CHAPTER IV.

DRUGS AND THEIR ACTIONS.
## CHAPTER IV.

**Drugs and their actions:**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Terminological distinction and definition of psychotropic drugs.</td>
<td>112</td>
</tr>
<tr>
<td>2. Classification.</td>
<td>112 - 115</td>
</tr>
<tr>
<td>3. Theories.</td>
<td>116 - 125</td>
</tr>
<tr>
<td>4. Chemical structures.</td>
<td>125 - 126</td>
</tr>
<tr>
<td>5. Modes of actions:</td>
<td>126 - 126</td>
</tr>
<tr>
<td>a) Modes of actions of Chlorpromazine</td>
<td>126 - 143</td>
</tr>
<tr>
<td>b) Modes of actions of Imipramine</td>
<td>143 - 153</td>
</tr>
<tr>
<td>c) Modes of actions of Diazepam</td>
<td>153 - 159</td>
</tr>
<tr>
<td>6. Dosage and route of administration</td>
<td>159 - 161</td>
</tr>
<tr>
<td>7. Side effects - of the three drugs used in the present investigation, viz., Diazepam (Calmose), Chlorpromazine (Largactil), and Imipramine (Tofranil)</td>
<td>162 - 169</td>
</tr>
</tbody>
</table>
Drugs and Their Actions.

"The classification and terminology of drugs used in psychiatry is almost as confusing as that used for psychiatric disorders" - (Dally - 1967).

According to Krantz and Carr (1965) the general term "psychotropic" refers to any substance which alters mental processes or behavior. Almost a similar view has been propounded by Freedman et al. (1972) stating that psychotropic drugs are those that affect psychic function and behavior.

Several classifications have been proposed for the drugs that are employed for their effects upon mental functions in man (Krantz and Carr - 1965; Goodman and Gilman - 1970). Broadly the classification of psychotropic drugs may fall under the following headings:

1) Chemical classification,
2) Pharmacological classification, and
3) Therapeutic Classification.

Let us explain each one briefly.

Chemical: Chemically, the psychotropic drugs fall within four general classes (Krantz and Carr - 1965). The first
group of chemicals contain the phenothiazine nucleus and includes chlorpromazine, promazine and others. The second group includes the Rauwolfia alkaloids reserpine, deserpidine, and rescinnamine. The third group embraces derivatives of alkyl diols; to this group belong meprobamate, phenoglycodol and others. The fourth classification comprises the derivatives of diphenyl methane and includes benactyzine, hydroxysine and other miscellaneous structures. These compounds have something in common as far as chemical constitution is concerned.

The antidepressive agents do not have a related chemical structure. Imipramine has a structural similarity to the phenothiazines; isocarboxazid, nialamide and phenelzine are hydrazine derivatives; the other antidepressive drugs have miscellaneous structures.

Pharmacological: It is apparent that since the biochemical lesions responsible for mental disturbances have not been delineated, the mechanism of the beneficial response to the psychototropic drugs cannot be described adequately (Krantz and Carr - 1965). However, certain investigating observations have been made which shed some light upon their action.
Berger (1965) classified the generally used psychotropic drugs into two categories. The first group affects the autonomic and central nervous systems and the second group affects only the central nervous system and has no autonomic component. The first group contains the phenothiazine derivatives, reserpine and the diphenylmethane derivatives. The second group of central nervous system relaxants embraces meprobamate and phenaglycodol.

These two groups of drugs differ in many respects in so far as their detailed pharmacologic actions are concerned. The drugs in the first group, which may be called autonomic depressants, block conditioned responses and lower the threshold to electroshock and chemically - evoked seizures in animals. They potentiate the action of hypnotics and elicit characteristic changes in the electroencephalogram similar to those following large doses of atropine. In normal individuals they evoke a state of insuption from their environment and tend to produce mood depression. They act in a non-specific manner on a variety of conditions by their actions on neuronal - regulating centers. Drugs in the second group do not alter conditioned reflexes and have little effect on abnormal human behavior. They increase the threshold for electrical or chemical seizures. They do not affect the hypothalamic re
regulating centers or normal responsiveness to stimuli. However, they selectively reduce exaggerated responses.

