Pharmacology is the study of the effects of chemical agents of therapeutic value or with the potential toxicity on biological systems. The word Pharmacology comes from the Greek words: pharmakon meaning “drug” and logos meaning “Knowledge”. Pharmacology is the study of how drugs interact with living organisms to produce a change in function. Pharmacology is the science of drug action on biological systems. Early pharmacologists focused on natural substances, mainly plant extracts. Pharmacology was developed in the 19th century as a new biomedical science that applied the principles of scientific experimentation to therapeutic contexts.

In its entirety, it embraces knowledge of the sources, chemical properties, biological effects and therapeutic uses of drugs. Pharmacological studies range from those that determine the effects of chemical agents upon subcellular mechanisms, to those that deal with the potential hazards of pesticides and herbicides, to those that focus on the treatment and prevention of major diseases by drug therapy. Pharmacologists are also involved in molecular modeling of drugs, and the use of drugs as tools to dissect aspects of cell function.

Drug
The word “drug” is derived from a French word “drogue” which means a “dried herb”. A drug is a chemical that affects physiological function in a specific way. According to WHO, a drug is any substance or product that is used or intended to be used to modify or to explore physiological system or pathological state for the benefit of the recipient (man or other animal).

A drug is used in the diagnosis, treatment, prevention, control or cure of the diseases. More generally, a chemical, which, in a solution of sufficient concentration, will modify the behaviour of cells exposed to the solution. Drugs produce only quantitative changes in the behaviour of cells; i.e., drugs increase or decrease the magnitude, frequency, and duration of the normal activities of cells. Drugs used in therapy never produce qualitative changes in cell behaviour short of producing death of the cell, e.g., a nerve cell cannot be made to contract or a muscle cell cannot be made to secrete saliva by use of a drug.

Scope of Pharmacology
The scope of pharmacology is rapidly expanding and provides the rational basis for the therapeutic use of the drug. It is a rather young science having first achieved independent recognition at the end of 19th century. Even though many remedies were used, doctors were reluctant to apply scientific principles to therapeutics. Drugs have been the most widely used form of therapeutic interventions. Reliance on natural products, mainly from plants predominated. In the 1920s, many synthetic chemicals were first introduced and the modern pharmaceutical companies began to develop.

Scientific understanding of drugs enables us to predict the pharmacological effect of a new chemical that will produce a specified therapeutic effect. This phenomenon is growing rapidly. Paul Ehrlich insisted that the drug action is to be understood in terms of conventional chemical interactions between the drugs and tissues.

The scope of pharmacology has expanded greatly over the last decade to incorporate many new
approaches such as computer-assisted drug design, genetic screens, protein engineering and the use of novel drug delivery vehicles including viruses and artificial cells. Our society needs pharmacologists who understand the basis of modern therapeutics for careers within academic, pharmaceutical and governmental laboratories to study and develop tomorrow’s drugs.

**Divisions of Pharmacology**

**Behavioural pharmacology** is the study of the effect of drugs on behaviour. Research includes topics such as the effects of psychoactive drugs on the phenomena of learning, memory, wakefulness, sleep, drug addiction, and the behavioural consequences of experimental intervention in enzyme activity and brain neurotransmitter levels and metabolism.

**Cardiovascular pharmacology** concerns the effect of drugs on the heart, the vascular system and those parts of the nervous and endocrine systems that participate in regulating cardiovascular function. Researchers observe the effects of drugs on arterial pressure, blood flow in specific vascular beds, release of physiological mediators and on neural activity arising from central nervous system structures.

**Biochemical and Cellular pharmacology** uses the methods of biochemistry, cell biology and cell physiology to determine how drugs interact with, and influence, the chemical “machinery” of the organism. The biochemical pharmacologist uses drugs as probes to discover new information about biosynthetic pathways and their kinetics, and investigate how drugs can correct the biochemical abnormalities that are responsible for human illness.

