Introduction
INTRODUCTION

There is an evidence of drug use and misuse in early civilization. The old Greeks believed that, God dispensed with prosperity and pestilence, which naturally created a bond between super nature, powers, religion and the use of drugs. A Chinese surgeon is also said to have administered a narcotic draught called “Fa Shuan” to his patients before operations and similarly, the sleep producing properties of cannabis are cited in the Arabian Nights. Thus, drugs are used in the treatment of ailment and for pleasure, from ancient time.

The Vedic writings describe about medicinal use of herbal preparations. Charaka, a renounced ancient Indian physician and later Sushruta and Vaghbhata described various medicinal preparations and elixirs for the treatment of disease and maintenance of good health and longevity of life.

It is cited in Indian mythology that various drugs were used in India since very early times (Mitra, 1968). Bhang, ganja are used during worship of Lord Shankar, in India. There is an ample evidence to show, that in the age of Puranas and at the time of Mahabharat and Ramayan some form of liquor (Somrasa) was freely drunk by kings and his countries and also by the people belonging to the lower strata of society (Barlingey, 1968).
Muslim traders probably introduced opium in India during 9th century A.D. During the Mughal regime, a beverage comprising of alcohol, opium, Indian hemp and poppy capsule was a popular drink among the richer classes (Kurien, 1949).

Till 1939 the Chinese were badly addicted to opium. So, the Emperor Tao Kung appointed a commissioner named Lin Tse Hsu to ban the opium trade in China. Thus, the first opium war started in 1940 near Canton (Chourasia, 2000). It was the world first war against the drug abuse.

Wikler (1967) reported that before World War II, narcotic addiction was distributed throughout America at a low level but after the war, it went to high, concentrating in the slum areas of large metropolitan cities.

The qualitative change in India’s drug abuse scenario occurred after the sixties, when new varieties of narcotics drugs viz. heroin, smack, brown sugar, angel dust etc. and psychotropic substances e.g. LSD, barbiturates, amphetamine etc. started surfacing on the scene (Banerjee, 1963; Govt. of India, 1977 and ICMR, 1977). The official and media reports point out that India has emerged as one of the major transit countries for the smuggling of morphine and heroin from the Golden Triangle (Laos, Mynmar and Thailand) and Golden Crescent (Afghanistan, Iran and Pakistan) countries.
DRUG DEFINITION

The word drug has come from the French word "Drogue" which means "a drug herb", because the drugs are usually isolated from the natural products (plants). However, some new synthetic drugs have also been developed recently.

The drug is also defined as "a chemical agent, which may affect living process" (Gaddum, 1953).

According to George Edward Trease (1966) "a drug is mainly concerned with naturally occurring substance having a medicinal action".

National Commission on Marijuana and Drug Abuse, USA (1973) mentioned drug as "any substance other than food which by its chemical nature affects the structure of a living organism".

Somewhat similar, viewpoint is given by Mc Connell (1977) who stated that "a drug is any chemical, which when taken in relatively small amounts, significantly increases or decreases cellular activities somewhere in the body".

The WHO has introduced many changes in the nomenclature of drug from time to time. Currently accepted definition according to the WHO expert committee (1974) mentioned "a drug is any substance that when taken into the
living organism, may modify on or more of its function. It may be natural or synthetic in nature”.

Modi (1988) described “drug as a substance destined for administration to man for use in the diagnosis, treatment, investigation, prevention of disease or for modification”.

Barar (1995) defined drug as “a substance used for the diagnosis, prevention, treatment or alleviation of the symptoms of disease”.

**SOURCE OF DRUGS**

Usually drugs are obtained from vegetable, animals, and mineral sources. Also a majority of them are synthetic or semi-synthetic compounds. Drugs are also obtained from microorganisms. Hence, precisely drugs can be categorized as;

1. Mineral drugs e.g. Arsenic, Magnesium sulfate, Iron salt Copper salt etc.

2. Animal drugs e.g. Insulin, Thyroid extract, Heparin, Antitoxic sera etc.

3. Plant drugs e.g. Morphine, Hashish, Quinine, Atropine, etc.

4. Synthetic drugs e.g. Heroin, Aspirin, Sulfonamides, Amphetamine, Pentazocine, Nalorphine. and LSD etc.
5. Micro organism drugs: Bacteria and fungi isolated from soil are some important sources of antibacterial substances e.g. Penicillin.

**CLASSIFICATION OF DRUGS**

Since there is no conformity in the relation between chemical structure and pharmacological activity therefore it would be unwise to arrange all drugs from a purely structure point of view. For example, amines are found in the series of analgesics, vasopressors, antihistamines, antimalarials etc. Similarly lactones are found in cardio-tonic drugs.

Therefore, it is relevant to arrange the drugs according to their medicinal use. Thus drugs, which act on the various physiological functions of the body, can be grouped together as (i). Pharmacodynamic agents whereas, (ii) those which are used to fight pathogenic organisms are grouped together as Chemotherapeutic agents.