**Therapeutic** : According to Krantz and Carr-(1965) the major psychotropic agents are those with apparent or confirmed efficacy in the treatment of psychotic patients. The minor psychotropic agents are those used in the treatment of neurotic and psychosomatic reactions. The psychomaneptics are used in the treatment of depression.

Drugs presently employed in the treatment of psychoses are primarily phenothiazines (chlorpromazine, trifluoperazine etc.) and butyrophenones, but the rauwolfia alkaloids are also mentioned because of their importance in the history of psychopharmacology (Goodman and Gilman - 1970). Certain other related agents are tetrabenazine and lithium salts. Drugs used in the treatment of anxiety and neurotic conditions include meprobamate, benzodiazepine derivatives (Goodman and Gilman - 1970) and, in addition, some barbiturates and non-barbiturate sedatives, e.g., amylobarbitone, thiopentone sodium, phenobarbitone, chlormal hydrate etc. Drugs employed (Goodman and Gilman - 1970) in the treatment of depression include monoamine oxidase (MAO) inhibitors, and debensazepine derivatives, such as imipramine (Tofranil).
Avenues of approach to an understanding of drug actions in the brain, according to Krants and Carr (1965), have been the following:

1. **Neurotransmitter substances in the central nervous system:** That the enzyme inhibition by drugs will prevent chemical transmitter destruction, is the underlying concept.

2. **Biochemical — metabolic changes:** Drugs may help to modify enzymic and metabolic fragment interchanges at subcellular levels. Energy exchange in terms of glucose utilization and phosphate turn-over and blood flow changes in the brain may explain the effects of some drugs.

3. **Electrical functions of the brain:** Drugs may produce changes in electrical activity of specific brain regions.

Let us explain each of the above mentioned concepts briefly.

**Effects of Neurotransmitters in the Central Nervous System:**

A number of chemical substances like, epinephrine, nor-epinephrine, 5-HT etc. have been identified in
the brain which may function in the transmission of nerve impulses within the central nervous system (Krantz and Carr - 1965). Although definite evidence in support of the concept is lacking, it has been pointed out that drugs that modify behavior, electrical activity in the brain, and biochemical processes elicit marked changes in the concentration of these chemicals in specific areas of the central nervous system (Krantz and Carr - 1965).

The discovery of Serotonin in the brain and the observations of Vogt (1954) that nor-epinephrine is also present and distributed in a manner similar to serotonin, has suggested that these agents act as chemical neuro-mediators. It has been proposed that reciprocal systems may function within the brain stem (Krantz and Carr - 1965). Reserpine impairs the capacity of tissue cells of the central nervous system to store serotonin in (a chemical neuro mediator) and exerts a pharmacologic effect by releasing free amine. The major actions of reserpine, on the other hand, is said to be related to a loss of serotonin or nor-epinephrine by brain cells. Chlorpromazine, on the other hand, elicits a sedative response similar to reserpine, though its action is not mediated through the release of serotonin. Chlorpromazine inhibits the "Sympathetic-like" system by blockade of nor-epinephrine, a neurotransmitter, (Krantz
and Carr - 1965). Thus, chlorpromazine and reserpine act to produce similar effects by different mechanisms (Brodie and associates - 1959).

"By studying compounds that have a selective effect in releasing the amines serotonin and nor-epinephrine centrally, but not peripherally, and vice versa, and a compound that releases brain nor-epinephrine without releasing brain serotonin, it has been possible to shed light on the role of these amines in the action of reserpine" (Brodie - 1960). The evidence indicates that, as mentioned by Krantz and Carr (1965), the loss of brain nor-epinephrine is probably not the cause of reserpine-induced sedation. The enzyme monoamine oxidase (MAO) is reported to have an important role in the regulation of the nor-epinephrine and serotonin content of "storage" compartments of the cells of the brain. MAO inhibitors are said to cause a rapid rise in the nor-epinephrine content of brain, sympathetic ganglia, and heart tissue (Spector - 1963). This action is believed to be associated with the behavioral stimulation produced by the administration of MAO inhibitors in animals (Krantz and Carr - 1965).