**Immunopharmacology** It deals with the immunological actions of drugs in immune response and development of antibodies in response to a drug.

**Chemotherapy** is the area of pharmacology that deals with drugs used for the treatment of microbial infections and malignancies (cancer). Pharmacologists work to develop chemotherapeutic drugs that will selectively inhibit the growth of, or kill, the infectious agent or cancer cell without seriously impairing the normal functions of the host.

**Clinical pharmacology** is the study of pharmacodynamics and pharmacokinetics in human beings. Clinical pharmacologists study how drugs work, how they interact with other drugs, how their effects can alter the disease process, and how disease can alter their effects. Clinical pharmacologists are in the forefront of research using data from the human genome project to determine how and why individuals respond differently to drugs.

**Pharmacotherapeutics** is the study of the use of drugs in the diagnosis, prevention and treatment of disease states. Therapeutics mainly focuses on the correlation of the actions and effects of drugs and other chemical agents with the physiological, biochemical, microbiological, immunological, or behavioural factors influencing disease conditions. It also considers how disease may modify the pharmacokinetic properties of a drug by altering its absorption into the systemic circulation and/or its disposition.

**Pharmacoepidemiology** is the study of drug effects at the population level. It is concerned with the variability of drug effects between individuals in a population, and between populations. Pharmacoepidemiological studies also take into account patient compliance and other factors that apply when the drug is used under real-life conditions.

**Pharmacoeconomics** is the branch of health economics which aims to quantify in economic terms the cost and benefit of drugs used therapeutically.

**Drug discovery, Drug development and Regulatory affairs** encompasses, but is not limited to; target discovery and validation, medicinal chemistry, combinatorial chemistry, molecular modeling and drug design, structure-pharmacological function relationships, functional genomics and proteomics, high throughput screening, identification and development of natural products, nutraceuticals, pharmacokinetics and pharmacodynamics, clinical testing and drug regulation/registration, clinical contracting and pharmacoepidemiology and pharmacoeconomics.

**Drug Metabolism and Disposition** is the study of the pharmacokinetics of drugs as well as the enzymatic metabolism of drugs.

**Endocrine pharmacology** is the study of actions of drugs that are either hormones or hormone derivatives, or drugs that may modify the actions of normally secreted hormones.

**Neuropharmacology** is the study of drugs that modify the functions of the nervous system, including the brain, spinal cord, and the nerves that communicate.
with all parts of the body. It helps to probe the neurochemical disorders underlying specific disease states to find new ways to use drugs in the treatment of diseases.

**Molecular pharmacology** deals with the biochemical and biophysical characteristics of interactions between drug molecules and those of the cell. The methods of molecular pharmacology include precise mathematical, physical, chemical and molecular biological techniques to understand how cells respond to hormones or pharmacologic agents, and how chemical structure correlates with biological activity.

**Systems and Integrative Pharmacology** is the study of drug action and toxicity in the whole animal.

**Toxicology** is the study of the adverse or toxic effects of drugs and other chemical agents. It is concerned not only with drugs used in the treatment of disease, but also with chemicals that may present household, environmental, or industrial hazards.

**Veterinary pharmacology** concerns the use of drugs for diseases and health problems unique to animals.

**RECENT ADVANCES AND RELATED SCIENCES**

**Biotechnology:**
Originally, this was the production of drugs or other useful products by biological means (e.g. antibiotics from microorganisms or production of monoclonal antibodies). Currently in the biochemical sphere, biotechnology refers mainly to the use of recombinant DNA technology for a wide variety of purposes, including the manufacture of therapeutic proteins, diagnostics, genotyping, production of transgenic animals, etc.

**Pharmacogenetics:**
This is the study of genetic influences on responses to drugs. Originally, pharmacogenetics was focused on familial idiosyncratic drug reactions, where affected individuals show an abnormal – usually adverse – response to a class of drug. It now covers broader variations in drug response, where the genetic basis is more complex. It explains the inheritance of characteristic patterns of interaction between chemicals (drugs) and organisms. Pharmacogenetic studies illuminate many intraspecific and interspecific similarities, and differences in pharmacodynamic and pharmacokinetic mechanisms.