According to Goodman and Gilman (1985) drugs may classified as follows: -

1. Drugs acting on the central nervous system e.g. Morphine, Pentazocine etc.
2. Local anesthetics e.g. Cocaine, Procaine etc.
3. Drugs acting at synaptic and neuroeffector junction sites e.g. Epinephrine, Dopamine etc.
4. Autacoids e.g. Histamine, Betazole etc.

5. Cardiovascular drugs e.g. Digitoxin, Gitoxin etc.

6. Salts and Ions

7. Drugs affecting renal function and electrolyte metabolism e.g. Benzothiadiazides, Chlorothiazide etc.

8. Drugs affecting uterine motility e.g. Oxytocin, Ergot alkaloids etc.

9. Gases and Vapors

10. Heavy metals and heavy-metal antagonists

11. Locally acting drugs e.g. Emollients, Demulcents etc.

12. Chemotherapy of parasitic diseases e.g. Bephenium, Hycanthone etc.

13. Chemotherapy of microbial diseases e.g. Kanamycin, Penicillins etc.

14. Chemotherapy of neoplastic diseases e.g. Cyclophosphamide etc.

15. Drugs acting on the blood and blood forming organs e.g. Pyridoxine, Iron etc.

16. Hormones and hormone antagonists e.g. Prolactin etc.
17. Vitamins e.g. Vitamin B-complex etc.

**ACTION OF DRUG**

Many times the terms ‘action’ and ‘effects’ of a drug are being used as synonymous. However, it is useful to term the initial consequences of drug-cell interaction as ‘action’ of the drug, the remaining events that follow are called drug effects.

According to Satoskar, *et al.* (1986) a drug may act as:

1. Extracellular e.g. osmotic diuretics and plasma expanders.
2. On the cell surface e.g. digitalis, penicillin etc.
3. Inside the cell e.g. antimalignancy compounds and steroid hormones.

The magnitude of a chemical effect at any given time is function not only of the dose but also of the duration of time elapsed since the chemical made contact with the reactive tissue. According to them there are three distinct phases in all time-action curves as shown in Fig.1, while the fourth phase is present and pronounced with some chemicals and absent with other. Phase I (Ta) is time of onset of action. Phase II (Tb), Phase III (Tc) and Phase IV (Td) correspond to peak time phase, duration of action and residual effect respectively.
**Fig. 1.** Hypothetical curve showing time of action of a chemical. \( T_a \) = Latency time, \( T_b \) = Peak time, \( T_c \) = Persistence time and \( T_d \) = Residual effect.

**TYPE OF DRUG ACTION**

According to Barar (1995) the drug action may be of following types,

a). Stimulation: Increase in the activity of specialized cells is called stimulation e.g. Amphetamine stimulates the CNS.

b). Depression: Decrease in the activity of specialized cells is called depression e.g. Quinidine depresses the myocardium while barbiturates depress the CNS.

c). Irritation: The term irritation indicates that a drug produces effects on the growth, nutrition and morphology
of living tissues. Irritation is thus a phenomenon not restricted to specialized cells but can occur in all the body tissues e.g. heavy metals like mercury and silver are irritants.

d). Replacement: Drugs may be used as replacement when the production of endogenous substances is reduced e.g. Insulin in diabetes mellitus.

e). Anti-infective agents: Drugs are used for prevention, arrest and eradication of infections. They act specifically on the causative organisms e.g., Antibiotics.

f). Modification of immune status: Vaccines, sera and certain other agents act by altering the immune status.

**FACTORS MODIFYING ACTION OF DRUG**

While action is an inherent property of a substance, the nature and extent of the effect manifestations in an organism that is exposed to the substance depend on a variety of factors. The obvious ones are the dose and duration of exposure.

They also include such less obvious factors such as the species and strain of the animal, its sex and age and its nutritional and hormonal status, genetic variation. Various environmental factors also play a part. In addition, the effect of a drug may be influenced by simultaneous and consecutive exposure to other chemicals.
The drug effects may be modified in a number of ways, which include an alteration of the absorption, distribution and excretion of a drug, an increase or decreases of its biotransformation and changes of the sensitivity of the receptor at the target organ.

According to Sodermann (1951) the following factors modify the action of drug, i) dose, ii) method of administration, iii) habit and tolerance, iv) idiosyncrasy, v) age and vi) diseases.

**DRUG ABUSE**

Drug abuse refers to the use, usually by self-administration of any drug in a manner that deviates from the approved medical or social pattern within a given culture. It may therefore be seen that drugs have been used and misused in different cultures since time immemorial.

Of late, the problem of drug abuse has assumed a considerable importance. In fact, drugs were in use even in the remote past. These were mainly used to get relief from the pain and misery and to attain a state of calmness. There are instances of the use of addictive drugs in various countries from ancient time.