Enzyme inhibition produced by drugs may exert a potent effect on the actions of neurotransmitter substances.
MAO can be inhibited by a number of antidepressant drugs. When animals are given reserpine following the treatment with MAO inhibitors, they are not sedated but are made hyperactive. The amount of serotonin in the brain of these animals shows very little decrease. If MAO inhibitors are given alone, an increase in serotonin in the brain, followed by an increase in nor-epinephrine, has been reported (Zeller - 1963).

Several entirely new kinds of enzyme inhibitors though have been discovered with in vitro and in vivo activity, the subject has caused considerable controversy, and some workers contend that MAO has no important role in the inactivation of extra-neuronal catecholamine (Kopin and Axelrod - 1963).

Crossland (1960) has reviewed the evidence for chemical transmission in the central nervous system and has pointed out that "recent studies have neglected the main body of investigations on acetylcholine and its related enzyme systems." It has been shown that acetylcholine has a stimulating action on the brain and under some circumstances it shows inhibitory effects also. Drugs are known that produce sedation and excitation and at the same time modify the acetylcholine content of the brain. Acetylcholine
obviously plays an important but poorly understood role in brain function. It is disappointing, as Crossland points out, that so far it has not been possible to find any general relationship between abnormalities of acetylcholine metabolism and the incidence of mental illness or nervous disease.

The discovery of imidiazol-N-methyl transferase, an enzyme that is responsible for the principal pathway of histamine metabolism, in the brain is likely to be of some significance in terms of the role of histamine in central nervous system function. It is remarkable that chlorpromazine inhibits the methylation of histamine by this enzyme. This action is antagonistic to the anti-histaminic effects of chlorpromazine. The role of histamine in the brain in terms of behavioral effects is unknown (Krantz and Carr - 1965).

Biochemical metabolic changes:

The significance of glucose utilization and oxygen consumption by the brain is known. Drugs can produce biochemical effects and behavioral changes. If cholinergic transmission or synaptic transmission by other neurotransmitters is accomplished by the synthesis of these substances, then the influence of psychoactive drugs on neural activity would be lowering the supply of glucose and
interfering with oxidative metabolism in the brain (Krantz and Carr - 1965). Chlorpromazine has been shown in very high doses to inhibit cerebral oxidation and to inhibit adenosine triphosphate (ATP) synthesis. Reserpine seems to have little influence on oxygen uptake, phosphorylation, or enzymic breakdown of high energy phosphate compounds (Krantz and Carr - 1965).

Metabolic fragments of the psychotropic drugs may be the active form of these drugs in the central nervous system. The individual metabolic pattern, in such cases, may determine the effectiveness of the drug in the particular patient (Krantz and Carr - 1965).

The available supply of oxygen and glucose being the determinant of normal brain function, it would be expected as mentioned by Krantz and Carr (1965) that biochemical and functional disorders would be associated with changes in brain circulation. Kety and his associates (1948) and others have investigated cerebral blood flow changes using LSD-25 intravenously found that the doses that elicited the characteristic psychological effects, did not produce changes in cerebral blood flow, vascular resistance, oxygen or glucose utilization in either normal or schizophrenic subjects. A similar lack of change in cerebral blood flow has been reported in schizophrenia during mental activity
tests and after chlorpromazine (Krantz and Carr - 1965).

The drugs which influence behavior and abnormal mental conditions, as mentioned by Krants and Carr (1969), may be associated with changes in cerebral circulation and metabolism, but the area involved may represent a very small fraction of the total brain vascular supply. Since the over-all blood flow or metabolism is measured by this method, the effects would be obscured if they take place in a localized minute area (Krantz and Carr - 1965).

**Electrical functions in the brain:**

Drugs alter the electrical activity within the central nervous system. In such conditions, special attention has been given to the reticular formation which receives and transmits corticopetal impulses. Intense stimulating impulses when introduced into the reticular formation via sensory stimuli, produce a desynchronization pattern in the cortex, with rapid low voltage electrical impulses. Very regular high voltage waves of electrical activity are recorded in the thalamus. This is the awake, or alert pattern.