**Pharmacogenomics:**
This recent term overlaps with pharmacogenetics, describing the use of genetic information to guide the choice of drug therapy on an individual basis. The underlying assumption is that differences between individuals in their response to therapeutic drugs can be predicted from their genetic make-up. On this principle, discovering which specific gene variations are associated with a good or poor therapeutic response to a particular drug should enable the tailoring of therapeutic choices on the basis of an individual’s genotype. So far, the concept is largely theoretical, but if proven valid, the consequences for therapeutics will be far reaching.

**SOURCES OF DRUGS**
Until the start of the 20th century, the substances for the treatment of any disease were obtained from natural sources. Among the natural sources plants were mainly used. Sometimes minerals and occasionally animals were also used. Now a days most of the drugs are manufactured in the laboratories and microorganisms also serve as a good source of drugs.

**(i) Plant sources:**
Various parts of the plants like root, stem, leaf and barks were used for the treatment of diseases. Many plants used as drugs can no longer be considered for rational treatment. Some of them such as **digitalis**, **belladonna** remain important. The pharmacologically active constituents of plants are grouped according to their physico-chemical properties and include alkaloids, oils, gums, mucilage, glycosides and carbohydrates.

**(ii) Animal sources:**
Dry skin of toad is used for treating tooth ache and bleeding gums in China. Later it was found that the toad skin contains **adrenaline**.

**Vitamin A** is obtained from the liver of cod fish.

**Insulin** is extracted from porcine and bovine pancreas.

**(iii) Mineral sources:**
**Kaolin** for the treatment of diarrhea.

**Calomel** for constipation.

**Iron** for general weakness in anaemia.

**Gold** for arthritis.

**Aluminium hydroxide** and **magnesium trisilicates** as antacids.
(iv) Synthetic sources:
Majority of drugs in use today are prepared synthetically from chemical substances. Semi-synthetic drugs are naturally occurring substances that have been chemically altered. Some examples are sulphonamides, thiazides, diuretics, oral antidiabetic drugs, synthetic steroids, etc. Pharmacological activity is the function of the chemical and physical properties of drugs. The chemical structure can be modified in search of better, more potent and safer drugs.

(v) Recombinant DNA technology:
This innovative technology is now being used for the production of human insulin by introducing insulin gene into harmless strains of *Escherichia coli*. The amino acid sequence of insulin thus produced is identical to endogenous human insulin.

A synthetic human growth hormone is also being prepared by recombinant technology. Thus in the future, recombinant technology would be used for producing more drugs derived solely from animal or human sources.

CLASSIFICATION OF DRUGS
Drugs may be classified according to one or more of the following ways:

- their anatomical site of action,
- their therapeutic activity,
- their mode of action,
- their chemical structure, etc.

E.g. adrenaline can be classified respectively as,
- a drug acting on cardiovascular system,
- a drug used for cardiac arrest,
- an agonist drug binding with adrenergic receptors,
- a catecholamine.

PRINCIPLES OF PHARMACOLOGY
Pharmacodynamics is the study of the molecular, biochemical and physiological effects of drugs on cellular systems and their mechanisms of action. It also correlates drug action with its chemical structure (SAR – structure & activity relationship).

Pharmacokinetics (kinein means “to move”) is the study of the factors which determine the amount of chemical agents (drugs) at their sites of biological effect at various times after the application of an agent or drug to biological systems. It deals with the absorption, distribution, metabolism (biotransformation) and excretion of drugs and their relationship to their pharmacological response.

Relationship between man and drug

ABSORPTION
Absorption is the movement of a drug from its site of administration into the central compartment (plasma) and the extent to which this occurs. It is therefore important for all routes of administration, except intravenous injection.

Oral ingestion is the most common method of drug administration. It also is the safest, most convenient, and most economical.

