can take only very small doses of opioids.

In infants the dose should be calculated according to the weight of the infant. For this purpose Clark's formula should be applied.

$$\text{Infant dose} = \frac{\text{weight in pounds}}{150} \times \text{Adult dose}$$

Old persons require lesser doses on account of decreased ability to inactivate or excrete the drug. Above 60 years of age the dose should be decreased to 3/4 th of adult dose.

2. Body Weight: For abnormally lean or obese individuals the dose of the drug should be suitably adjusted according to the weight of the patient.

3. Sex: Women are usually more susceptible than men to the effects of certain drugs partly because of lesser muscular mass. Doses

for the women should be less than men. Morphine produces sedation in men but in women sedation may be preceeded by excitement. Ephedrine produces nervousness, excitation and tremors of extr-emeties in women.

Precautions should be observed in giving drugs to women during pregnancy, menstruation, labour and lactation.

During pregnancy uterine stimulants, strong purgatives and drugs likely to have teratogenic effects should be avoided. Especially during first trimester no drug should be given unless absolutely necessary. (See Page 28).

During *menstruation* salicylates and strong purgatives should be avoided as they may increase the bleeding.

During *labour* morphine should be avoided as it crosses placenta and depresses respiration in the new born.

During *lactation* drugs may be excreted through milk and affect the infant e.g. some purgatives, Penicillin, Chloramphenicol, oral anticoagulants. (See Page 37).

4. Routes of Administration: When the drug is given intravenously onset of action is rapid and intense in character. When the drug is given orally onset of action is slow but duration is prolonged.

Magnesium sulphate when given orally acts as a purgative. When given intravenously it acts as C.N.S. depressant.

Oral dose of a drug is always greater than when it is given parenterally. The dose for subcutaneous or intramuscular injection is greater than intravenous dose e.g. oral dose of ergometrine is 0.5 to 1 mg., intramuscular dose is 0.25 to 1 mg. and intravenous dose is 0.125 to 0.5 mg.

5. Time of Administration: Presence of food in stomach delays the absorption of drugs. Onset of action is slow. When the drug is given on empty stomach, it may act as irritant and nausea and vomiting may occur. Hypnotics are more effective when given at bed time. If given during day time they are less effective and higher dose is required to produce sleep.

6. Effect of Climate: In hot and humid climate the metabolism is low. Purgatives act better in summer. Diuretics act better in winter. Oxidation of drugs is low at higher altitude.

7. Racial Difference: Castor oil acts as a purgative in most of the population but it is ineffective in case of Chinese people. When ephedrine is instilled in the eyes of fair coloured people, there is dilatation of pupil of eye but in Negroes this effect of ephedrine is absent.

8. Dosage Form (Preparation) of Drug: Onset of action is rapid when the drug is given in liquid form or as a powder as compared to drug given in the form of a tablet or a pill as these have to be disintegrated slowly before absorption.

9. Age of Drug: Activity of many drugs is modified if they are kept for a long time. Drugs should not be used after expiry date. Out dated Tetracyclines give rise to excretion of amino acids in urine. Chloroform and carbon tetrachloride become toxic if kept for long.

10.Absorption, Distribution and Excretion of Drugs: Drugs which are rapidly absorbed and excreted quickly can not maintain effective concentration for a prolonged period e.g. sulphonamides, salicylates, penicillin. Doses of these drugs have to be administered more frequently. Drugs which are quickly absorbed but excreted slowly are liable to accumulate in the body and may produce toxic effects e.g.digitalis. Doses of such drugs have to be administered much less frequently after the desired therapeutic effects have been obtained with initial doses.

11.Pathological Condition: When liver or kidneys are not functioning properly, intensity and duration of action is increased. Under such circumstances, the dose of the drug has to be decreased to avoid appearance of toxic effects.

Severity of the disease to be treated necessiates modification of dose. A patient suffering from severe pain will tolerate large doses of morphine. Dose of diphtheria antitoxin does not depend on the age of the child but upon the amount of toxin that has to be neutralized. Dose of insulin depends upon the severity of diabetese mellitus irrespective of the age of the patient.

12.Tolerance: It is unusual resistance to ordinary dose of the drug. It is seen with Opioids (morphine, pethidine) when taken repeatedly over prolonged period. Doses many times the usual therapeutic dose is required to obtain the same therapeutic effect. There is usually *cross-tolerance* amongst the members of the same chemical group. (See Page 53).

13.Tachyphylaxis: It is rapidly developing tolerance seen after repeated administration of drug at short intervals.This occurs with indirectly acting drugs such as ephedrine which acts by releasing noradrenaline from adrenergic stores. After repeated administration these stores are exhausted. Pharmacological action is not restored even after increase in dose. (See Page 54).

14.Idiosyncracy: All individuals do not respond in a similar way to the same drug. The term idiosyncracy (*idiso* = one's own or peculiar, *sykrasi* = a mixing together) is used to describe abnormal drug response on the administration of first dose. Difference in

response may be attributed to genetic conditions affecting drug metabolism as well as to receptor sensitivity.

The study of genetic factors affecting drug response is known as *pharmacogenetics* e.g. suxamethonium, a skeletal muscle relaxant has duration of action 4-6 minutes in most of individuals. In some persons due to genetic abnormality it can not be metabolised, the action of the drug may remain for many hours, with very serious consequences. (See Pages 56-59).

15.Hypersusceptibility: In some patients the expected response of drug may be exeggerated e.g. 10 mg of morphine produces sleep usually for 4 to 6 hours. In cases of hypersusceptibility sleep may be much prolonged (10 to 12 hours) alongwith other depressant effects.

16.Allergy: It is the abnormal response of drug resulting from antigen-antibody reaction leading to liberation of Histamine and Histamine-like substances and therefore there may be skin rashes, urticaria, bronchoconstriction and fall of blood pressure. Allergic reactions may occur immediately or may be delayed for many days.

Immediate and acute allergic reaction leads to ACUTE ANAPHYLACTIC SHOCK which is dangerous to the patient and may be even fatal, e.g. penicillin, sera, vaccines. One must take every precaution to prevent such mishaps.

(*i*) Before giving penicillin injection, one must enquire from the patient about previous allergic reactions to drugs and history of diseases such as bronchial asthma, eczema etc.

(*ii*)A test dose shold be given. Few drops are injected into the skin and response of the patient is watched for the next 10-15 minutes. If redness and swelling occurs at the site of injection, the patient may be allergic to penicillin and he should not be given full dose of penicillin.

(*iii*) Even if the test is negative one must keep drugs ready to deal with emergency of acute anaphylactic shock i.e. injections hydrocortisone and adrenaline. Antihistamines usually do not play any important role in the management of acute anaphylactic shock. Antihi-stamines should be given after the administration of hydrocortisone and adrenaline.

Sometimes skin rashes or urticaria alongwith fever and pain in joints and swellig of lymph nodes may occur after few days of administration. It is delayed type of allergy. It is called SERUM SICKNESS type reaction.

17.Combination of Drugs: When two or more than two drugs are given together, action may be increased or decreased.

I. Synergism means increase in the action of drug due to presence of another drug. It is of two types:

(a) *Summation (Addition)*: When the final effect of two drugs is equal to algebric sum of effects of two individual drugs, it is called addition synergism. Such drugs act on the same receptors or the mechanism of action is the same e.g. general anaesthetics, like ether and chloroform.

(b) *Potentiation*: When the final effect is much more than the simple addition of action of two drugs the phenomenon is known as potentiation. It is believed that two drugs act through different mechanisms. e,g. Co-trimoxazole (Septran) consists of sulpham-eth-oxazole and trimethoprim. The mode of action of these two drugs is different. Sulphamethoxazole competes PABA and trimethoprim acts against folic acid. Combination of these two drugs results in bacter-iocidal action instead of becteriostatic action of individual drugs.

II. Antagonism means decrease in the action of drug due to presence of another drug. It is of three types.

(a) *Chemical Antagonism:* There is chemical reaction e.g. Sodium Bicarbonate acts as antacid by neutralizing HCI of stomach through chemical reaction.

(b) *Physiological Antagonism:* When two drugs e.g. histamine and adrenaline which are otherwise normally present in the body have opposite action on two different types of receptors, the antagonism is known as physiological antagonism. Histamine causes fall in blood pressure and bronchoconstriction by action on histamine receptors. Adrenaline causes rise in blood pressure and bronchodilatation by action on adrenergic receptors.

(c) *Pharmacological Antagonism:* Both the drugs act on the same receptors. The drug which occupies the specific receptors and initiate action is called AGONIST e.g. acetylcholine, adrenaline. The drug which occupies the specific receptors, does not initiate action and blocks action of other drug is called ANTAGONIST e.g. atropine, propranolol.

Pharmacological antagonism is of two types:

(*i*) *Competitive:* There is a sort of competition between agonist and antagonist. Final effect of drugs depends upon their concentration. If the concentration of the antagonist is more it will block the action of the agonist. If the concentration of the agonist is increased the antagonism will be overcome, e.g. acetylcholine (agonist) and atropine (antagonist).

(*ii*)*Non-Competitive*: In this case the antagonist occupies the receptors and forms a firm binding with the receptors so that drug-receptor-complex cannot be broken down easily. Antagonism cannot be

overcome by increasing concentration of the agonist e.g. adrenaline (agonist) and phenoxybenzamine (antagonist).

18. Drug Dependence (Drug Addiction): It is a state of periodic or chronic intoxication which is detrimental to the person and to the society. There is need to continue the drug. It becomes almost impossible to carry normal physical function without the drug. (See Page 78-87)

Following are components of phenomenon of addiction:

(*i*) EUPHORIA: It is sense of happiness and forgetfullness from worries.

(*ii*) TOLERANCE: In order to achieve the same state of euphoria the person must take large quantity of the drug. It is believed that tolerance is partly due to increased production of enzymes of liver concerned with metabolism of the drug.

(*iii*)PSYCHIC DEPENDENCE (HABITUATION): The person desires to take the drug but if the drug is not provided no harm occurs to the person, e.g. tea, coffee (caffeine) and smoking.