Despite the fact that such substances are not new to India, there is an ample evidence to show that the use of mood-altering, habit-forming drugs and substances had not created alarming propositions till recently (Chopra, 1965; Rao, 1966
and ICMR, 1977). The dramatic change in the Indian drug scenario took place only after the sixties. Indian Narcotic Control Bureau Bulletin (1988) suggests, that almost one third of the drug captured in Europe comes from India. It is true that India has of late, become an important conduit through which drugs pass to the Western World. But it was only since the sixties that the international drug traffickers, who till then had used India as a conduit only, also started pushing drugs to the Indian society. This plague spread like wild fire in the eighties and has hit the Indian youths enormously. The college and school students, the unemployed youths and the offspring of broken families are the most seriously affected. Cities like Delhi, Mumbai, Kolkata and Chennai etc. have large number of addicts. Among the North-Eastern States, Manipur, Mizoram and Nagaland also have large number of drug addicts (Mohan et al. 1981; Khan and Krishna, 1984). The qualitative change in Indian drug abuse scenario occurred after the sixties, when new varieties of narcotic drugs and psychotropic substances started surfacing on the scene. The rough estimates are that by the end of the century, India may have more than one and half million of drug addicts.

**CLASSIFICATION OF ABUSIVE DRUGS**

According to Parikh (1990) the abusive drugs may be classified as follows:

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1. Narcotics: Such as opium, morphine, heroin, codeine, hydromorphone, meperidine, methadone and other analgesics e.g., pentazocine etc.

2. Depressants: Such as chloral hydrate, barbiturates, glutethimide, methaqualone, benzodiazepins and others.

3. Stimulants: Such as cocaine, amphetamine, methylphenidate and others.

4. Hallucinogens: Such as LSD, mescaline and peyote, phencyclidine etc.

5. Cannabis: Such as ganja, bhang, charas, marijuana, THC, hashish and its oil.


7. Volatile anaesthetic solvents e.g. toluene.

8. Steroids: Such as anabolic steroids.

**DRUG ADDICT**

As per section 2 (i) of the Narcotic Drugs and Psychotropic Substances Act, 1985 "an addict" means a person addicted to any narcotic drug or psychotropic substance. Literally “addiction” means a habit or vice, especially drugs. “Habit” is the tendency to perform certain actions regularly. Therefore, a
person is said to be addicted when drug becomes a part of his way of life and it becomes difficult for him to give up the same.

According to World Health Organization (1973), an addict is one whose disease is characterized by an overpowering desire to take re-course to drugs and then tendency to enhance the dosage to satisfy his physical craving and use it as a psychological satisfaction.

The symptoms of drug addicted boy or girl are loss of interest in studies, hobbies, games and sports, irregular attendance in school or college, irregular eating, and sleeping, withdrawal from family and society, impulsive or irritated behaviour, low productivity and spending of long hours in the bathroom or lonely places.

**DRUG ADDICTION IN INDIA**

Edward *et al.* (1981) defined drug addiction as “a behavioural pattern of drug use, characterized by overwhelming involvement with the use of a drug (compulsive use), the securing of its supply and a high tendency to relapse after withdrawal.”

In India, people use drugs as mood elevating media since early days. The rural people and tribes used these drugs to relieve them from various physical and psychic ailments. So also, sadhu, tantriks and fakir took ganja, charas etc.
occasionally to aleviate them from worldly suffering and to get ecstasy and heavenly pleasure.

Interestingly, with the influx of western life in Indian youth, the intake of drugs has increased extensively. It is a devastating menace to the society, which has inculcated into the breaking of family and social norms resulting into the deadly impact on the society.

Drug addiction and illicit traffic in narcotic drugs and psychotropic substances not only affect the health of the individual citizen but also is a menace to the entire nation. The de-addiction clinics all over the country testify the gravity of the problem (Majumdar, 1995).

The rising trend of drug addiction can be understood from the following data available from ‘Crime in India 2000’ published by National Crime Record Bureau, New Delhi.

Table- 1

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**UNION TERRITORIES**

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LEGISLATION

Stipulating the adverse effects of these drugs of addiction, the Indian Government has framed some laws to restrict the production, possession and sale of these abusive drugs.

Thus, through an Act, the law relating to narcotic drugs was consolidated and amended by making stringent provisions for the control and regulation of operations relating to narcotic drugs and psychotropic substances, and the Narcotic Drugs and Psychotropic Substances Act (NDPS) was enforced from 14th Nov. 1985 in India (Barowalia, 1992).

The N.D.P.S. Act. 1985 has amended the previous existing laws relating to narcotic drugs and strengthened the control over these drugs.

A Psychotropic Substance, according to the Act, means any substance, natural or synthetic or any natural material included in the scheduled list of psychotropic substances.

Narcotic Drugs covered under the Act are: (a). cannabis (hemp), charas, ganja; (b). coca leaf; coca derivatives including cocaine, crude cocaine and all preparations containing more than 0.1 percent cocaine; (c). Opium, its derivatives such as morphine codeine, thebaine and their salts; diacetylmorphine (heroin) and its salts; and all preparation containing more than 0.2 percent morphine or any diacetylmorphine and (d).
any other narcotic substance or preparation which the Central Government may declare to be a abusive drug.