Factors affecting drug absorption from the GIT
1. Biotransport of drugs through cell membranes:
   Pharmacokinetic factors
   - their anatomical site of action,
   - their therapeutic activity,
   - their mode of action,
   - their chemical structure, etc.

2. Physicochemical properties of the drug/formulation
   (a) Physical state
   (b) Solubility – dissolution, ionisation, pKa, etc.
   (c) Polymorphism and salt formation

3. Dosage forms
   (a) Particle size
   (b) Disintegration/dissolution time
   (c) Type of formulation

4. Effect of pH on ionization and drug absorption
   (a) Particle size
   (b) Disintegration/dissolution time
   (c) Type of formulation

5. Age
6. Factors at the absorption site
   (a) Blood flow
   (b) Total surface area
   (c) GI motility and transit time
   (d) GI pH
   (e) Presence or absence of food
   (f) Presence of other agents
   (g) Presystemic metabolism of drugs

7. First pass metabolism
8. Pharmacogenetic factors
9. Disease states

**BIOAVAILABILITY**

The term bioavailability is used to indicate the extent to which a drug reaches its site of action or a biological fluid from which the drug has access to its site of action. US FDA defines bioavailability as “the rate and extent to which the therapeutic moiety is absorbed and becomes available at the site of action”. When the drug is given in intravenous or intra arterial route, the bioavailability is 100%.

**BIOEQUIVALENCE**

Two drug products are considered to be pharmaceutical equivalents if they contain the same active ingredients and are identical in strength or concentration, dosage form, and route of administration. Two pharmaceutically equivalent drug products are considered to be bioequivalent when the rate and extent of bioavailability of the active ingredients in the two products are not significantly different under suitable conditions.

**HALF LIFE (t½)**

The period of time required for the concentration or amount of drug in the body to be reduced to exactly one-half of its given concentration or amount.

**AREA UNDER CURVE (AUC)**

It is the area under the plot of plasma concentration of drug (not log concentration) against time after drug administration. The AUC is of particular use in estimating bioavailability of drugs, and in estimating total clearance of drugs (ClT). The ratio of the AUC after oral administration of a drug formulation to that after the intravenous injection of the same dose to the same subject is used during drug development to assess a drug’s oral bioavailability.

**VOLUME OF DISTRIBUTION (Vd)**

It is the volume which a drug appears to have been distributed after administration. To calculate the theoretical volume of distribution we shall assume that a drug has been completely absorbed from its site of application, has reached equilibrium in its distribution among the several tissues of the body, and that no biotransformation or excretion of the drug has occurred, if one knew the dose of the drug administered and the average concentration of the drug in the body, the apparent volume into which the drug had been dissolved (Vd) could be determined from the relationship: concentration = mass/volume. Since these idealized conditions are unobtainable in practice, the volume of distribution of a drug can only be approximated using the experimental data,

\[
V_d = \frac{\text{Amount of drug in the body (dose in mg)}}{\text{Concentration of drug in plasma (mg/L)}}
\]

**BIOTRANSFORMATION**

Biotransformation is the process of biochemical alteration of drugs in the body whereby they are usually rendered less active or inactive, though sometimes, they may be activated from their inactive original forms. Drug metabolism or biotransformation reactions are classified as either phase I functionalization reactions or phase II biosynthetic (conjugation) reactions. Phase I reactions introduce or expose a functional group on the parent compound such as occurs in hydrolysis reactions. Phase I reactions generally result in the loss of pharmacological activity, although there are examples of retention or enhancement of activity. In rare instances, metabolism is associated with an altered pharmacological activity. Phase II conjugation reactions lead to the formation of a covalent linkage between a functional group on the parent compound or phase I metabolite and endogenously derived glucuronic acid, sulfate, glutathione, amino acids, or acetate. These highly polar conjugates generally are inactive and are excreted rapidly in the urine and faeces.