(*iv*) PHYSICAL DEPENDENCE: Gradually the patient starts depending on the drug for ordinary physical activities and sufficient concentration of the drug should be present in the body, mainly in the extracellular fluid, without which he can not do day to day work. The drug becomes a sort of essential food for the addict.

(*v*) WITHDRAWAL SYMPTOMS (ABSTINANCE SYNDROME): If the drug is not provided to the addict, he develops certain symptoms which are usually opposite to the pharmacological action of the drug e.g. morphine normally produces sleep, relief of pain and constipation. If it is not provided to the addict he will have restlessness, pain throughout the body and diarrhoea. Sometimes withdrawal symptoms may be very serious and may prove fatal.

Drugs responsible for addiction are: Morphine, heroin, pethidine, ethyl alcohol, barbiturates etc.

ADVERSE DRUG REACTIONS

These are unwanted or unexpected effects of drug treatment. They occur quite often. In most of the cases they are not serious. But occasionally they could be so serious as to endanger life. e.g. acute anaphylactic shock with penicillin, severe hypoglycaemia after excessive insulin administration, severe hypertension after discontinuing clonidine, shock after sudden stoppage of corticosteroid therapy.

Adverse drug effects can be divided into two groups:

I. Predictable Reactions: They usually occur early in the course of treatment; occur quite often and are dose-related. They are of two types:

(*a*) *Due to excessive pharmacological activity of the drug*: They are liable to occur with C.N.S depressants, cardioactive drugs, hypotensive agents and hypoglycaemic drugs. All patients are at risk of developing this type of reaction if high doses are given. Patients with renal disease, liver disease and at extreme of ages (very young and very old) are particularly susceptible.

(*b*) *Withdrawal symptoms or rebound responses after discontinuation of treatment:* Acute Addisonian crisis may be precipitated by sudden stoppage of corticosteroid therapy. Withdrawal symptoms occur after narcotic analgesics, barbiturates and drugs liable to cause addiction.

These drugs should be gradually withdrawn to avoid such mishaps.

II. Unpredictable Reactions: They occur usually infrequently, and are not dose dependent. They are of the following types:

(a) *Drug Allergy*: It is a common adverse effect. It is not predictable and is not dose-related. It varies from mild erythematous skin reaction to acute anaphylactic shock. Allergic reactions frequently occur with penicillins and sulphonamides.

(b) *Genetically Determined Effects:* Major toxicity of some drugs is restricted to individuals with a particular genetic abnormality. Patients with glucose-6-phosphate dehydrogenase deficiency are liable to develop acute haemolytic anaemia after exposure to antimalarial drug, primaquine and sulphonamides. Patients with a typical pseudocholinesterase are unable to metabolise the skeletal muscle relaxant, suxamethonium; they develop prolonged paralysis and apnoea. (See Page 57).

(c) *Idiosyncracy*: unusual, unexpected drug effect which can not be readily explained or predicted in individual recipient is called Idiosyncracy. Example: Aplastic anaemia with Chloramphenicol.

Drug induced faetal abnormalities are also included in this group. (See Page 28).

On account of their great clinical significance, drug toxicity and drug allergy will be described in detail.

DRUG TOXICITY

Toxicity is the most important adverse effect and is the ultimate limitation of the use of a drug. As compared to desirable pharmacological effect of a drug, toxic effect is accompanied by a change in

the body which is either too extensive to be compatible with life or is irreversible causing long lasting or permanent damage. It should be understood that every drug is potentially toxic if administered in high doses; in other words a completely nontoxic drug does not exist. Very potent drugs i.e. drugs which produce a measurable pharmacologic effect in very small doses, and drugs with low margin of safety are more liable to produce toxic effects.

Overdosage: Toxicity due to overdosage occurs either intentionally (suicide or murder) or accidentally. Children are frequently poisoned by drugs left within their reach. In hospitals, poisoning occurs occasionally by a mix up of labels or by miscalculation of the dose administered to a newborn or premature infant.

Improper Storage: Some drugs when stored improperly may cause serious toxic effects e.g. Paraldehyde which is a polymer of acetaldehyde with no free aldehyde groups, on exposure to light ad air, is decomposed to acetaldehyde and acetic acid. After consumption of partially decomposed paraldehyde fatal poisoning may occur. Tetracyclines with expired shelf life cause excretion of aminoacids.

Precipitation or aggravations of infections: Antimicrobial drugs may produce such toxic effects indirectly.

Cytotoxic drugs and corticosteroids lower the resistance of the body because of their immunosuppressive activities. Latent or dorment infection may be activated.

Broad spectrum antibiotics by disturbing the normal flora of the body may selectively encourage the growth of some pathogens e.g. bacterial (staphylococcus, pseudomonas), fungal (candida) and viral (zoster virus) infestions may occur after drug therapy.

Drug interactions: Simultaneous administration of a number of drugs without taking into account their possible synergistic action can produce toxic effects.

The above mentioned causes of drug toxicity are predictable and, therefore, preventable. Intelligent application of principles of drug therapy may lead to lessening the incidence of serious toxic effects of drugs.

DRUG TOXICITY IN VARIOUS ORGAN SYSTEMS

Liver, kidneys and haematopoietic system are particularly liable to serious drug toxicity. Other systems may also be involved.

LIVER

A variety of liver disorders may be induced by drugs. The disease may be acute or chronic.

I. Acute Hepatic Injury:

(*a*) *Hepatocellular Necrosis:*

(*i*) By direct action: Halogenated hydrocarbons (chloroform, carbon tetrachloride, halothane) may, particularly after repeated administration, cause severe hepatocellular necrosis.

(*ii*) Indirectly by interference with certain metabolic pathways: Mercaptopurine, methotrexate, asparaginase, large doses of tetracycline particularly if given I.V severe overdosage with paracetamol or the taking of excess of alcohol.

(*b*) *Cholestatic jaundice* is caused by methyltestosterone, progestogens used in oral contraceptives (norethisterone, norethynodrel, ethynodiol and lynoestrenol), antibiotics (rifampicin, novobiocin).

(*c*) *Hepatocanalicular jaundice* is caused by chlorpromazine, erythromycin estolate.

(*d*) *Hypersensitivity:* Phenylbutazone, indomethacin, ibuprofen and related drugs and ketoconazole may give rise to a hypersensitivity type of hepatocellular damage.

II. Chronic Hepatic Disease:

(*a*) *Chronic Active Hepatitis* may occur with isoniazid, methyldopa, paracetamol, sulphonamides. It resembles viral infection.

(*b*) *Hepatic Cirrhosis* may occur from the long term taking of ethyl alcohol or inorganic arsenicals. Cirrhosis may follow upon chronic active hepatitis.

KIDNEY

As most drugs or their metabolites are excreted by kidneys, their adverse effects are liable to occur in these organs.

I. Acute Renal Damage: Various sites in the kidneys may be involved.

(*a*) *Glomerulonephritis*: Hydralazine, phenylbutazone and sulphonamides may damage glomeruli.

(*b*) *Acute Tubular Necrosis:* Aminoglycoside antibiotics (Gentamicin, streptomycin) damage proximal tubules. First generation cephalosporins, cephaloridine and cephalothine cause proximal tubular damage. The antifungal amphotericin may produce proximal or distal tubular lesions. Overdosage with paracetamol cause acute tubular necrosis.

(*c*) *Acute Interstitial Nephritis:* Sulphonamides, co-trimoxazole, rifampicin, fenoprofen, ibuprofen, phenylbutazone, and thiazide diuretics may cause it. It is regarded as hypersensitivity reaction.

II. Non-acute Renal Damage:

(*a*) *Nephrotic Syndrome:* Gold injections, mercurials, penicillamine, phenindione, probenecid, tolbutamide may cause nephrotic syndrome. This is usually reversible.

(*b*) *Analgesic Nephropathy:* There is papillary necrosis, possibly because of ischemia which is caused by damage of the vasa recta. Normal doses of paracetamol do not cause kidney damage. There may be danger from the long-term use of aspirin.

(*c*) *Crystalluria*: It occurs with less soluble sulphonamides such as sulphathiazole. During treatment of malignant conditions with chemotherapeutic agents, breakdown of nuleoproteins releases urates which may be precipitated in the renal tubules. Allopurinol is used to prevent it.

(*d*) *Renal Stones:* Excessive consumption of mixtures containing alkali with calcium together with milk for the treatment of duodenal ulcers may cause calcium containing stones. They also occur when excessive amounts of vitamin D are given, after prolonged therapy with corticosteroids. Treatment of skeletal cancer or myeloma with chemotherapeutic agent causes calcium stones.

(e) *Lupus Erythematosus:* A number of drugs including hydralazine, isoniazid, nitrofurantoin and procainamide may cause disseminated lupus erythematosus. On stoping the drug, the patient usually recovers.

(*f*) *Retroperitoneal Fibrosis:* Methysergide and very occasionally other drugs may cause this condition; ureteral obstruction may occur.

HAEMATOPOIETIC SYSTEM

A variety of blood dycrasias may occur due to drug toxicity. The most serious is *bone marrow depression* resulting in aplastic anaemia, thrombocytopenia, granulocytopenia. All three together are called *pancytopenia.*

Cytotoxic drugs and antimetabolites used for treatment of cancer depress the bone marrow. Most serious toxic effect of chloramphenicol is bone marrow depression. Two types of toxicity may occur in this case: (*i*) direct dose-dependent toxicity to the bone marrow (*ii*) idiosyncracy which is not dose related.

Megaloblastic anaemia occurs with phenytoin and primidon. It responds to treatment with folic acid. It also occurs with methotrexate.

Haemolytic anaemia: Drug induced autoimmune haemolytic anaemia occurs with methyldopa, chlorpromazine, phenytoin, methysergide, levodopa and mefenamic acid.

Drug induced immune haemolytic anaemia my occur with penicillin, some cephalosporins and cephamycins, quinine, rifampicin, sulphonamides, chlorpropamide and chlorpromazine.