The Act has made stringent provision for the purpose of preventing trafficking and use of narcotic drugs and psychotropic substances.

The punishment is of rigorous imprisonment for different terms under the various provisions of the Act.

**SOME DRUG RELATED TERMS**

1. **Acute Test:** These tests are designed to determine the dose or concentration of a particular chemical or effluent or the level of an agent that will produce a specific effect on a group of test organisms during a single exposure under controlled conditions.

2. **Sub-acute Test:** These are tests produced after sub-acute exposure, eliciting sub-acute toxicity. Sub-acute effects occur from repeated exposures over a period of several days or months (upto 3 months).

3. **Chronic Test:** Chronic tests are conducted to determine the prolonged (i.e. chronic) exposure usually months or years to a drug at effective dose level, which would have significant adverse effects on organism.

4. **Lethal Dose (LC50 or LD50):** This is one of the most common ways to express acute tests. LC50 is statistical estimate of the
dose (concentration) necessary to kill 50% of a large population of test species under stated conditions. Experimentally, this is achieved by administering a drug or chemical at graded dose to a group of animals and then observing the resultant mortalities in a set time period of usually, 96 hours or so.

5. **Effective Dose (ED$_{50}$):** This is the dose (mg/kg), which would be expected to produce a desired response in 50% of the test animals (Satoskar and Bhandarkar, 1986).

6. **Therapeutic Index (TI):** It is an approximate assessment of the safety to the drug. It is expressed as the ratio of the median lethal dose to the median effective dose.

   Therapeutic index (TI) = $\text{LC}_{50}$/ED$_{50}$

   As the drug metabolism varies from species to species, the therapeutic index would also very in a similar fashion. Therapeutic index supplies reliable information when both the LC$_{50}$ and ED$_{50}$ are determined for the same species. The large is the therapeutic index, the safer in the drug.

7. **Half-life ($t_{1/2}$):** The half-life ($t_{1/2}$) of a drug is the time in hours to reduce the drug concentration in blood; plasma or serum to one half after equilibrium is reached (Dandiya and Kulkarni, 1995).
Barar (1995) states, "The half-life (t\textsubscript{1/2}) is the time in which measure (concentration or effect) declines by one half'. It can be measured in three major ways.

**i). Plasma half-life:** It is the time in which the plasma concentration of the drug falls by one half.

**ii). Biological half-life:** It is the time in which the total amount of drug in the body after equilibrium of plasma with other physiological compartments (fats, muscle etc.) is halved.

**iii). Biological effect half-life:** It is the time in which the pharmacological effects of the drug have declined by one half.

**8. Drug Dependence:** According to Barar (1995), "it is a psychic and physical state which results from the interaction between a living organism and a drug, characterized by behavioural and other responses and includes a compulsion to take the drug on a continuous or periodic basis to avoid the discomfort".

Drug dependence may be divided into two types;

**i). Physical Dependence:** Physical dependence refers to biological changes that underline withdrawal syndrome. It is a phenomenon of physiological dysfunction when the drug is withdrawn (Goodman and Gilman, 1985). Edwards *et al.* (1981) have proposed the term neuroadaptation as a substitute for physical dependence.

Six types of dependence have been described by Barar (1995). These are,
1. Morphine (opioids) type
2. General CNS depressant type
3. Cocaine type
4. Amphetamine type
5. Hallucinogen (LSD) type, and
6. Cannabis (marijuana) type

ii). **Psychic Dependence:** It is a condition in which a drug produces a feeling of satisfaction and a psychic drive that requires periodic or continuous administration of the drug to produce pleasure or to avoid discomfort. (Goodman and Gilman, 1985).

9. **Tolerance**

Drug tolerance is a state of decreased responsiveness to the pharmacological effects of a drug resulting from regular and repeated use. And physical dependence is a phenomenon of physiological dysfunction when the drug is withdrawal. Sometimes physical dependence is associated with tolerance, especially in the drugs acting on nervous system.

10. **Withdrawal Syndrome**

These are symptoms of illness during the discontinuation of drug administration. The illness is due to the toxic effect of the metabolites. The character and the severity of the withdrawal symptoms that appear when a drug is discontinued depend upon many factors, including the particular drug, the
total daily dose used, the interval between doses, the duration of use and health and personality of the addict.

**MECHANISM OF DRUG ACTION**

When a drug is taken its effects usually occur as the result of a complex series of processes.

Ariens, *et al.* (1976) divided the drug action in the following phases.

![Diagram of drug action phases](image)

**Fig. 3.** Schematic representation of three phases of drug action.

1. **Pharmaceutical Phase:** It is a period beginning from the administration of substance to starting of absorption. It is also known as ‘exposure phase’. The phase has two stages (i). disintegration of dosage form and (ii).dissolution of active substance for absorption. During this phase the chemical can
be altered to another compound that may be more or less potent than the parent compound.