Although there is controversy, the majority of the findings agree that chlorpromazine inhibits the EEG arousal pattern though not to the same degree as the
barbiturates or scopolamine, atropine or benactyzine. So far as hypnotics and chlorpromazine are concerned, there seems to be a clear difference in their effect on the electrical function of the reticular system (Krantz and Carr - 1965).

Reserpine produces an alert EEG pattern in contrast to barbiturates which evoke a pattern of sleep (Krantz and Carr - 1965). But some workers have not found an alteration in EEG arousal patterns in animals, even after administration of large doses of reserpine (Krantz and Carr - 1965). Apparently it seems that the effect obtained is related to the experimental situation, because some investigators reported that reserpine will elicit periods of synchronization (resting pattern), alternating with periods of desynchronization (alert pattern) (Krantz and Carr - 1965).

Various other drugs, particularly the sympathomimetics and parasympathomimetics, have been studied to see their effects upon the electrical activity of the ascending reticular formation. In general, behavioral arousal coincides with desynchronization, arousal pattern, but a number of important exceptions are reported. For example, sympathomimetic drugs which can evoke arousal - may not be associated with behavioral arousal; on the other hand, the resting pattern obtained after anticholinergic drugs is not
followed by tranquilization (Krantz and Carr - 1965).

Other studies with regard to cerebral synaptic transmission have revealed that psychopharmacologic agents will inhibit transcollosal responses (Krantz and Carr - 1965). Morraszi and Hart (1955) reported that epinephrine, nor-epinephrine, mescaline, LSD-25, and serotonin have an inhibitory effect. Synaptic transmission, is also depressed by barbiturates, whereas chlorpromazine and reserpine have no effect. Chlorpromazine and reserpine are supposed to abolish the inhibitory effect of mescaline.

Different studies dealing with EEG patterns in normal and psychotic states and the influence of drugs on the EEG have shown that there is a difference between the spontaneous cortical electrical activity of normal subjects and schizophrenic subjects. In addition a striking similarity has also been reported between LSD-25 - treated normal subjects and schizophrenic patients. A quantitative analysis illustrates these differences and similarities (Goldstein et al. - 1963). Future work of this type, as suggested by Krantz and Carr (1965), may serve to elucidate the finer details of brain functions and schizophrenic behavior and find out the way to the study of the basic effects of drugs in the central nervous system.
There are many problems which we come across in endeavouring to formulate a broad hypothesis involving the mechanism of action of the psychotropic drugs (Krantz and Carr - 1965). Thus, an understanding of their pharmacologic actions seems to be richly rewarding in terms of understanding brain functions and mental illness.

CHEMICAL STRUCTURE:

Chlorpromazine:

Phenothiazine has a three-ringed structure in which two benzene rings are linked by a nitrogen and a sulfur. Usual substitutions are at position two and ten. Substitution of a chlorine or methoxy group in position two increases the potency of phenothiazine for depressing motor activity and for altering psychotic behavior in humans. The nature of the substituent at position ten also influences pharmacological activity. Phenothiazines can be divided into three groups on the basis of substitution at this site. Chlorpromazine, triflupromazine include in the group of an aliphatic side chain. This is the least potent group of the phenothiazines as can be seen by the dosage range (Goodman and Gilman - 1970). Chlorpromazine is 10- (3-dimethylaminopropyl)- to 2 chlorophenothiazine (Goodman and Gilman - 1970; Ben - 1969).
Imipramine:

The iminodibenzyl nucleus, is the basic constituent of the tricyclic anti-depressants. It consists of two benzene rings attached to each other by a nitrogen atom and an ethylene bridge. In Imipramine the iminodibenzyl nucleus is substituted in position five with a dimethylamminopropyl - side chain. Imipramine is 5- (3-dimethylaminopropyl) - 10, 11-dihydro- 5H - dibenzepene (Ban - 1969; Brucke et al. - 1970; Goodman and Gilman - 1970).

Diazepam:

The benzodiazepine nucleus originates from the benzo[a]diazepine structure. Diazepam, a benzodiazepine derivative, differs from chlor Diazepoxide in having a methyl group in position 1, a carbonyl in position 2 and no N-oxide in position 4. It is 7-chloro - 1 - methyl - 5 - phenyl - 3H - 1, 4-benzodiazepine - 2 (1H) - one. (Band- 1969; Brucke et al. - 1970).