In patients who lack the enzyme glucose-6-phosphate dehydrogenase in their red blood cells, haemolytic anemia occurs with primaquine, sulphonamides. (For details see pages 58-59).

Agranulocytosis: Cytotoxic drugs and non-steroidal anti-inflammatory agents are the main causes of agranulocytosis or granulocytopenia. Also sulphonamides, thiouracils, tolbutamide, chlorpropamide, chloramphenicol, frusemide, impiramine and pyrimethamine are some of the drugs out of more than hundred drugs responsible for this blood disorder.

Thrombocytopenia: Cytotoxic drugs and other drugs used for treatment of leukaemia cause a marked fall in platelets. Also many other drugs have been reported to cause this defect in some individuals. These include sulphonamides, chloramphenicol, ampicillin, chlorpropamide, tolbutamide, non-steroidal anti-inflammatory agents, frusemide, gold, arsenicals, PAS, potassium perchlorate, quinidine, quinine and troxidone.

Non-thrombocytopenic purpura: Many drugs have been reported to cause capillary purpura without a reduction in platelets. The drug may combine with a capillary cell and lead to damage with consequent small local haemorrhage.

Leukaemia: Immunosuppressive therapy particularly after renal transplantation is associated with an increased incidence of leukaemia. Chloramphenicol and phenylbutazone have been reported to cause acute myeloblastic leukaemia.

SKIN

A drug eruption may be due to topical application (Contact dermatitis) or to the ingestion of a substance. Drug eruption of the latter type are abrupt in onset and symmetrical in distribution. A great variety of *drug eruptions* may occur with different drugs.

Acne-form: Oral contraceptives, anticonvulsants, corticosteroids; isoniazid, lithium, rifampicin.

Vesicular or bullous: Barbiturates, frusemide, sulphonamides.

Lichenoid: Chloroquine, methyldopa, PAS.

Pigmentation: Busulphan, griseofulvin, mepacrine.

Eczematous: Allopurinol, warfarin.

Exfoliative dermatitis: Cimetidine, gold, phenylbutazone, phenytoin.

Erythema nodosum: Barbiturates, sulphonamides.

Erythema multiforme: Barbiturates, salicylates, sulphonamides.

Exanthematic: Ampicillin, phenindione.

Stevens-Johnson Syndrome: Phenylbutazone, sulphonamides.

Systemic lupus erythematosus: Grisefulvin, hydralazine, sulphonamides.

Urticaria: Benoxaprofen, cephalosporins, cephamycins, griseofulvin, imipramine, penicillin, aspirin.

Psoriasis: Practalol, chloroquine, lithium.

Photosensitivity: Chlorpromazine, antihistamines, benoxaprofen, griseofulvin, sulphonamides, sulphonylureas and tetracyclines.

Alopecia: It usually occurs with cytotoxic drugs. It may occur with carbimazole, oral contraceptives, gold, heparin, lithium, methyldopa, propranolol, warfarin and many other drugs.

GASTROINTESTINAL TRACT

Nausea, vomiting, diarrhoea, constipation and abdominal cramping occur with many drugs. This may be decreased by giving the drug with food.

Nausea and Vomiting usually occurs with cardiac glycosides (digitalis), dopamine agonists (levodopa, bromocriptine), narcotic analgesics (morphine, pethidine), antimitotic drugs (mustine), non-narcotic analgesics (aspirin, phenylbutazone, indomethacin), and aminophylline.

Almost all non-steroidal antiinflammatory drugs can cause *gastrointestinal bleeding.* Potassium chloride tablets may cause blee-ding and ulceration of small intestine.

Phenylbutazone, indomethacin, reserpine and corticosteroids cause activation of gastric ulcer.

NERVOUS SYSTEM

A wide range of adverse effects involving central as well as peripheral nervous system occur with drugs.

Extrapyramidal symptoms: Chlorpromazine and other phenothiazines, reserpine, metoclopramide, thiethylperazine (torecan).

Ototoxicity: Aminoglycoside antibiotics (streptomycin gentamicin, kanamycin), ethacrynic acid, frusemide, salicylates.

Peripheral Neuropathy: Isoniazid (in slow acetylators), prothionamide, amiodarone.

Hallucinations: Digitalis.

Convulsions: Isoniazid, prothionamide, chloroquine.

Ataxia: Streptomycin, phenytoin, phenobarbitone, primidone, sulthiame, metronidazole, nimorazole, lithium, diazepam particularly in the elderly.

Nystagmus: Phenytoin.

CARDIOVASCULAR SYSTEM

A variety of drugs toxic to cardiovascular system are used in therapeutics.

Cardiac arrhythmias may be precipitated by halogenated general anaesthetics (chloroform,halothane, cyclopropane, trichlorethylene, methyoxyflurane), amitriptyline, imipramine, levodopa, digitalis.

Hypertensive crisis: Sudden stoppage of clonidine; tyramine containing foods.

Myocardial Depression: Emetine, Chloroform.

LUNGS

Some drugs may adversely affect lungs, particularly in patients suffering from bronchial asthma.

Bronchoconstriction may occur with the use of beta blockers especially in asthmatics.

Allergic Form of Asthma may be precipitated by penicillin, streptomycin, iron-dextran infusion, anaesthetics and even by sodium cromoglycate.

Pulmonary Fibrosis occurs with methysergide, busulphan, practalol, and nitrofurantoin.

Pulmonary Oedema may occur from overloading with i.v. fluids and also follow i.v. administration of diamorphine.

Pulmonary Eosinophelia may be caused by sulphonamides, penicillin, tetracyclines and impiramine.

Pulmonory alveolitis may occur with amiodarone.

EYES

Prolonged use of some drugs is responsible for ocular toxicity.

Optic neuritis: Ethambutol, quinine.

Retinal Damage: Chloroquine (with prolonged high dosage).

Subacute Myelo-optic Neuropathy: Clioquinol (There have been many cases in Japan).

Increased Intraocular Pressure: atropine like drugs, crtico-steroids.

Corneal Opacities: Chloroquine, Practalol.

Toxic Cataract can be due to chloroquine, prolonged use of corticosteroids, phenothiazines, naphthalene, carbromal, ergot, galactose, lactose and paradichlorobenzene.

GYNAECOMASTIA

Abnormal development of breast in males may occur from takig digoxin, reserpine, methyldopa, spironolactone and oestrogens.

TERATOGENICITY

Drug-induced birth defects may occur by drug therapy in pregnant females. The dangerous period for teratogenesis is usually the first trimester of pregnancy when organogenesis occurs.

The problem of drug induced teratogenesis was highlighted dramatically by the thalidomide disaster. Thalidomide was developed as a mild sedative and being free from other serious toxic effects it was commonly prescribed. Approximately 10,000 malformed babies were born during the three year period of 1958-61 as a consequence of pregnant women having taken thalidomide. The thalidomide disaster called attention to the importance of establishing the potential teratogenicity of a new drug. Unfortunately one encounters in this area great difficulties. Animal models are not always informative e.g. thalidomide is highly teratogenic in man, it has much less teratogenecity in many common laboratory animals. Because of these difficulties, it is a general rule to advise pregnant women to avoid taking drugs, particularly new drugs, during the first trimester of pregnancy.(See Drugs and Pregnancy on Page 28).

MUTAGENICITY

A compound may produce permanent alteration in the germ cell thereby changing the hereditary constitution (Genotye) of the offspring. Mutations provide a wide range of adverse defects.

Although barbiturates, phenolic compounds, acridines, sulphonamides, steroid hormones, vitamins, caffeine and nicotine have been successfully used in the production of experimental mutations, immunosuppressive drugs (which depress the production of immune bodies) used over prolonged period as in case of organ transplantation lead to increased incidence of cancer. Alkylating agents being highly

reactive form highly active radicals which bind covalently to nucleic acids or proteins.

CARCINOGENICITY

It is the production of malignant tumours. As a result of drug therapy rapid and abnormal proliferation of tissue can occur e.g. Oestrogen-induced endometrieal cancer in postmenopausal women on long term oestrogen therapy. Chemicals present as environmental pollutants present in air, food, drinking water, cigarette smoke may cause mutagenesis and carcinogenesis. Vinyl chloride, used in the manufacture of polyvinyl plastics and also used in propellant in hair spray, on prolonged exposure may produce malignant tumour in the liver. Since mutagenicity and carcinogenicity are basicallly the same toxic reactions, mutations in bacteria is frequently used to establish the role of a chemical in carcinogenesis.

DRUG ALLERGY

Drug allergy is an acquired qualitatively altered response of the body to a drug due to antigen-antibody reaction. It occurs as a result of exposure to a drug so that drug or its metabolite acts as sensitizing agent. The allergy is manifested on reexposure to the same or immunologically related drug.

Drugs with big molecules (proteins, peptides, polysaccharides) act as antigens. Drugs with relatively low molecular weight and simple chemical structure act as haptens (incomplete antigens) and become complete antigens after combination with a body protein. Sensitization by antigens cause the formation of specific antibodies either circulating in the blood or fixed in the tissues.

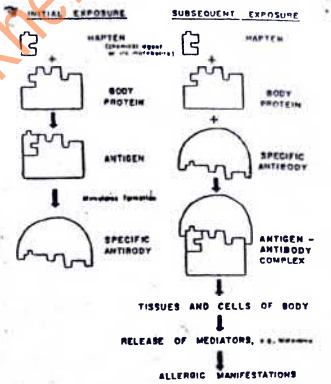


Figure 1-18. Schematic presentation of the mechanism of the allergic reaction

Upon readministration of the drug, the antigen reacts with the antibody. The antigen-antibody reaction ultimately releases mediators (Histamine, SRS-A, serotonin, bradykinin etc.) which elicit various manifestations. (Figure 1-18) These appear mainly in skin, respiratory tract, gastrointestinal tract, blood and blood vessels.

Following are the distinctive featurs of allergic reactions to drugs:

(*i*) There is no correlation with known pharmacological properties of the drug. These are abnormal, unexpected and qualitatively different responses.