2. **Pharmacokinetic Phase:** It is also known as toxicokinetic phase and is most important for forensic toxicologist. It has the following stages,

a). **Absorption:** It is a process by which the chemical substances are made available to the body fluids, which distribute the chemical to organ systems. Beside physio-chemical properties of the chemical, the solubility, concentration, circulation to the site of absorption, area of absorbing surface and the route of administration etc. influence the absorption rate considerably (Kornetsky, 1976; Goodman and Gillman, 1985).

b). **Distribution:** The main body fluid for distribution for a drug is the plasma. Some fraction of drug binds with plasma protein, such as albumin binds with acidic drugs and α- acid glycoprotein with basic drugs while some fraction dose not bind with serum protein. This non-binding fraction of drug rapidly crosses the capillary wall by means of diffusion and filtration. But the protein bound fraction does not pass the capillary wall and is slowly released thereby giving long action. Thus plasma protein plays an important role in process of drug action.

c). **Biotransformation:** It may be defined as “the biologically catalyzed conversion of one chemical into another”. It should
be differentiated from a). purely physical-chemical process and b). metabolism. The former affects chemical conversion, such as photolysis, oxidation and reduction but doesn't involve the bio-catalysis. The later i.e., metabolism involves chemical conversion in biological system and is carried out under the influence of enzymes.

The term biotransformation includes biologically catalyzed conversion of drugs.

The chemical reactions concerned in the biotransformation of drugs are classified as phase-I and phase-II reactions. Phase-I reactions usually convert the parent drug to more polar metabolites by oxidation, reduction, hydrolysis and degradation reactions. The resulting metabolites may be either more active or less active than parent molecule or may be inactive.

Phase-II reactions, which are also called synthetic or conjugation reactions, involve coupling between the drugs or its metabolites and an endogenous substrate, such as glucoronic acid, sulfuric acid, acetic acid or an amino acid (Testa and Janner, 1976; Reeves, 1981; Goodman and Gilman, 1985, Cohen, 1986; and Levi, 1994).

d). Excretion: The principal routes of elimination of drugs and their metabolites are urine and bile but some other elimination
routes are also existing (Casarett and Doull, 1980, Sharma, 1998).

These routes are as follows:

i). **Renal Excretion**: Kidneys are the most important route of elimination of drugs and their metabolites from the body.

ii). **Biliary Excretion**: The blood from Gastro Intestinal Tract (GIT) passes through liver before reaching for general systematic circulation. Liver can remove the drugs from blood and prevent their distribution to other part of body. Since liver is the site of metabolism of most compounds, the particular chemical and its metabolites may be excreted directly into the bile without re-entering the blood stream to be excreted by renal system.

iii). **GIT**: Many compounds are excreted in the faeces. The excretion may be due to the agents, which are not absorbed after oral ingestion.

iv). **Exhaled**: Many volatile compounds are excreted unchanged in the expired air. For example, fluorobenzene and some alcohols etc. are excreted by this route.

v). **Sweat**: Generally very small amount of chemicals are excreted by this route. However, diethyl dithiophthalate, a drug used for leprosy is largely excreted in the sweat.
vi). **Saliva**: Some sulfonamides, barbitone are excreted in the parotid saliva of man.

vii). **Milk**: Certain chemicals are partly excreted into milk of lactating mammals.

viii). **Vaginal Secretion**

La Du, *et al.* (1980) represented the fate of drug in the body by the following figure.

<table>
<thead>
<tr>
<th>absorption</th>
<th>distribution</th>
<th>excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>Interstitial fluid</td>
<td>Cells</td>
</tr>
<tr>
<td>Drug X</td>
<td>X</td>
<td>+ RX</td>
</tr>
<tr>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>P</td>
<td>P'X Storage</td>
<td>Y</td>
</tr>
<tr>
<td>PX</td>
<td></td>
<td>Y</td>
</tr>
</tbody>
</table>

**Fig. 3.** Broken lines represent membranes, X= free drug, P = protein, R = receptor, PX= drug protein complex in plasma, P'X = complex of drug with non-specific binding sites in tissues, Y= metabolic product of X and RX = drug-receptor complex.

3. **Pharmacodynamic Phase**: The pharmacodynamic phase comprises the interaction between the molecules of the drug and the specific sites of action i.e. the receptor. The various drugs exert their biological effects upon binding with an
appropriate ligand, which may be an endogenous or exogenous substance. These effects are preceded by a series of biochemical activities, the signaling, which vary according to the structural characteristics of the receptors.

According to Mailman and Lawler (1994) these receptors are 1). G- protein coupled receptors, 2). ligand-gated ion channels, 3). voltage-gated channels and 4). intra-cellular receptors. They are show in the following figure,

![Diagram of receptors](image)

**Fig. 4.** Schematic representation of the four classes of receptors; 1. G-protein coupled receptor, 2. Ligand-gated ion channel, 3. Voltage-gated ion channel and 4. Intracellular receptor.