Modes of Actions of:

A.

Chlorpromazine was first synthesized by Charpentier
(1952, as cited by Goodman and Gilman - 1970) long after the synthesis of Phenothiazine in 1883. Soon after this, Lobarot and coworkers (1952, as cited by Goodman and Gilman - 1970) described the ability of this compound to potentiate anaesthetics. Delay, Deniker and others (1952, as mentioned by Brooke et al - 1970) used Chlorpromazine (CPZ) first for the treatment of psychotic patients. In 1953, Courvoisier (as cited by Goodman and Gilman - 1970) and his associates described an amazing large number of actions (e.g., gangliolytic, adrenolytic, antifibrillatory, anti-edema, anti-convulsant etc.) manifested by CPZ and hence the name Largactil, the French Trade name. In view of its actions on various organs in the system, its effect can broadly be discussed under the headings of central, peripheral and endocrinai.

(a) Central Effects:

1) Effects on the Spinal Cord:

Largactil appears to have only insignificant direct effects on spinal cord. Dasgupta, Werner (1954) demonstrated that CPZ diminishes the crossed extensor reflex in the decerebrated cat to a considerably greater extent than in the spinal preparation. Domino et al. (1962a)
found that the effect of CPZ on spinal cord was due to inhibition of reticular reflex activating areas in the medulla rather than facilitation of bulbar inhibitory mechanisms. Hudson (1966) found that CPZ tended to depress monosynaptic and polysynaptic reflexes by acting on interneuronal mechanism in the spinal cord.

ii) **Effects on Medullary, Mesoencephalic and Diencephalic autonomic functions**:

Courvoisier et al. (1952; as cited by Brucke et al. - 1970) found that CPZ acts on chemoreceptor triggerzone and produces marked inhibition of apomorphine emesis in dogs. It is assumed that there is either competition for the receptor site or direct depression of this area which produces the above effect. It has no effect against nausea due to vestibular stimulation.

Acting on medulla oblongata and hypothalamus, CPZ inhibits the central regulatory mechanism of circulation. Gourdan et al. (1955; as cited by Brucke et al. - 1970) reported that CPZ injected into the vertebral artery elicits a fall in blood pressure and similar findings were shown by Tangri and Bhargava (1960) after injecting CPZ into the vertebral. Wang et al. (1964) found by carotid occlusion that
**CPZ inhibits vasopressure reflexes in the isolated perfused head of dogs.**

Courvoisier et al. (1953; cited by Brucke et al. - 1970) found that CPZ lowers body temperature particularly in a low temperature environment. The hypothermia appears to be due to inhibition of hypothalamic regulatory centers, though a concomitant effect on peripheral vasculature may also play a role. CPZ also antagonises the hyperthermia produced by pyrogens (Courvoisier et al. - 1953). Due to inhibition of certain hypothalamic centers it stimulates appetite resulting in considerable gain of body weight. CPZ prevents the morphine-induced stimulation of "sympathetic centers," does not influence the biochemical events accompanying the excitation of hypothalamic sympathetic centres. Dasgupta et al. (1954) demonstrated that the "sham rage" reaction is blocked by small doses of CPZ, indicating that CPZ inhibits those central sympathetic mechanisms in the hypothalamus which are involved in the sham rage reaction.

**iii) Influence on bio-electrical phenomena in the CNS:**

Large doses of CPZ result in an EEG characteristic of drowsiness with the appearance of slow theta waves, 5 - 6 per second with low voltage, whereas, small doses of CPZ cause an enhancement of alpha activity. EEG.
Synchronizing effect of CPZ was first described by Tersian (1954; as cited by Brucke et al. - 1970) and later confirmed by many authors (Das et al. - 1954; Longo - 1954; Rinaldi and Himwich - 1955a, 1955b; Gamgloff and Monnier - 1957; Longo - 1960).