(*ii*)They are not dose dependent. Very small doses may cause very severe effects.

(*iii*) There is delay between first exposure to the drug and the development of reaction. It recurs upon repeated exposure even to traces of the drug.

(*iv*) They occur in a small number of patients receiving the drug.

(*v*) They disappear on stopping the administration of drug and reappear on exposure to a small dose.

(*vi*) The same drug produces different effects in different patients.

(*vii*) Patients with allergic diseases e.g. eczema, are more likely to develop allergy to drugs.

(*viii*) Some drugs e.g. penicillin, are more likely to cause allergy than other drugs.

(*ix*) It is possible to achieve desensitization.

Manifestations of Drug Allergy:

Acute Reactions: It occurs suddenly following th administration of the drug; within minutes if drug has been given I.V. It may manifest itself as *Acute Anaphylactic Shock*. It occurs with penicillin, blood products, vaccines, iron injections, horse serum and a huge variety of other drugs. There is severe fall in blood pressure, bronchoconstriction and sometimes death due to loss of fluid from the intravascular compartment, bronchospasm and sometimes laryngeal oedema. Urgent treatment is required. *First 1 ml of Adrenaline Injection should be given I.M.* to raise the blood pressure and to dilate the bronchi. It may be repeated after 3 minutes according to the clinical condition. Then hydrocortisone 100 mg I.M. or I.V. is administered followed by antihistamine (H_1 receptor blocker) e.g. chlorpheniramine 10 mg slow I.V. Hydrocortisone acts by reducing vascular permeability and by suppressing further response to the antigen-antibody reaction.

Subacute Reactions: These occur usually between 1 and 24 hours, occasionally after a few days. Urticarial rashes and angioneurotic

oedema are probably the commonest type of drug allergy. They are usually accompanied by itching. The eyelids, lips and face are usually affected. They respond to adrenaline, ephedrine, antihistamines and corticosteroids. Rarely there is oedema of larynx which may be fatal if tracheostomy is not done. Other manifestations are exfoliative dermatitis, necrotic epidermolysis, conjunctivitis, arthralgia, lupus erythematosus, agranulocytosis, aplastic anaemia, thrombocytopenia, fever, rhinitis and bronchial asthma.

Delayed Reactions: These occur about 1 to 3 weeks after administration of the drug. *Serum Sickness Syndrome* is characterized by urticaria, fever, arthralgia and lymphadenopathy. Treatment is with corticosteroids and antihistamines.

Prevention of Allergic Reactions: Drug history of the patient should always be taken. If a patient says he is allergic to a certain drug then that drug should not be given without careful testing. As allergic reaction could be very dangerous,even fatal, patient should always be told about his drug allergy and he should be advised to always tell the doctor whom he consults in future for any illness and the nurse who administers the drug.

In some patients it may be necessary to administer the drug to which he has developed allergy, for instance antituberculosis drugs. Such patients can be hyposensitized by giving small amounts of allergen, which are then gradually increased, usually after every few hours until a normal dose is tolerated. This is done under cover of either an antihistamine or of an adrenal steroid or both, to prevent reactions during the procedure. A full kit for treating acute anaphylactic shock should be handy during the procedure.

DRUG DEPENDENCE

Drug dependence is the condition in which the person has a continuing desire to take the drug. This occurs after excessive, repeated and persistent self-administration of a drug without regard for medically or culturally accepted patterns. Continuous use of drug leads to tolerance so that he has to take progressively higher doses of the drug to achieve the desired effect. Eventually the person is dependent upon the drug i.e. he cannot do without it. There are many patterns of dependence and degrees of its intensity. Dependence may be emotional or physical. In case of physical dependence, if the drug is stopped there may be withdrawal symptoms.

Drug dependence has assumed alarming situation in most of the countries of the world. There has been no substantial success in eradication of this extremely serious problem even in resourceful countries.

The task is particularly difficult as no single factor can be identified as the basis for drug taking experiences. Drugs may be taken for a variety of reasons; to reduce tension and anxiety, influence mood, decrease fatigue and boredom; facilitate social interaction, change acivity level, heighten sensation and awareness, satisfy curiosity or reduce pain and as an identification of subculture or rebillion against society. Patterns of drug taking vary from the intermittent or experimental use of a particular drug to a compulsive "poly drug abuse" pattern i.e. taking a variety of drugs in a disorganised and dangerous manner on a daily basis. On account of such multitude of problems of diverse nature, there seems to be no solution of existing magnitude of drug dependence in the near future.

Before describing salient features of drug dependence of various groups of drugs abused most frequently, it seems appropriate to give a general description of various components of drug dependence.

(*a*) *Euphoria:* It is the sense of happiness, well being and foregetfullness from worries. In many cases this is the purpose of starting the drug.

(*b*) *Tolerance:* In order to achieve the same state of euphoria, the person has to take progressively larger quantities of drugs (see page 91,95).

(*c*) *Psychic Dependence (Habituation):* The person desires to take the drug but if the drug is not provided, no harm occurs to the patient. Dependence is emotional e.g. taking tea or coffee, smoking.

(*d*) *Physical Dependence:* Gradually the person depends for ordinary physical activities on the drug. Sufficient concentration of the drug or its metabolite should be present in the body without which he cannot perform day to day work. It becomes a sort of essential food for the person.

(*e*) *Withdrawal Symptoms (Abstinence Syndrome):* If drug is not provided to the patient he develops certain symptoms which are opposite to that of the usual pharmacological actions of the drug e.g. morphine normally produces sleep, relief of pain and constipation. If the drug is not provided to an addict then he will suffer from restlessness, pain throughout the body and diarrhoea. Sometimes withdrawal symptoms may be very serious and may prove fatal if drug is not provided to him.

The drugs most frequently abused may be grouped into six major classes: (*i*) Opioids (*ii*) C.N.S. depressants including alcohol, hypnotics and tranquilizers (*iii*) C.N.S. stimulants, the amphetamine group and cocaine (*iv*) Cannabis (*v*) Psychedelics, and (*vi*) miscellaneous substances.

OPIOIDS

Opium has been in use since prehistoric times. Opium and its derivatives are effective pain killers. At present the most abused opioid is heroin. Others are morphine, codeine, and synthetic narcotics, pethidine and methadone.

With these drugs the desire to continue taking the drug is strong, tolerance develops and there is both psychic ad physical dependence.

In U.S.A. and U.K. use of *heroin* reached epidemic proportions during the middle to late 1960s particularly amongst males (15 to 35 year age group) of lower socioeconomic strata of large urban areas. After a slight decline in heroin use during the early 1970s, there has been a resurgence of the problem. Also there has been a shift to smaller cities and more rural areas. A greater number of affluent members of the society are now using heroin. In Pakistan, heroin addiction at present is the most serious problem.

The great popularity of heroin is possibly due to more euphoria produced by it than in case of morphie. On a weight for weight basis heroin is the more potent drug.

The user's first experience is generally by "sniffing" allowing the drug to be absorbed from the mucous membrane of the respiratory tract. This initial experience may be unpleasant often being accompanied by nausea, vomiting and anxiety. A state of relaxation, peace and freedom from worries and tension-a sense of euphoria-may be experienced. Such pleasure effects provide positive reinforcement for continued use. If heroin use is continued tolerance to these euphoric effects develops. To maximize the effects, the user begins to inject the drug subcutaneously and eventually intravanously. The intravenous injection of heroin produces a warm flushing of the skin and pleasurable sensations in the lower abdomen. This is called a 'rush', 'kick', 'thrill' or 'jolt'. These effects produce further positive reinforcement for continued drug use.

As tolerance develops, more drug must be used more frequently to achieve the same effects. The user becomes acutely aware of his physical dependence. The craving thus becomes part of a desire to avoid the effects of withdrawal.

Withdrawal Syndrome of Heroin: Initially there is feeling of distress and then the person is anxious and restless. Tension builds up. There is lacrimation, rhinorrhoea, yawning and sweating. Restless sleep may occur, known as the "yen", lasting for several hours. He wakens in a state of extreme restlessness and misery. Tremors occur and after 48 hours or so, his symptoms become more severe with added nausea, vomiting and abdominal cramps. Muscle spasms may occur. There is marked chilliness with alternate flushig and perspiration.

Pilomotor activity (goosflesh) is prominent and the skin appears like that of a plucked turkey ("cold turkey"). It takes about a week for these patients to recover even if no treatment is given. During a period of withdrawal the patient can be helped with methadone, perhaps supplemented by a tranquillizer such as chlorpromazine.

Persons who inject themselves with heroin may suffer from hepatitis, cellulitis, thrombophlebitis, septicaemia and tetanaus. Deterioration of the personality occurs and there is rejection by the society.

C.N.S. DEPRESSANTS

CNS depressants subject to abuse include ethyl alcohol, sedatives -hypnotics (mainly barbiturates) and tranquillisers.

Ethyl Alcohol (Ethanol):

Alcoholism represents the major drug problem in U.S.A., Europe and other countries of the world. Alcoholism is an excessive drinking by the individual that adversely affects his health or impairs social functioning or both. It usually starts with social drinking and this is followed by occasional further drinking to produce euphoria and release emotion or to relieve anxiety and depression. This is done frequently and more and more alcohol is required to produce the same effects as tolerance develops. Environmental factors play a role in reinforcing chronic use of alcohol. Majority of problem drinkers are in lower socioeconomical groups in urban areas especially men under 25 years.

Apart from deterioration in social behaviour the chronic alcoholic may develop acute hepatitis, chronic hepatitis, portal cirrhosis of liver, pancreatitis, gastritis and vitamin deficiency states. Thiamine deficiency may result in Korsakoff's psychosis, Wernicke's encephalopathy, beri beri, polyneuropathy or cardiac enlargement and failure.

End stage of alcoholism may include deterioration of personality, blackouts, recurrent infections and transfer to dependence on other drugs such as heroin.

Repeated use of alcohol leads to pharmacodynamic tolerance so that a higher blood concentration is necessary to produce intoxication in tolerant than in normal individuals.