1. **G-Protein Coupled Receptor:** The G-protein coupled receptor (Fig. 4-1.) binds with ligand, which results in the activation of the G-protein converting GTP (guanosine
triphosphate) into GDP (guanosine diphosphate). It activates or inhibits a specific enzyme (adenylate cyclase or phospholipase C), followed by the formation of a “second messenger”, such on cAMP from ATP. The second messenger then initiates the cellular response. This class of receptors includes muscarin, dopamine, serotonin, opioids and other neurotransmitters.

Studies of the binding of opioid drugs and peptides to specific sites in brain and other organs have suggested the existence of perhaps as many as eight types of opioid receptors. In the CNS, there is a firm evidence for four major categories of receptors, designated μ (mu), K (kappa), δ (delta) and σ (sigma) (Goodman and Gilman, 1985).

2. Ligand-Gated Ion Channel: The second class of receptors is transmembrane proteins with an ion channel (Fig. 4-2.). Upon binding with a ligand, the receptor undergoes conformational change resulting in the opening of the channel. This process allows changes of Na⁺, K⁺, Cl⁻ or Ca⁺ concentration across the plasma membrane. Nicotinic cholinergic and gamma-aminobutyric acid (GABA) receptors belong to this class. In addition, glutamate and chemicals such as diazepam, barbiturates and picrotoxin also act on this type of ion-channel receptors.

3. Voltage-Gated Ion Channel: The voltage-gated conductance channel (Fig. 4-3.) is located across plasma membrane of excitable cells such as neurons and their axons. At present, no
endogenous ligands are known. However, the neurotoxins and saxitoxin bind to a site near the extra cellular opening of the Na⁺ channel and block the entry of Na⁺ through the channel, thereby interfering with the conduction of nerve impulse.

4. **Intra cellular Receptor**: Intracellular receptors are located in the cytosol or nucleus (Fig. 4-4.). The main receptors are estrogen, androgen, glucocorticoid and mineral corticoid.

The ligand that binds with the receptor may be an agonist or antagonist. An agonist induces the physiologic function of the receptor whereas an antagonist blocks its function.

**BIOAVAILABILITY OF DRUG**

The amount of the drug that reaches the systematic circulation is called bioavailability. It is called “fraction of the dose” because the total dose of the drug is not completely absorbed. The absorption depends on physio-chemical properties of the drug, the solubility, concentration, area of absorbing surface and route of administration (Goodman and Gilman, 1985 and Sharma, 1998).

**DRUG-DOSE EFFECT RELATIONSHIP**

The magnitude of the drug effect is a function of dose administration. It basically depends upon the manner, dose quantity, number of dose, time interval between doses and the total duration of drug administration.
When a drug is administered in a single dose a distribution of the drug occurs, the concentration falls rapidly. Following this initial distribution phase, the kinetic of drug biotransformation and elimination is apparent. An effect of a single dose of drug may be characterized by its time of peak effect, magnitude of peak effect and duration. Usually half-lives are required to eliminate 98% of the drug from the body when given as a single dose.

On the other hand, if the drug is administered repeatedly and frequently in relation to its half-life, besides undergoing the routine process of ADME and pharmacodynamic phases, the excess of drug may accumulate into the body and the lesser amount of it is eliminated than the amount administered. Repeated administration of a drug is characterized by the time response relationship, which is shown as follows.

**TIME-RESPONSE RELATIONSHIP**

If a drug is administered for a long period in a constant dose, the effect of the drug may represent the following curves.
Fig. 5. Hypothetical time – response curve. a = cumulative effect from accumulative drug and b = forms the development of cellular adaptation or tolerance.

Both conditions may be possible in different situations. For example, drug-receptor interaction is decreased due to development of tolerance.

**DRUG ACCUMULATION**

If a drug elimination rate is slow and one nevertheless attempts to achieve a therapeutic effect with a constant repeated dosage schedule, it may result in the accumulation of some amount of drug into body tissues.

The accumulated amount in the body depends on the drugs half-life. For example, temazepam is little accumulated whereas diazepam is strongly accumulated in same period administration due to the their different $t_{1/2}$. 
The plateau principle may explain why cumulative toxicity occurs sometimes. According to Rowland and Thomas (1996) a rise of drug concentration to a plateau (steady state) level during repeated administration of a constant dose, can be shown by the following graph.

![Graph showing intensity over time](image)

**Fig. 6.** Schematic representation of drug concentration in body during repeated administration.

**ACCUMULATION INDEX**

According to Avram, *et al.* (1974) the accumulation index (Rac) of a drug is the quantity, which is determined from the following relationship.

\[
Rac = \left( \frac{1}{1 - e^{-kt}} \right)
\]

Where, the function \( e^{-kt} \) is the fraction of the initial amount remaining in the body at time \( t \).

Several tissues act a storage depot in which drug or chemical tends to accumulate due to certain affinity for those
tissues. For example the arsenic is taken up in bone, lead in the skeleton, cadmium in kidney and liver, charcoal localized in spleen, CO accumulates in blood.

According to Sharma (1998) these tissues are as follows:

1. **Liver**: Liver acts as major depository when a drug is taken cumulatively for a prolonged period.