There is no agreement in the literature as to the effect of CPZ on the EEG arousal reaction elicited by direct and indirect stimulation of the reticular formation (Brucke et al. - 1970). CPZ causes only a slight increase in threshold for arousal produced by direct electrical stimulation of the brainstem (Goodman and Gilman - 1970). According to Killam and Killam (1956) CPZ increases reticular activity which in turn stimulates filtering mechanisms in the reticular formation that act to reduce the inflow of stimuli in selective manner. Hiebel et al. (1954; as mentioned by Brucke et al. - 1970) first observed that CPZ in small doses (2 mg./Kg. I.V.) prevents the EEG arousal induced by afferent stimulation and intravenous epinephrine injection which has been confirmed by experiments on different animals - (Longo et al. - 1954; Monnier - 1956; Bradley and Hance - 1957; Martin et al. - 1958; Monnier et al. - 1959; as cited by Brucke et al. - 1970). Complete inhibition is observed only after large doses of CPZ (Killam - 1957).
CPZ (1 mg./Kg. I.V.) enhances the inhibitory effect of the reticular formation on acoustically evoked potentials in the cochlear nucleus and in the medial geniculate body.

Bradley (1963; as cited by Goodman and Gilman - 1970) observed the selective effect of CPZ upon collaterals from sensory pathways impinging upon the reticular formation — the arousal mechanisms within the reticular formation are not depressed by CPZ and experimental animals may be alerted if stimuli can get through. Bradley and co-workers (1966) showed that cells in the reticular formation that are inhibited by non-epinephrine are also inhibited by CPZ. Killam (1968) reported a differential sensitivity of units in the reticular formation to CPZ and also made attempt to localize the excitatory and inhibitory effects of CPZ to units in the reticular formation.

According to Preston (1956); Killam (1957); Killam and Killam (1959) the specific relay nuclei of the thalamus are not significantly influenced by CPZ. Takaori and Deneau (1962a) found that in monkeys with chronically implanted electrodes CPZ slightly raises the threshold for behavioral arousal elicited by stimulation of the nucleus ventralis posterior. The diffuse thalamic projection system is barely depressed by CPZ as evidenced by thalamo-
cortical recruiting responses (Dasgupta et al. - 1954; Killam and Killam - 1956;). According to Goodman and Gilman (1970) a low-frequency stimulation (5 to 12 cycles per second) of the diffuse thalamic projection system produces responses in the cortex that increase in amplitude with time (the recruiting response). Chlorpromazine increases the amplitude of the response. It is not certain whether this effect of chlorpromazine is direct or indirect, since the enhancement is also noted in sleeping animals.

CPZ appears to have direct effects on Limbic system. Preston (1956) found that every large doses (25 mg./Kg.) of CPZ elicit spontaneous seizure activity in the hippocampus particularly in the amygdaloid nuclei and extremely large doses (40 mg./Kg.) cause spreading of spikes to the cortex. Smaller doses either have no effect or exert some depressant action of the evoked seizure like patterns in the limbic system area. Killam and Killam (1958) have indicated that CPZ may depress the arousal response of the limbic system which is characterized by slow, high voltage waves. It has been mentioned by Goodman and Gilman following the experiment conducted by Danniro (1962) that the doses of CPZ that have no behavioral depressant effect have no action on the threshold and duration of hippocampal after discharge.
The actions of CPZ upon the basal ganglia are of interest since the drug is known to cause parkinsonism syndrome. It decreases spontaneous firing in single units of the caudate nucleus and globus pallidus, whereas the firing rates following sciatic stimulation are markedly increased. Adey and Dunlop (1960) found that this apparent stimulant effect upon the extrapyramidal system may be related to parkinsonism.