Chronic maintenance of high blood alcohol level produces a state of physical dependence.

Withdrawal Syndrome of Alcohol: The most frequent symptoms during withdrawal from alcohol is *tremulousness*. This usually occurs within 12 to 48 hours with reduction of alcohol and within 6 hours with abstinence. One sees a mild tremor of the hands which may even

involve all extremities as well as the trunk and tongue. Tremulousness usually deminishes within 72 hours but may persist for 5 days.

Hallucinations may occur either during the tremulousness state or independently of that state. Hallucinations may also occur during severe alcoholic intoxication as well as during periods of partial or complete cessation of drinking.

Seizure disorders may be associated with tremulousness or may be present without any other symptoms. The seizure is of grand mal type. It is usually not preceeded by an aura. Seizures are less common in alcohol withdrawal than in barbiturate withdrawal.

Delirium tremens appears about 72 to 96 hours after cessation of drinking. There is confusion, disorientation, delusions, hallucinations, psychomotor agitation and autonomic dysfunction. The patients may have profuse sweating, tachycardia, hypertension and fever. This condition requires hospitalization and intensive medical care. Chlordiazepoxide helps to reduce the psychomotor agitation. Recovery from the alcoholic abstinence syndrome occurs usually within 5 to 7 days.

The treament approach for alcoholism includes psychological, social and rehabilitation services. A number of treatment techniques have been employed. These include 'deterrent' drugs such as disulfiram (Antabuse), referal to self-help groups such as Alcoholic Anonymous, and a number of behaviour modification techniques. Individual and group psychotherapy may be of some help.

Sedatives and Hypnotics-Barbiturates: The most frequently abused sedatives and hypnotics include the short acting barbiturates (e.g., pentobarbitone, secobarbitone), glutethimide (Doriden), methyprylon (Noludar) and methaqualone (Mandrax); tranquillizers, particularly diazepam (Valium), chlordiazepoxide (Librium) and amitriptyline (Tryptinol) an antidepressant with sedative properties. The characteristics of these drugs are similar.

The sedative-hypnotics are among the most prescribed medications in the world. The drug abuse may begin with a prescription for intermittent use at night to decrease anxiety and ensure sleep. This can progress to nightly use with increased doses, and end in daily use to maintain adequate levels of anxiety free function. Those who become dependent on these drugs in this way are frequently middle aged women who take the drugs orally.

Recently there has been a marked increase in the use of illicit depressants in teenagers. The extent of use varies and generally occurs with the use of other drugs such as marihuana, alcohol and amphetamines.

With repeated administrtion, drug disposition and pharmacodynamic tolerance develop. Physical dependence develops. The withdrawal syndrome is similar to that seen with alcohol.

Withdrawal Syndrome of Barbiturates: With the short acting barbiturates, the time necessary to develop dependence is shorter and the withdrawal syndrome is more abrupt in onset and more severe than with the longer acting barbiturates.

In the first 12 to 16 hours after withdrawal of short acting barbiturates, there is a rebound increase in nightly REM slep, nightmares are frequent as well as feeling of having slept badly. There is increase in anxiety, restlessness, tremulousness and weakness. There may be accompanying cramps, nauses, vomiting and orthostati hypotension within next 24 hours; symptoms progress and coarse hand tremors and muscle twitchings occur. During second and third days when symptoms reach their peak. convulsions may occur. About half of the patients develop a delirium marked by sensorial clouding, hallucinations (visual and auditory) and disorientation (time and place). This occurs between the fourth and seventh days of abstinence. Hyperthermia, tachycardia and agitation also occur at this time. Exhaustion and at times fatal cardiovascular collapse can occur. The abstinence syndrome is completed by eighth day.

With the longer acting barbiturates and benzodiazepines, seizures may not occur until the seventh or eighth day of abstinence.

Treatment of withdrawal syndrome of barbiturates is essentially supportive; fluids and electrolyte losses are replaced and complicating medical problems are treated. Unlike opioid withdrawal, withdrawal from depressants can be life threatening.

C.N.S. STIMULANTS

CNS stimulants subject to abuse include amphetamines, cocaine, methylphenidate (Ritalin), phenmetrazine (Preludin) and diethylpropion.

Amphetamines: This group includes amphetamine, dexamphetamine and methamphetamine. There is wide spread abuse of these drugs in industrial societies of North America, U.K., Japan and Sweden. Individuals who abuse amphetamine belong to two classes. Many middle class women who are prescribed for obesity, narcolepsy, depressive syndromes and for reduction of fatigue, and students, truck drivers and atheletes who use amphetamines to increase their productivity, become dependent on amphetamines as they become more tolerant to the drugs effects. Oral preparations are used, frequently with hypnotics to ensure sleep.

The other group consists of poly-drug abusers who seek the drug for its mood-elevating properties. Methamphetamine is the drug of choice because of its more pronounced central effects and less peripheral effects. The drug is taken orally on occasion although sniffing and intravenous routes are used predominantaly.

Following intravenous injection there is sense of increased mental activity and physical strength, a feeling of power is experienced and there is little need for food or sleep. After 3 to 6 hours, the effects are dissipated and a feeling of fatigue and depression results. Use of amphetamines may be occasional, limited to parties or may become more regular.

With the development of tolerance larger and more frequent doses are necessary and toxic signs and symptoms may appear. These include grinding the teeth, touching and picking at the face and extremities, and suspiciousness and a feeling of being watched. Stereotyped, repetitious behaviour is common. With prolonged uses, there may develop a psychotic state that resembles schizophrenia.

When treatment of dependence is attempted, many users find it difficult to abstain from this drug taking habit but may respond to the use of phenothiazine tranquillizers.

With cessation of amphetamines, major physiological symptoms do not occur. There may be anxiety, depression, increased appetite, lassitude and prolonged sleep. There is marked increase in REM sleep and nightmares occur. Some persons experience headache, profuse sweating, muscle cramps, disorientation and confusion. The physical discomfort that is experienced reinforces the absuer's craving for the amphetamines.

Cocaine: It produces psychocative effects similar to those of amphetamines i.e. mood elevation, hyperacivity and decreased need for food or sleep. Cocaine abuse is seen more in middle class individuals in urban areas. It is generally sniffed but may be taken intravenously. Its use is generally intermittent. Cocaine is much shorter acting than the amphetamines. With intravenous use, its effects last only 5 to 15 minutes. Psychological dependence and compulsive use occur. There is no physical dependence. Tolerance is not a problem.

Sometimes it is injected with heroin or morphine by those who are drug dependents. Mixture of cocaine and heroin is called 'speedball'.

Sniffing of cocaine leads to perforation of nasal septum. Chronic user experiences the sensation of something crawling under the skin 'Cocaine bugs'. Generally the user scratches these areas, leading to excoriations and sores, which promptly become infected.

Continued and frequent use of high doses leads to psychosis which is often indistinguishable from acute paranoid schizophrenia.

CANNABIS

Marihuana and hashish are derived from the hemp plant, *cannobis sativa*. The plant is grown in many parts of the world. All parts of the plant contain varying amounts of the major psychoactive principle delta-9-tetra hydrocannabiol, its active isomer delta-8-THC and numerous other cannabinoids. The deried mixture of crushed leaves and flowering tops with or without the stems and seeds is known as marihuana. Hashish, thought to be 4 to 8 times more potent than marihuana, is obtained by compressing the flowering tops of the plant, which secrets a clear varnish-like resin. The best quality resin comes from plants grown in Chinese Turkistan. *Bhang* is the word used in the Indo-Pakistan subcontinent for the dried leaves and flowering shoots. *Charas* is the name for the resin.

Cannabis has a long history of use in many societies, especially in Eastern countries, as a form of folk medicine for recreational purposes and religious rites. During the last 30 years there has been a great increase in the use of Cannabis in U.S.A. and Western Europe. Although majority of users are in the 18 to 25 years age group, there has been increased use in older age groups as well.

Marihuana is usually smoked in pipes or home made cigarettes. Hashish is smoked in a variety of small pipes, including the water pipe. Both preparations may be taken orally in food or drink, althogh this route is less common.

The major psychological effects of marihuana include a greater awareness for the senses, euphoria, a dream-like state and mood fluctuations. There may be a sense of relaxation and sleepiness when alone, whereas in a group there is more spontaneous laughter and talk. Short term memory and impaired perception of time and distance also occur. The major physical effects associated with smoking marihuana include bloodshot eyes and increased pulse rate. It is considered one of the least toxic drug abused.

Inattention, apparent daydreaming, listlessness and general behavioral changes often occur with the habitual use of marihuana. The person becomes indolent and non-productive.

A varying degree of tolerance to some of the physiological and psychologic effects appear to develop. Some degree of cross tolerance between cannabinoids and alcohol has been reported. Physical dependence on cannabis has not been demonstrated. However some heavy chroic users may have difficulty giving up their drug.

PSYCHEDELICS
(HALLUCINOGENS)

These drugs produce distinctive alterations in perception, thought, feelings, mood and behaviour. These are called "mind expanding" due to innate capacity of mind to see more than it can tell and to experience more than it can believe while under the influence of these drugs. These are probably among the oldest psychoactive drugs being used as an adjunct in religious rites of some societies.

Psychedelics include Lysergic acid diethylamide (LSD), Phencyclidine, Psilocybin, Mescaline, diethyltrytamine, dimethyltryptamine and dipropyltryptamine.

Lysergic Acid Diethylamide (LSD) was produced in 1938. Its hallucinogenic properties were discovered in 1943 but not used until 1960s, when educated young people with middle class background seeking a mystical transcendental experience started taking it in large numbers. Its use was mostly intermittent, usually done as a group activity. In the 1970s the publicity of the possibility of chromosomal damage and birth defects brought about a dramatic decrease in the use of LSD.