2. **Brain**: Some drugs have high affinity for the brain tissue. For example, drugs like barbiturates and psychotropic drugs have been found to enter the brain rapidly after intravenous administration in animals.

3. **Erythrocytes**: Drugs like binding with hemoglobin i.e. localizes p-nitroalanine localizes in the erythrocytes. Similarly, another chemical like CO and some ions are also localized with erythrocytes.

4. **Kidney and other body tissues.**

5. **Body fat**: Tissues and areas in the body rich in fat tend to store some chemicals that are highly soluble in liquids. These chemicals tend to localize in adipose tissues.

**PENTAZOCINE - A Drug Selected for Present Study**

Pentazocine was first synthesized and studied by Archer, *et al.* (1962) at the Sterling-Winthrop Research Institute USA. It is an agonist-antagonist compound used as an analgesic after 1970 to relieve from pain (Casy, 1970). Fraser and
Rosenberg (1964) mentioned, that the drug has a low addiction liability so the Harrison Narcotic Act of 1967 in USA did not cover it till recently. Similarly in India it was not in the list of NDPS Act of 1985 till year 2001.

**Chemistry**

Pentazocine is benzomorphan derivative which bears a very close resemblance to morphine. It possesses a main skeleton of morphine, lacking only the ether bridge and the functionalities of ring C being replaced by methyl and alkyl fragments at C-5 and C-9, N- bonding with 3,3-dimethylallyl group (Clouet, 1972, Goodman and Gilman, 1985).

![Pentazocine](image)

It is a white coloured crystalline powder of m.p. 147°C to 158°C and almost insoluble in water, slightly soluble in acidic aqueous solution but soluble in alcohol, acetone, ether and chloroform. The lactate isomer of pentazocine has more analgesic property (Goodman and Gilman, 1985).
Pentazocine and Receptors

In CNS, there is a evidence of four major categories of receptors designated as $\mu$ (mu), $K$ (kappa) $\delta$ (delta) and $\sigma$ (sigma). Pentazocine interacts with three major opioid receptors of CNS viz. $\mu$ (mu), $K$ (kappa), and $\sigma$ (sigma). It interacts with $\mu$ (mu) as weak antagonist, so it may be used in the treatment of narcotic physical dependant patients. It also interacts with $K$ (kappa) as moderate and $\sigma$ (sigma) as weak agonist. The main agonistic effects of pentazocine are analgesia, sedation and drowsiness, hallucination and euphoria, respiratory depression etc.

Pharmacological Effects of Pentazocine

Most of the agonistic effects of pentazocine are generally similar to that of the morphine like opioids. It produces following symptoms on different body systems.

I. Central Nervous System

a). Analgesic: It reduces the sensation of pain without simultaneously reducing other sensation such as touch and pressure (Robert and Levi, 1975). Pentazocine obtuses the response to painful stimuli due to its agonistic action on $K$ (kappa) receptor of CNS.

When pentazocine is compared to morphine and meperidine as analgesic, it is found that 10mg morphine is =
30 mg of pentazocine = 75 mg of meperidine. The onset of analgesia is within 15 minutes and the duration is three hours or more. Krantz and Carr (1969) have asserted that the relief of severe pain by a drug must be accompanied by a false euphoria and hence, it causes drug addiction. Its half-life is 2.1 hours after intramuscular administration.


c). Euphoria: Many investigators have considered the relief of severe pain by pentazocine is accompanied by a sense of euphoria (Goodman and Gilman, 1985).

II. Respiratory Depression: Several investigators have studied the depressive effect of pentazocine on the respiration.

III. Cardiovascular System: Pentazocine in prolonged therapeutic doses raises blood pressure and pulse rate (Keats and Telford, 1964).

IV. GIT: The effects of low dose of pentazocine on the GIT are qualitatively similar to those of the opioids. The large doses (30 to 45 mg) increase the transit time through the intestinal tract. The pentazocine produces less elevation of biliary pressure (Goodman and Gilman, 1985).
V. Renal Effect: Pentazocine causes a decrease in effective renal pressure flow but there is no decrease in glomerular filtration rate (GFR). It also produces urinary retention (Goodman and Gilman, 1985).

Toxicity

Pentazocine intoxication occurs from overdose of drug or prolongation. The most commonly reported unwanted effects are sedation, followed by sweating and dizziness or light-headedness. Nausea also occurs, but vomiting is less common than with morphine. Nalorphine like psychotomimetic effects such as uncontrollable thoughts, anxiety, nightmares, hallucination and euphoria has been reported. The clinical picture of overdosage with pentazocine alone rarely causes death. High doses produce marked respiratory depression associated with increased blood pressure and tachycardia.

Repeated administration over long periods may cause extensive fibrosis of subcutaneous and muscular tissue.

Withdrawal symptoms

The pathophysiologic disturbances from abruptly termination of drug administration are known as withdrawal symptoms, sometimes called as abstinence syndrome. Some studies have documented the characteristic and the severity of the pentazocine withdrawal symptoms. The mild withdrawal symptoms are restlessness, insomnia, sneezing, lachrymation.
diaphoresis, and paraesthesia. The intermediate withdrawal symptoms include tremor, sweating, severe chills and leg muscle cramps followed by abdominal cramps, nausea, vomiting, itching and rhinorrhoea. The severe withdrawal symptoms include depression, hyperthermia (fever) and significant loss of body weight.