CPZ seems to have only very weak direct effects on the cortex. Delgado and Mihailovic (1956) (also mentioned by Goodman and Gilman - 1970) found that in monkeys, the threshold for eliciting motor reactions is not influenced or only slightly increased by CPZ. CPZ has been reported (Gangloff and Monnier - 1957; also mentioned by Goodman and Gilman - 1970) to increase the threshold and to prolong the after discharge in the sensory-motor cortex.

iv) Biochemical effects on the CNS:

The inhibitory effects of CPZ on enzyme systems containing the prosthetic group, flavin-adenine dinucleotide (FAD) appears to be rather specific (Helper et al. - 1958; Dowkins et al. - 1959). CPZ acts like a flavin antagonist (Yagi et al. - 1956; Low - 1959) and FAD is claimed to antagonise the EEG. Effects of CPZ (Yagi et al. - 1960).
The enzyme inhibiting effect of CPZ and the property of decreasing cell membrane permeability (Spirites and Guth - 1961-1963; Seeman and Bialy - 1963) could possibly explain the effect on the respiratory enzymes and the uncoupling oxidative phosphorylation by CPZ (Domina - 1962b). By the same mechanism, the inhibition of normal tissue respiration by large doses of CPZ can be explained.

Dopkin et al. (1954) reported that CPZ inhibits the liberation of acetylcholine in cat brain and they obtained similar results by using human cortical tissue obtained during lobotomy of schizophrenic patients. CPZ influences the action of nor-epinephrine, dopamine and 5-HT in brain. The concentration of these amines in brain is not altered by CPZ (Brodie et al. - 1956b; Vogt - 1957; Holzer and Hornykiewicz - 1959; Starbuck and Heim - 1959; Pletscher and Gey - 1959, 1960; Ehringer et al. - 1960; Gey and Pletscher - 1961a; and also quoted by Brucke et al. -1970). Cammanni et al. (1959) found that CPZ blocks the preventive action of MAO inhibitor against reserpine induced catecholamine release from the adrenal. CPZ reduces the increase of 5-HT after in vivo injection of 5-hydroxytryptophane (Gey and Pletscher - 1962a). CPZ accelerates the enzymatic breakdown of catecholamines particularly nor-adrenaline derived from dopa; Axelrod et al (1961b), and Hertting
(1961) had demonstrated that CPZ increases the turnover of exogenous nor-epinephrine and inhibits the uptake into peripheral storage sites (also Martin et al - 1960). The principal effect of CPZ is on the reticular formation, hypothalamus, the nuclei of the extrapyramidal system and possibly rhinencephalon, where nor-adrenaline, dopamine and 5-HT are rich. The correlation between localization of cerebral amines and those brain areas on which CPZ acts indicates the importance of biochemical results regarding the mechanism of action of CPZ. The existence of nor-adrenergic and dopaminergic mechanisms which may be involved in impulse transmission within reticular system (Rothbailer - 1959) and extrapyramidal system (Hornykiewicz - 1964b, c) respectively gives additional weight to this view. It is however, unclear whether CPZ exerts main effect on cerebral catecholamines by blockade of catecholamine receptors (Carlson and Lindquist - 1963; also discussed by Brucke et al. - 1970), or by inhibiting either storage of monoamines (Gey and Pletscher - 1964) or disposition of the metabolites (Anden et al. - 1964b; also discussed by Brucke et al - 1970).

Since recent biochemical studies have shed new light on the parkinson syndrome in man, it should be feasible to use a similar approach to the problem of pheno-
thiazine induced "parkinsonism" (Curzon - 1968; Brucke et al. - 1970).

Montagu (1957) and later, Carlson et al (1958) and Schumann (1959), demonstrated that the brain contains dopamine (3-hydroxy-tyramine). Bertler and Rosengren (1959) found dopamine to be especially localized in the caudate nucleus and putamen of various animal species. This observation has been confirmed in man (Sano et al. - 1959; Ehringer and Hornykiewicz - 1960; Bertler - 1961a) and has been extended to include the substantia nigra and the external pallidum (Hornykiewicz - 1963, 1964a). CPZ by blocking the receptor or by inhibiting the uptake of newly formed amines into storage sites prevents action of dopamine thus produces extrapyramidal symptoms. A different explanation has also been proposed by Himwich and Rinald (1957) (as discussed by Brucke et al. - 1970). According to this view, large doses of CPZ increase the electrical activity (hyperactivity) of the ascending reticular activating system (ARAS) and the hyperactivity extends up to the descending reticular formation which might be the cause for the uncoordinated extrapyramidal hyperactivity.

\[ \text{v) Influence on Behavior:} \]

CPZ reduces motor activity even with doses which
have no significant sedative effect. It was found that animals had no interest in food and their reactivity to external stimuli was often found reduced (Brucke et al. -1970). Das et al. (1954) found that normally aggressive rhesus monkeys were tamed by CPZ.