LSD is the most potent psychedelic known. Usually it is taken orally. Within 20 minutes, there is increased alertness, muscle weakness, hyperreflexia, tremors, pupilary dilatation, increased pulse, raised blood pressure, temperature, increased perspiration and piloerection. Within 1 to 2 hours psychedelic effects are fully evident. Perception is hightened and distorted. The altered perceptin is characterized by intensification of colours, prologed and overlapping afterimages and melting of undulating objects. There is feeling that one can vizualize sound waves from music or hear colour. Mood is highly variable and labile. Time perception is altered and time seems to pass slowly. Distances change. A mystic sense of oneness with the universe may be experienced in cojunction with the disintegration of self-boundries an experience that can be quite frightening. Effects begi to clear within 12 to 24 hours, followed by fatigue and tension which persist for next 24 hours.

Tolerance to LSD develops rapidly, with repeated daily doses becoming ineffective within 3 to 4 days. Tolerance is lost after discontinuance of the drug. Physical dependence does not occur.The desire to continue taking the drug is slight.

Chlorpromazine 50 mg I.M. may counter the psychotic effects of LSD.

Phencyclidine is a cheap and easily available hallucinogen used in many poor communities by many young teenagers. In low oral dosage it causes stupor, similar to that of alcoholic intoxication. In

higher doses, either inhaled or injected, disordered thought processes occur similar to those seen in schizophrenia. There may be feelings of depersonalization and changes in body and feelings of apathy, estrangement or alienation may be experienced. Hallucinations can occur unpredictaby for days, weeks or months.

Psilocybin is present in the mushroom Psilocybe mexicana which grows in certain areas of Mexico. It has hallucinatory properties similar to those of LSD and mescaline.

MISCELLANEOUS SUBSTANCES

Volatile Solvents: These are found in many household products including spot removers, dry cleaning fluids, airplane glues, plastic cement, tube repair kits, petrol as well as aerosol propellents. They have been used, particularly by the age group 10-12, for their intoxicating effects. They are inhaled by placing the substance into a paper or plastic bag so that vapours can be trapped and inhaled. Effects similar to alcohol intoxication are experienced. With larger doses drowsiness, stupor, unconsciousness and coma may occur. Deaths have occured usually from suffocation.

Nitrous Oxide: Commonly known as laughing gas, it has sometimes been inhaled for intoxicating and eupherogenic effects which occur within 15 to 30 seconds and persist for less than 3 minutes.

Properties of nitrous oxide and ethyl ether were recognized as early as 19th century and these drugs were used for their intoxicating effects before their potential as ansesthetics was appreciated.

Caffeine: Tea, coffee and cocoa are drunk throughout the world but true dependence does not occur. Tea contains caffeine and theophylline, coffee contains caffeine and cocoa contains caffeine and theobromine.

Tea contains high amount of caffeine than coffee but less is used in making an infusion. Instant coffee contains a higher percentage of caffeine than ground coffee beans, but less is used in making a cup of the beverage. Powdered instant coffee contains 3 to 4% caffeine. Decaffeinated coffee contains only 0.3% caffeine.

Caffeine causes an increase in mental alertness but with excessive use many people suffer from isomnia, anxiety and tachycardia. It causes only psychic dependence.

Nicotine: It is the active principle of tobacco which is smoked throughout the world as cigarettes, cigars and pipes. Chronic use of tobacco causes tachycardia, increased peripheral resistance, hypertension, increased plasma free fatty acids, increased incidence of coronary artery disease, chronic bronchitis and increased risk of cancer.

Nicotine causes dependence. Chewing gum, *NIcarette*, which contains either 2 mg or 4 mg of nicotine is used to help those who cannot give up smoking. When chewed nicotine is slowly released into the mouth and absorbed by the buccal mucosa.

STANDARDIZATION OF DRUGS

BIOASSAY

In order to ensure efficacy and safety of drugs used in therapeutics, it is essential that amount of active drug present not only in all the batches of a pharmaceutical product of a manufacturer but also in such products of different manufacturers should be uniform and in accordance with standards laid down in the pharmacopoeia. If it is not so, there would be marked variation in the amount of active drug present in such products resulting in therapeutic failure or toxicity due to variation in potency.

Estimation of potency of an active principle in a product can be done by chemical, physical or biological methods.

Whereas chemical and physical methods are very commonly used for finding out the concentration of the active drugs, these methods may be inadequate in certain cases, being too insensitive or having not been fully established. Potency of such drugs is estimated by biological methods. The procedure employed for this purpose is called biological assay (*Bioassay*).

Biological methods are very sensitive for the estimation of neurotransmitters and autacoids (acetylcholine, histamine, serotonin, bradykinin, and other peptides). Their vey low concentration, in nanograms, can be determined by bioassay. However, biological methods are rather troublesome, difficult to perform, expensive, time consuming and not so accurate as physical and chemical methods. Inaccuracy is due to inherent biological variation. Statistical methods are available to estimate the error.

Principles of Bioassay:

1. The potency of the unknown preparation is compared with that of standard product under identical experimental conditions.

Reference standards are prepared and preserved by "Expert Committee on Biological Standardization of World Health Organization" and distributed to suitable laboratories of different countries.

2. Active principle should be identical in both the standard and the preparation to be assayed.

3. Assay experiment may be designed, in which the effect observed is not the same as the desired therapeutic effect. Insulin can be assayed by its effect of causing convulsions in mice, although this effect is not the normal purpose for which insulin is used in therapeutics.

Methods of Bioassay:

1. *Determination of Threshold Dose in Animals*: Minimum dose of the drug which produces a certain observable effect is compared with the dose of the standard necessary to produce the same effect. Digitalis can be standardised by this method. Preparation of the unknown drug is slowly infused into the vein of the anaesthetized cats until the heart stops. The same experiment is repeated with the standard. The ratio of the minimum dose of the unknown and standard is established.

2. *Recording of Responses of Unknown and Standard Drugs in the Same Preparation Repeatedly:* The effect of the unknown and of the standard are observed on the same preparation repeatedly. The dose of the unknown is then adjusted until its effect is equal to that of the standard. Guinea pig illeum for determining histamine and rat uterus for oxytocin are some of the preparations used in this method.

3. *Percentage of Effects:* LD50 and ED50 of the unknown is determined in a number of animals and compared with similar values obtained with the standard drug.

Biologically Standardized Drugs: Following drugs are standardized by biological methods:

1. Antibiotics: Tetracyclines, streptomycin, gentamicin, kanamycin, vancomycin, nystatin.
2. Prepared Digitalis.
3. Vitamin D.
4. Immunological Products: Antitoxins, antisera, vaccines.
5. Hormones:Insulin, oxytocin, calcitonin, salcatonin, serum gonadotrophins, corticotrophin.
6. Blood and related products: Factor VIII, Factor IX, protamine sulphate.
7. Enzymes: Chymotrypsin, hyaluronidase, pancreatin.

PHARMACOPOEIA

In order to ensure the maintenance of the good standard of drugs, many countries of the world publish their own pharmacopoeias.

Pharmacopoeia is an official book published under legal authority of the Government of the country who appoint Pharmacopoeia Commission and its Committees of Experts to prepare pharmacopoeia and to revise it after every 5 years.

Pharmacopoeia describes the standards of drugs included in it. It gives description of their physical properties and tests for their identity, purity and potency. Drugs manufactured and sold in the country must conform to the specifications and standards laid down in

the Pharmacopoeia, according to whose standards the drug is claimed to have been prepared.

In Pakistan, British Pharmacopoeia (B.P) is usually followed. Other pharmacopoeias in use are: United States Pharmacopoeia (U.S.P), European Pharmacopoeia (E.P) and International Pharmacopeia (P.I). Also Pharmaceutical Codex (B.P.C) and National Formulary (N.F) are used.

British Pharmacopoeia was first published in 1860. Its latest edition was published in 1988. It consists of two volumes. Volume I comprises of Monographs of Medicinal and Pharmaceutical substances. In each Monograph, information about the drug regarding its source, chemical and physical composition, method or methods of assay, storage, main actions and uses, usual dose range and pertinent information is given. Volume II comprises of Monographs of Formulary, Blood Products, Immunological Products, Radiopharmaceutical Preparations and Surgical Materials.

Drugs listed in Pharmacopoeias and other official publications are called *Official Drugs*. All drugs thus may be divided into two groups, official and non-official.

As official publications are usually revised after every five years or so, a large number of drugs are being developed in the meantime. Many of these drugs are useful, safe and effective. Such drugs are described in non-official publications. When pharmacopoeia is revised some of these drugs are added in the new edition of the Pharmacopoeia. Some less useful and unsafe drugs already listed in Pharmacopoeia are deleted from it.

DRUGS ACT

In most of the countries of the world, manufacturing, distribution, sale and import and export of drugs is regulated by Drugs Act and rules enforced in the country. Before the creation of Pakistan, Drugs Act 1940 and its rules were enforced in India. These rules remained applicable for many years in Pakistan. In 1972 Generic Drugs Act was enforced. According to it the drugs were to be sold under Generic Names (Internationally Approved Names based on the chemical structure of drugs) and not under Trade Names (Proprietory, Patent Names). There are advantages as well as disadvantages of both Generic and Trade names.

Generic Drugs Act was replaced by *DRUGS ACT 1976* and at present this act and rules made thereunder are enforced in Pakistan. It is necessary for the members of the medical profession to understand the implications of this act and avoid violation of the act during performance of their professional duties.

Drugs of standard quality must always be used in hospitals, dispensaries, pharmacies and clinics so that patients get the maximum benefit from the modern drugs.

Govt. has appointed Drug Inspectors whose duty is to ensure that standard drug are being manufactured and sold in the country. They take samples of drugs and send to Drugs Testing Laboratory for analysis. If drugs are not of standard quality, they register case against the defaulter in the Drugs Court established by the Govt. for this purpose. If found guilty, the defaulter is punished under the Drgs Act 1976.

Given below are definitions of some commonly used terms regarding drugs as given in the Drugs Act:

Drug is a substance or a mixture of substances that is manufactured, sold, stored, offered for sale or represented for internal or external use in the treatment, mitigation, prevention or diagnosis of disease in human beings or animals. Surgical ligatures, sutures, bandages, absorbent cotton, disinfectants, adhesive plasters, gelatin capsules and antiseptic solutons are also included amongst drugs for the purpose of Drugs Act 1976.