**FIRST PASS EFFECT**

It is explained as the biotransformation and/or excretion of a drug by intestinal, hepatic and biliary mechanisms following absorption of the drug from the
gastrointestinal tract, before the drug gains access to the systemic circulation.

**CLEARANCE (Cl)**

The clearance of a drug is the volume of body fluid from which the drug is completely removed by biotransformation and/or excretion, per unit time. In fact, the drug is only partially removed from each unit volume of the total volume in which it is dissolved. Since the concentration of the drug in its volume of distribution is most commonly sampled by analysis of blood or plasma, clearance is most commonly described as the “plasma clearance” or “blood clearance” of a substance.

\[
\text{Clearance } Cl = \frac{V_d \times 0.693}{t_{1/2}}
\]

Renal plasma (or blood) clearance \( Cl_R \) is the volume of plasma (or blood) freed of a substance by only renal mechanisms, per unit time.

**Non renal clearance** is the clearance by the fecal route \( Cl_F \), respiratory route \( Cl_R \), salivary route \( Cl_S \) and biliary route \( Cl_B \).

**EXCRETION**

Excretion is the irreversible transfer of drugs and/or their metabolites from the internal to the external environment. The main routes by which drugs and their metabolites leave the body are:

- the kidneys – most of the drugs
- the hepatobiliary system – mainly basic drugs; doxycycline, rifampicin, etc.
- the lungs – volatile drugs & anaesthetics agents
- other routes – sweat, tears, saliva – bromide, iodide
  - milk – steroids, sulphonates, etc.
  - hair, skin – arsenic

Excretory organs, the lung excluded, eliminate polar compounds more efficiently than substances with high lipid solubility. Lipid-soluble drugs thus are not readily eliminated until they are metabolized to more polar compounds.

**RECEPTOR**

A cellular macromolecule, or an assembly of macromolecules, that is concerned directly and specifically in chemical signaling between and within cells. Combination of a hormone, neurotransmitter, drug, or intracellular messenger with its receptor(s) initiates a change in cell function. The regions of the receptor macromolecule to which ligands bind are referred to collectively as the recognition site(s) of the receptor. Those at which the endogenous agonist binds are termed primary or orthosteric sites whereas other ligands may act through allosteric sites. Thus, a receptor is a macromolecular protein to which a drug molecule binds and produces specific response.

**Agonist**

It is a ligand which binds to a receptor and alters the receptor state resulting in a biological response. Agonists may act by combining either with the same site(s) as the endogenous agonist or, less commonly, with a different region of the receptor macromolecule. Agonists in the second category are sometimes referred to as allosteric activators or allosteric agonists.

Some agonists (e.g., glutamate) may only be effective in the presence of another ligand (e.g., glycine) that binds to a different site on the receptor macromolecule. Under these circumstances, glutamate is referred to as the primary agonist and glycine as a co-agonist.

**Spare/reserve Receptors**

A pharmacological system has spare receptors if a full agonist can cause a maximum response when occupying only a fraction of the total receptor population. Thus not all of the receptors in the tissue are required to achieve a maximal response with some high efficacy agonists.

**Partial Agonist**

It is an agent which combines with a specific receptor but produces only a sub-maximal response even when there is 100% receptor occupancy. It also prevents the full agonist from binding to the receptor.

**Inverse Agonist**

Inverse agonist is a ligand that by binding stabilizes a receptor in its inactive conformation. An inverse agonist may combine either with the same site as a conventional agonist, or with a different site on the receptor macromolecule. Conventional agonists increase receptor activity, whereas inverse agonists reduce it.
Antagonist
It is a drug that reduces the action of another drug, generally an agonist. Many antagonists act at the same receptor macromolecule as the agonist. It may bind to the receptor but do not activate it to produce the biological response.

Affinity
It is the tendency of the drug to bind to its receptor. A full agonist and antagonist have the same affinity but the antagonist lacks intrinsic activity.