**Physical Dependence**

It is a state of physiological dysfunction when the drug is withdrawn and it is developed due to the biological changes. Many authors like Musser and Nell (1960), Krantz and Carr (1969), Scholar *et al.* (1969), Sandoval and Wang (1969), Hart (1969), WHO (1970), Goodman and Gilman (1985) and Tripathi (1988) have reported the development of pentazocine physical dependence.

**Tolerance**

Drug tolerance is a state of decreased responsiveness to the pharmacological effect of a drug, resulting from regular and repeated use of drug. Sometimes, tolerance is associated with the physical dependence specially, in CNS acting drug. Pentazocine is also CNS acting drug, so it develops tolerance. It has been mentioned by the report of WHO (1970), Goodman and Gilman (1985) and Tripathi (1988).
Liability for Abuse

On the basis of early testing pentazocine was not believed to have a significant potential for abuse and it was released for general use subject to no special controls. Subsequently, cases of compulsive self-administration of parenteral pentazocine were reported. It may develop the psychotomimetic effect such as uncontrollable thoughts, anxiety, nightmares, hallucination, and euphoria. The availability of the oral preparation has greater appreciation of its potential for abuse. Despite the absence of legal controls addicts in India to any significant extent did not misuse pentazocine until 1980. However, its abuse became extensive in India during the period of 1990 to 2000 due to its easy availability from the open market till 2001 when, it has been covered under the provision of NDPS Act (1985).

Therapeutic Use

Pentazocine is used primarily as an analgesic. It is often employed in situations where there is chronic severe pain. The risk with pentazocine is lower than that associated with use of the morphine like drugs in similar circumstance.

Chronic Exposure

When exposed to low concentration continuously or over a period of time, its immediate effects appear similar to acute exposure.
But there are some consequences with the prolonged dosages, which are not observed in a single dose. They include slightly decrease of pharmacological effects from cellular adaptation of pentazocine receptors, bioaccumulation of pentazocine in some body organism and increase it the risk of biochemical variation from cumulative intake of pentazocine.

In general, prolonged pentazocine use produces, effects similar to those of morphine and other opioids. When the pentazocine administration is abruptly discontinued, some distinct withdrawal symptoms such as restlessness, legs and abdominal cramps, nausea, vomiting, lachrymation and elevation of body temperature etc. may emerge.

Absorption, Fate and Excretion

Pentazocine is well absorbed from the gastrointestinal tract and from subcutaneous and intramuscular sites. Concentration in plasma coincides closely with the onset, duration and intensity of drug intake. The peak value occurs 15 minutes to 1 hour after oral administration. The metabolism in the liver is extensive and about 20% of pentazocine enters the systematic circulation (Ehrnebo et al. 1977).

The action of the drug is terminated largely by biotransformation in the liver. The kidney excretes the metabolite products. There is considerable variability between
individuals in terms of rate of pentazocine metabolism. Smokers metabolize 40% more pentazocine than non-smokers (Brogden et al. 1973).

**Treatment of Pentazocine Overdosage**

The intravenous administration of Methylphenidate (Ritaline) is an appropriate means of treatment of pentazocine overdose. So also the respiratory depression produced by pentazocine lactate could be reversed by the injection of naloxone hydrochloride.

**THE PRESENT STUDY**

As seen earlier pentazocine is a popular abusive drug easily available from the market to the addicts, hence it is chosen here for the present work.

Visualizing the meance of the pentazocine drug abuse and its toxicity, some work pertaining to prolonged administration of pentazocine has been undertaken in the laboratory.

For this work, pentazocine lactate has been selected and it's pharmacological, haematological and biochemical effects had been studied on albino rats.

The therapeutic dose of pentazocine for human being intramuscularly administration is 30 mg in every 4 or 6 hours interval (Musser and Nell, 1960; Goodman and Gilman, 1985.
and Barar, 1995.) In the present investigation the effective dose (ED$_{50}$) for albino rats was calculated on the above basis.

The detailed results regarding pharmacological, haematological and biochemical studies of regular administration of pertazocine to rats for prolonged period are summarized in subsequent chapters of the thesis.

The present thesis comprises of five chapters.

First chapter deals with the introductory details of drug abuse. It includes several aspects of pertazocine drug including its pharmacological action, toxicity and therapeutic uses.

The second chapter contains the study of pharmacological effects of prolonged administration of pentazocine to albino rats. It comprises of experimental setup and procedure, observation, results and discussions with reference to the work of other scholars.

The experimental setup with procedure, results and discussions of hematological and biochemical studies of chronic pentazocine administration are discussed in chapters three and four of the thesis respectively.

Finally, the estimation of accumulated pentazocine from some common vital organs is epitomized in the chapter five.