Adultrated Drug means a drug which consists in whole or in part of any filthy, putrid or decomosed substance or which contains any foreign matter or which has been manufactured, packed or held under unsanitary condition wherby it may have been contaminated with dirt, filth or any other foreign matter or whereby it may have been rendered injurious to health, or it has been mixed with any substance so as to reduce its quality or strength.

Counterfeit Drug means a drug the label or outer packing of which is an imitation of, or resembles or so nearly resembles as to be calculated to deceive the label or outer packing of a drug of another manufacturer.

Misbranded Drug means a drug which is not labelled in the prescribed manner or the label or container of which bears any statement, design or device which makes any false claim for the drug.

Spurious Drug means drug which does not contain the active ingredient of the drug which it claims to be or claims to be the product of a manufacturer, place or country whereas it is not truly such product or bears the name of a company but that company is fictious or does not exist.

Substandard Drug means a drug which is not of the standard quality in accordance with the prescribed specifications or those given in the most recent edition of publications such as Pakistan Pharmacopoeia, British Pharmacopoeia, British Pharmaceutical Codex, United States Pharmacopoeia.

Expiry Date of Drug means the date stated on the label of a drug after which the drug is not expected to retain its claimed efficacy, safety, quality, potency or after which it is not permissible to sell the drug.

Pakistan National Formulary (P.N.F.):

Federal Ministry of Health, Govt. of Pakistan registers drugs (both manufactured in Pakistan or imported from abroad) for marketting in the country. The registered drugs are published in Pakistan National Formulary (P.N.F.).

DEVELOPMENT OF NEW DRUGS

DRUG EVALUATION

Whereas the earlier drugs used by mankind were obtained from plants and animals, drugs in modern use are discovered, developed and manufactured in pharmaceutical industrial laboratories. Earlier drugs came into use mainly emperically or through chance observations. Drugs in modern era are developed with the concerted efforts of chemists, pharmacologists and clinicians after planned and organized studies, which are time consuming and expensive. Several thousand molecules may be tested before the discovery of a useful drug. Consequently costs involved in the development of a new drug are enormous.

New drugs may be obtained by the following three approaches:

1. *Modification of Structure of a Known Drug*: The old drug is used as a starting point by the medicinal chemist to prepare different compounds which are compared to the standard old drugs in animal tests e.g. Homatropine from atropine, hyoscine butylbromide from hyoscine, thiazide diuretics from carbonic anhydrase inhibitors. Such modifications and their pharmacological and therapeutic evaluations usually lead to new drugs which are more active, less toxic or easier to use than the original drug.

2. *Random Screening:* Thousands of new drugs prepared by chemists are submitted to pharmacological screening. A whole battery of different animal tests is carried out. Animal behaviour is observed. Several doses of the compound are given to group of mice and their behaviour is monitored by trained observers or automatic apparatus. Their activity, temperature, heart and respiratory rates are recorded and compared with control groups. All changes or lack of changes are registered on special forms. The profile of activity of the drug under investigation is compared with the profiles of standard drugs. This kind of test can detect many types of drugs such as sedative, hypnotic, tranquilliser, psychostimulant, [illegible] relaxant, analgesic, antipyretic, convulsant, sympathomimetic, parasympatholytic etc.,

If a compound is found to possess some activity in the primary screening, then it is subjected to more *detailed pharmacological and sometimes, biochemical study* devised in the light of the initial results. This investigation is done on whole animals and on isolated tissues. Mice, rats, rabbits, guinea pigs, cats and dogs are used in such studies.

3. *Synthesis of Substances which modify Biological Process:* New compounds modified from known hormone or substrate are evaluated for their effect on precisely defined biological tests. Compounds which interfere in physiological processes may prove useful in the treatment of human diseases.

Knowledge of the mode of action of a potential new drug greatly enhances prediction from animal to what will happen in man. However many useful drugs have been discovered and used without understanding their mode of action.

Pharmacokinetic studies in animals are also undertaken. These will eventually enhance the efficiency of clinical investigations.

Effects of graded single doses are usually studied in early pharmacological investigations. Occasionally chronic pharmacological studies with regular dosage for days or weeks are needed, as these are the drugs which are to be administered to human beings for prolonged period for the management of illness.

Preclinical Toxicity Studies:

Compounds which are potential useful drugs must be carefully evaluated for potential risk before clinical testing is begun. Preclinical toxicity testing consists of the following procedures:

Acute Toxicity Studies are done to determine the adverse effects of increasing single dose. LD50, ED50 and Therapeutic Index are determined. These studies are usualy done in two species through two routes of administration.

Subacute Toxicity Studies are done in two species, usually rats and dogs, which are exposed to a range of 3 doses. Generally drug is given daily upto a maximum period of 6 months. The appearance, activity, food intake, growth and reproductive ability in groups of animals are observed. Routine urine and blood examination is done. Microscopic examination of most tissues especially of bone marrow, liver and kidney of animals that die as well as sample animals killed at interval during the studies is carried out.

Chronic Toxicity Studies are done for 1 to 2 years in case of drugs which are to be used in human for prolonged period e.g. antiepileptics, antihypertensives. Histological examination of tissues of animals that die and the sample animals killed at intervals during thse studies is carried out. Main object of these studies is to know which organs are susceptible to drug toxicity.

Effects on Reproductive Functions including Teratogenicity: Extensive testing of new drugs in pregnant animals has become essential since the Thalidomide disaster. Animal tests include administration before mating to detect effects on fertility of both sexes, administration throughout pregnancy, monitoring the birth and development of young animals through to maturity and testing their reproductive performance.

Mutagenesis: Abnormalities of genetic material (genes, chromosomes) of cells may be caused by drugs so that a permanent change in the hereditary constitution (mutation) may occur. When mutation occurs in reproductive cells (spermatazoa, ova) then a hereditary defect occurs, which may appear in first generation progeny of the individual or in future generations. When mutation occurs in somatic cells then these tissues may develop abnormal characteristics and become malignant.

With the present knowledge it is difficult to etablish a causal association with the drug which may have been taken and then stopped a long time previously. However tests about effects on genetic structure of bacteria (Ames Test) or mammalian cells in culture are done to study this aspect of drug toxicity.

Carcinogenesis: Tumours can be induced by drugs and other chemicals, sometimes as a result of mutation.

Any irritant substance seems to be carcinogenic in animals under the right experimental conditions.

Anticancer drugs may be carcinogenic. They are usually also teratogenic and mutagenic.

Animal tests to predict carcinogenicity for man are in wide use, especially for certain groups of drugs which are under suspician e.g. oral contraceptives. These are administered for 7 years to beagle dogs or for 2 years to rats or for 1 year to mice.

Testing Drugs on Humans:

When a new compound considered to be a potential useful drug has been discovered in tests on animals, its rational clinical development is the next object. For this purpose drug is to be tested on human beings. In this regard studies are carried out in the following stages:

1. *Pharmacological Study:* In order to confirm the results obtained in animal experiments, the drug is tested on normal persons (healthy volunteers) as well as on patients.

These studies often begin with a dose-ranging study using 1/50 to 1/100 th effective dose in animals and increasing until the desired effect or adverse effects are seen. These studies should only be

performed by experienced staff under medical supervision and in premises with appropriate resusciative facilities and support.

2. *Establishment of Therapeutic Utility:* Having confirmed pharmacological action of the drug in human beings, studies are carried on larger number of patients to establish its potential therapeutic utility and dosage schedules as well as to have some idea about its toxicity.

3. *Formal Assessment of Therapeutic Merit:* Therapeutic utility having been established, the drug is compared with the existing remedies on patients so as to formally assess its therapeutic merit. Clinical trials are carried out for this purpose.

4. *Monitoring of Adverse Effects and Efficacy:* After the drug has been released into the market for general prescribing by doctors, safety and efficacy of the product is monitored. As serious adverse effects may appear quite sometime after introduction of the product, post-registration surveillance is necessary.

DRUG EVALUATION

Drug evaluation comprises of (*i*) clinical trials, followed by (*ii*) Surveillance programmes.

Clinical Trials are conducted to formally assess therapeutic merits of drug under investigation. Following are various types of clinical trials.

Randomised Controlled Trials: Clinical trial is conducted in equivalent groups of patients. Difference in age, sex, race, duration of disease may markedly affect the outcome of trial. Therefore, it is essential that various groups of patients involved in drug trial should be equivalent in all respects. For this purpose patients should be alloted to groups by random allocation. Treatments must be carried out in all groups concurrently as diseases may vary in severity with time, virulence of an organism may change, especially in epidemics, the weather and industrial atmospheric pollution may influence respiratory and cardiac disease and doctors and nurses may change in number and quality.

Double Blind Technique: As both doctors and patients are subject to bias due to their beliefs and feelings, a control device known as double-blind technique has been invented. The drug under investigation and a placebo (dummy) of identical appearance are given to groups of patients in such a way that the patient does not know whether he is receiving the active drug or placebo. The investigator or observer is also kept ignorant of whether the patient is receiving the active drug or placebo. At the same time, the technique provides

another control, a means of comparison with the magnitude of placebo effects.

The double blind technique being a sound device has been assumed to be a complete method of drug evaluation in itself.

Within-patient Comparison: In chronic diseases e.g. Parkinsonism, hypertension, anxiety, it is possible to give each of the traetments under test (new drug, old drug, placebo) to each patient thus conveniently using him as his own control. Each drug both preceeds and follow each other drug the same number of times to avoid the risk of bias due to 'carry-over' effect of the drug after its administration to the patient has been stopped.

Surveillance Programmes: The opinions and practice of physicians providing routine care are monitored to obtain information in the dosage, route, adverse effects, efficacy of the drugs etc.