- **Allosteric (allotropic) modulator**
  It is a ligand that increases or decreases the action of a drug by combining with a distinct site on the receptor macromolecule. **Allosteric enhancers** are modulators that enhance drug efficacy while having no effect on their own. **Allosteric antagonists** are modulators that reduce drug efficacy.

- **Allosteric (allotropic) interaction**
  It is an interaction between ligands that bind to distinct, non-overlapping recognition sites on the receptor macromolecule.

- **Syntopic interaction**
  It is an interaction between ligands that bind to the same recognition site or to recognition sites that overlap on the receptor macromolecule.

- **Allosteric transition**
  This is the isomerization of a receptor macromolecule between multiple conformational states.

Intrinsic Activity
It is the ability of the drug to evoke a specific response after binding to the receptor. It explains the property of a drug that determines the amount of biological effect produced per unit of drug-receptor complex formed. Two agents combining with equivalent sets of receptors may not produce equal degrees of effect even if both agents are given in maximally effective doses; the agents differ in their intrinsic activities and the one producing the greater maximum effect has the greater intrinsic activity.

Intrinsic activity is not the same as “potency” and may be completely independent of it. Meperidine and morphine presumably combine with the same receptors to produce analgesia, but regardless of dose, the maximum degree of analgesia produced by morphine is greater than that produced by meperidine since morphine has a greater intrinsic activity. Intrinsic activity, like affinity, depends on the chemical natures of both the drug and the receptor, but intrinsic activity and affinity apparently can vary independently with changes in the drug molecule.

Efficacy
It refers to the capacity of a drug to produce an alteration in a target cell/organ after binding to its receptor. A competitive antagonist, that occupies a binding site without producing any alteration in the receptor, is considered to have an efficacy of zero. Efficacy is generally independent of potency/affinity, and is related to the maximum effect that a particular drug is capable of producing. Efficacy is both agonist and tissue-dependent. Efficacy is related to intrinsic activity, which is the efficacy per receptor. In practice, the two terms are sometimes used synonymously.

**DRUG ANTAGONISM**
The effect of one drug is diminished or completely abolished in the presence of another. The mechanisms of drug antagonism include:

**Chemical Antagonism**
In this, a drug antagonizes the effect of another drug by simple chemical reaction in solution and as a result the effect of the drug is lost, e.g. use of chelating agents (like dimercaprol) that bind to heavy metal ions and thus reduce their toxicity.

**Pharmacokinetic Antagonism**
It describes the situation in which the antagonist effectively reduces the concentration of active drug at its site of action, e.g. rate of metabolic degradation of warfarin, an anticoagulant, is increased by phenobarbital. Phenobarbital acts by accelerating the hepatic metabolism of warfarin. Other pharmacokinetic aspects like rate of absorption of the active drug from g.i.t. or the rate of renal excretion may be increased.

**Antagonism by receptor block**
Receptor-block antagonism involves two important mechanisms:

1. **Competitive Antagonism**
   In competitive antagonism, the binding of agonist and antagonist is mutually exclusive. This may be because
the agonist and antagonist compete for the same binding site or combine with adjacent sites that overlap (syntopic interaction). Other possibility is that different sites are involved but that they influence the receptor macromolecule in such a way that agonist and antagonist molecules cannot be bound at the same time.

*It is of two types:*

(a) **Reversible, competitive antagonism**

In this type, the agonist and antagonist compete for the same receptor. The log concentration-response curve is shifted parallel towards the right without any reduction of the maximal response.

(b) **Irreversible or non-equilibrium, competitive antagonism**

In this type, the antagonist inactivates the receptors so that effective complex with the agonist cannot be formed even by increasing the concentration of the agonist. The log concentration-response curve is shifted parallel towards the right and also the maximum response is diminished.

2. **Non-competitive Antagonism**

Non-competitive antagonism describes the situation where the antagonist blocks at some point the chain of events that leads to the production of a response by the agonist. Agonist and antagonist can be bound to the receptor simultaneously; antagonist binding reduces or prevents the action of the agonist with or without any effect on the binding of the agonist e.g. verapamil prevent influx of calcium ions through the cell membrane and thus block non-specifically the contraction of smooth muscle produced by other drugs.

**Physiological Antagonism**

This describes the interaction of two drugs whose opposing actions in the body tend to cancel each other, e.g. histamine acts on receptors of parietal cells of the gastric mucosa to stimulate acid secretion, while omeprazole blocks this effect by inhibiting the proton pump.

**ADDITIVE EFFECT**

When total pharmacological actions of two or more drugs administered together is equivalent to summation of their individual pharmacological response, the phenomenon is termed as **additive effect**, e.g. combination of ephedrine and aminophylline in the treatment of bronchial asthma.

**SYNERGISM**

Facilitation of a pharmacological response by the concomitant use of two or more drugs is called drug synergism. This usually results in a total effect greater than the sum of their independent actions e.g. furosemide and intravenous aminophylline; codeine and aspirin; hydrochlorothiazide and reserpine.

**CUMULATION OR DRUG ACCUMULATION**

If a drug is excreted slowly, its repeated administration may build up a sufficiently high concentration of drug in the body to produce toxicity, e.g. digitalis, heavy metals. In some cases, accumulation of a drug may be desired, e.g. use of phenytoin in the treatment of epilepsy.

**THERAPEUTIC INDEX**

**Median effective, toxic and lethal doses**

The dose (mg/kg) of a drug which produces a desired response in 50% of the test population is called as **median effective dose** or ED<sub>50</sub>. The dose (mg/kg) of a drug which exhibits a toxic reaction in 50% of the population is called as **median toxic dose** or TD<sub>50</sub>. The dose (mg/kg) of a drug which would be expected to kill one-half of an unlimited population of the same species and strain is called as **median lethal dose** or LD<sub>50</sub>. Therapeutic index is an approximate assessment of safety of the drug. It is expressed as the ratio of the median lethal dose to the medial effective dose.

\[
\text{Therapeutic index (TI)} = \frac{\text{LD}_{50}}{\text{ED}_{50}}
\]

The larger the therapeutic index, safer the drug. For safer therapeutic application of the drug, its therapeutic index must be more than one e.g. penicillin has a very high therapeutic index while it is much smaller for the digitalis preparation.

**DRUG TOLERANCE**

When an unusually large dose of drug is required to elicit an effect ordinarily produced by normal therapeutic dose of a drug, the phenomenon is termed as drug tolerance. Tolerance is conventionally used to describe more gradual decrease in responsiveness to drug, taking days or weeks to develop, but the distinction is not a sharp one.
CROSS TOLERANCE
It is the tolerance to a drug that generalizes to chemically related drugs or that produce similar affects e.g. persons who develop tolerance to vasodilator effect of nitroglycerine are also resistant to other nitrates; chronic alcoholics are resistant to the actions of general anaesthetics like ether.

DRUG DEPENDENCE
Repeated administration of certain drugs may be habit forming or induce dependence. When the drug is not available or is withdrawn forcefully, the person develops withdrawal symptoms characterized by psychic disturbances like headache, restlessness, emotional upset, convulsions and/or vasomotor collapse. Examples of drugs known to cause drug dependence are opioids, alcohol, barbiturates, nicotine, etc.

TACHYPHYLAXIS (ACUTE TOLERANCE)
This refers to a spontaneous decline in the response to a continuous application of agonist, or to repeated applications or doses. If a drug is administered repeatedly at very short intervals, the pharmacological response elicited decreases progressively. This phenomenon is termed as tachyphylaxis or acute tolerance. Drugs like ephedrine, amphetamine, 5-hydroxy tryptamine, tyramine, etc., are known to cause tachyphylaxis.

Mechanisms of Tachyphylaxis
- change in receptors,
- loss of receptors,
- exhaustion of mediators,
- increased metabolic degradation,
- physiological adaptation and
- extrusion of drugs from the cells (in chemotherapy).