In hospitals, system is organized. Pharmacists and nurses are employed to collect data on standardised self-coding from consecutively admitted patients by using clinical records and having interviews with clinical staff and patients. Information regarding age, sex, weight, consumption of tobacco, alcohol, previous drugs, details of present therapy, reasons for its discontinuation, adverse or beneficial events during stay in hospital etc. is collected. After the patient has left hospital the final editing of data sheets is done.

Outside hospitals, surveillance programmes are more difficult and more expensive. Techniques include surveillance of prescriptions where these are eventually handled in a central office. Questionaires are sent to doctors using the drugs that are being monitored.

PLACEBOS

Placebo is an inert substance used as a dummy drug and, therefore, made to appear identical with the active drug.

Placebos are used for two purposes:

(*i*) As a control in scientific evaluation of drugs during clinical trials. In Randomised Controlled Trials the drug under investigation is compared with a placebo, the patient being unaware whether he is getting the active drug or placebo. In Double-Blind Technique both the patient and the investigator or observer are unaware whether the patient is getting the active drug or the placebo.

(*ii*) To benefit or please a patient (Latin, Placebo = I will please). This is not due to any pharmacological action but by psychological means.

Placebo Effect is not pharmacodynamic action in the strict sense of the word. It is independent of the chemcal nature or dosage of the administered substance.

Placebos are usually given to patients with mild psychological disorders who attributes their symptoms to physical disease. Alleviation of symptoms is usually temporary. Placebos may also be used in patients with chronic incurable diseases when they need a prop to sustain their courage.

An individual who feels changes of physical and mental state after taking a pharmacologically inert substances is called a *placebo-reactor*. Such suggestable people are likely to respond favourably to any treatment. Some 35% of the physically ill and 40% or more of the mentally ill respond to placebos.

NOMENCLATURE OF DRUGS

A drug may have more than one name. Actually, most drugs have at least three names.

Chemical Name: This indicates the molecular structure. Many of these names are complex and unwidely. This name describes the compound for chemists. It is obviously unsuitable for prescribing.

Official (Approved) Name: It is usually the abbreviated form of the chemical name. This name is used in pharmacopoeia and chosen by official bodies.

Proprietory Name (Brand, Trade Name): This is the name given by the company which markets the drug. It is the commercial property of a pharmaceutical company. It indicates a particular formulation of a particular substance by a particular manufacturer.

Since several companies market the same drug under different proprietory names, unnecessary confusion may arise. Whenever possible, drugs should be prescribed by their approved names.

Example:	Chemical Name	:	Acetyl-p-aminophenol
	Official Name	:	Paracetamol
	Proprietory Name	:	Calpol, Panadol

DRUGS INTERACTIONS

When two or more drugs are given at the same time, they may exert their effect independently or they may interact i.e. one drug may influence the action of the other drug. Modification of the action of a drug by another drug given concurrently or sequentially is called Drug Interaction. The result of the interaction may be an increase or decrease of the effect of other drug by another, or occasionally there may

be some other effect. Thus the interaction may be beneficial, neutral or detrimental.

Drugs may also interact with various foods, with chemicals used in laboratory tests or with certain endogenous physiological agents. Patients taking Monoamine Oxidase Inhibitors should not take foods containing tyramine such as cheese, yoghurt. Hypertensive crises may occur.

Interactions between drugs may occur *in vitro* (outside the body) or *in vivo* (inside the body). Usually the term incompatibility is used in reference to interactions in vitro.

Such interactions specially occur with intravenous fluids when drugs are added to the reservoir. The principal factor causing interaction is change of pH. No drug should be added to blood, amino acid solutions or to fat emulsion.

Some of the examples of *in vitro* drug interactions are given below:

(*i*) Thiopentone and suxamethonium interact chemically and should not be put in the same syringe. (*ii*) Heparin and benzylpenicillin also interact. In presence of dextrose, hydrocortisone ad sympathomimetics, activity of heparin is rapidly lost. (*iii*) Sympathomimetics, aminophylline, compound vitamin preparations and Vit C are liable to interact with a wide range of drugs.

Drugs interactions are drug reactions *in vivo*. They may be pharmacokinetic or pharmacodynamic.

Pharmacokinetic Interactions: Drug interactions may occur during absorption, transportation, metabolism, storage or excretion of drugs; when one drug alters these processes of the other drug thus increasing or reducing the amount of drug available to produce its pharmacological effects. These interactions are not easily predicted. Only a small portion of patients taking the combination of drugs is affected. Interactions occuring with one drug cannot be assumed to occur with related drugs unless their pharmacokinetic properties are known to be similar.

Interactions Affecting Drug Absorption: Either the rate of drug absorption or the amount of drug absorbed can be altered by drug interactions. A reduction in the total amount of drug absorbed is likely to result in ineffective therapy.

Gut motility, pH of gut contents, gut mucosal function, alteration in gut flora by antimicrobials and physico-chemical interactions within the gut are responsible for such drug interactions. Examples:

(*i*) Antacids containing calcium or aluminium interfere with the absorption of tetracyclines. (*ii*) Cholestyramine reduces absorption of

digitalis and thyroxin. (*iii*) Metoclopramide reduces absorption of cimetidine. (*iv*) Liquid paraffin interferes with the absorption of vitamin D. (*v*) Phenobarbitone significantly reduces the absorption of griseofulvin. (*vi*) Phenytoin and oral contraceptives reduce absorption of folic acid. (*vii*) Rate of absorption of paracetamol is reduced by anticholinergics and increased by metoclopramide.

Interactions due to Changes in Protein Binding of Drugs: Most drugs are loosly bound to plasma proteins. Protein-binding sites ar nonspecific and one drug can displace another thereby increasing the proportion of free drug available for pharmacological action thus enhancing its effects.

However this is of significance only in cases of drugs which are extensively protein bound (more than 90%). Examples: (*i*) Phenylbutazone, indomethacin, sulphonamides, tolbutamide and clofibrate displace anticoagulant warfarin from its plasma protein binding site thereby increasing anticoagulant action of warfarin. (*ii*) Dicoumarol, sulphonamides and salicylates, displace tolbutamide from its plasma protein binding site resulting in severe hypoglycemia. (*iii*) Sulphonamides displace bilirubin to cause kernicterus.

Interaction Affecting Drug Metabolism: Many drugs are inactivated by metabolism in the liver. Rate of metabolism of a drug may be increased by another drug due to enzyme induction of the hepatic microsomal enzyme system. This results in lower plasma concentration and a reduced effect of the drug. On withdrawal of enzyme inducer, plasma concentrations increase and toxicity may occur. Important enzyme inducers are phenobarbitone, phenytoin sodium, dichloralphenazone and rifampicin. Drugs affected include warfarin and oral contraceptives. Examples; (*i*) Phenobarbitone accelerates the metabolism of oral anticoagulants (warfarin), phenytoin sodium, griseofulvin and hydrocortisone due to induction of hepatic microsomal enzymes. (*ii*) Monoamine Oxidase Inhibitors interfere with metabolism of narcotic analgesics, barbiturates and tricyclic antidepressants and increase their effects.

Some drugs inhibit the metabolism of other drugs producing higher plasma concentrations thereby increasing their effect and risk of toxicity. Examples; (*i*) Isoniazid, PAS, chloramphenicol, disulfiram and dicumoral potentiate action of phenytoin by inhibiting its metabolism. (*ii*) Allopurinol, used for gout, is xanthine oxidase inhibitor. It potentiates toxic effects of azathioprim and 6-mercap-topurine which are also metabolised by xanthine oxidase.

Interactions Affecting the Renal Excretion of Drugs: Drugs are eliminated through the kidney both by glomerular filteration and by active tubular secretion. Competition occurs between drugs which

share active transport mechanism in the proximal tubule. Examples: (*i*) Probenecid delays the excretion of many drugs e.g. penicillins, some cephalosporins, indomethacin and dapsone. Aspirin may increase the toxicity of methotrexate by a similar mechanism. (*ii*) Sodium bicarbonate increases excretion of aspirin and barbiturates; ammonium chloride increases excretion of amphetamines.

Pharmacodynamic Interactions occur between drugs which have similar or antagonistic pharmacological effects or side effects. They may be due to competition at receptor sites or occur between drugs acting on the same physiological system. Their characteristics are; (*i*) They are usually predictable from a kowledge of the pharmacology of the interacting drugs. (*ii*) In general interactions demonstrated with one drug are likely to occur with related drugs. (*iii*) They occur in most patients who receive the interacting drugs.

Examples of pharmacodynamic interactions are (*i*) Alcohol, antihistamines and narcotic analgesics potentiate effects of hypnotics and sedatives. (*ii*) Aspirin and dipyridamole potentiate anticoagulant effect of heparin and phenindione. (*iii*) Metoclopramide antagonises effect of atropine, propantheline, benzhexol and narcotic analgesics on G.I. tract. (*iv*) Thiazides increase toxicity of digoxin and other cardiac glycosides (*v*) Ethacrynic acid and frusemide increase ototoxicity of aminoglycosides. (Gentamicin) (*vi*) Antihistamines and phenothiazine derivatives increase side effects (dry mouth, urine retention) of anticholinergic drugs such as benzhexol.

Relative Importance of Interaction: All drugs interactions are not necessarily of clinical importance. However, with the introduction of large number of new potent drugs and their frequent use, the subject of drug interaction has assumed great importance. Over the counter (OTC) sale of many drugs (without prescription of doctors) may lead sometime to dangerous drug interaction. It is the duty of all members of the medical profession to warn the patient who is already taking drugs prescribed by the physician for the treatment of his illness not to take any other drug for some new illness without consulting the doctor. This includes remedies for cough, common cold and pains in the body. For example, a patient on oral anticoagulant therapy if he takes aspirin he may have bleeding due to increased anticoagulant effect. Similarly effect of antihypertensive drug taken by a patient suffering from hypertension may decrease by most of the medicines taken for common cold.

The drugs most often involved in serious interactions are those with a small therapeutic index such as phenytoin and those where the dose must be carefully controlled according to the response, as with oral anticoagulants, antihypertensives, antidiabetics, cardiac glycosides, antiarrhythmics, antiepileptics and anticancer drugs.