Chlorpromazine produces a considerable degree of sedation when given for the first time in doses of 50 to 100 mg. The effect was described by Delay and Deniker in 1952 (also cited by Goodman and Gilman - 1970) as follows:

"............ sitting or lying, the patient is motionless in his bed, often pale and with eyelids lowered. He remains silent most of the time. If he is questioned, he answers slowly and deliberately in a monotonous, indifferent voice; he expresses himself in few words and becomes silent. Without exception the response is fairly appropriate and adaptable, showing that the subject is capable of attention and of thought. But he rarely initiates a question and he does not express his anxieties, desires or performances. He is usually aware of the improvement induced by the treatment but does not show euphoria. The apparent indifference or the slowing of responses to external stimuli, the diminution of initiative and of anxiety without a change in the state of waking and consciousness or of intellectual faculties constitute the psychological syndrome attributed to the drug."
These authors subsequently named this syndrome, characterized by psychomotor slowing, emotional quieting, and affective indifference, the neuroleptic syndrome (Goodman, Gilman - 1970).

Beside the classical observations of Belay and Deniker (1952), many investigations have been conducted on the influence of CPZ on human behavior (Heimann and Witt - 1955; Kornetsky - 1960), often utilizing batteries of psychological tests. In one comparative study, an unexpected finding was that CPZ had a greater hypnogenic effect than the same dose of Secobarbital (Kornetsky and Humphries - 1958); the performance in psychological tests was not as good as before administration of the compounds, and the after-effects were equally pronounced after administration of both agents.

Courvosier et al (1953) demonstrated first that CPZ (1 mg./Kg. S.C.) selectively blocks the conditioned avoidance response in rats. Similar effects have been observed by Alexander and Horner (1961) and Windsor (1957). Rutledge et al. (1957) observed the effect of CPZ in response to central and peripheral stimulation that the depression of conditioned response to a peripheral stimulus was found to be complete at a dose that failed to block the response
to direct cortical stimulation. Thus, CPZ appeared selectively to attenuate response eliciting properties of peripheral stimuli. Mirsky and Kornetsky - 1968, as discussed by Goodman and Gilman (1970) observed that CPZ impairs vigilance in human subjects performing continuous pursuit rotar and tapping speed tests. The drug (CPZ) produces relatively little impairment of digit symbol substitution test.

(b) **Peripheral Effects** :

1) **Adrenolytic, Cholinolytic, Antihistaminic and Antiserotonin effects** :

CPZ antagonises the peripheral effects of epinephrine, acetylcholine, histamine and serotonin (5-HT) both in vivo and vitro. Courvoisier et al (1953) found that all effects of epinephrine are blocked by CPZ or even could reverse the variety of actions of epinephrine. But Martin et al (1960) demonstrated that not all effects are diminished by CPZ. The vasopressor effect of nor-epinephrine is diminished but never completely blocked or reversed (Brucke et al - 1970). The rise in blood pressure induced by occlusion of bilateral carotid artery and by electrical stimulation of the central end of the cut vagus nerve is blocked by CPZ. The contractions induced by epinephrine of the isolated rabbit uterus (Courvoiser et al - 1953;
Kopera and Armitge - 1954) or isolated aortic strip (Martin et al. - 1960) are also blocked by CPZ. Nasmyth (1955) found that the epinephrine induced release of ascorbic acid from the adrenal gland is potentiated by CPZ. According to Axelord et al. (1961b) and Hertting et al. (1961) CPZ inhibits the uptake of exogenous nor-epinephrine into catecholamine storage sites.

The cholinolytic and antihistamine effects are considerably weaker than those of promethazine (Courvoisier et al. - 1953; Kopera et al. - 1954).

CPZ blocks the actions of 5-HT quite effectively and impairs the uptake of 5-HT by the brain.

ii) Effects on Heart circulation and Vasculature:

The actions of CPZ on the cardiovascular system are complex because the drug produces the direct effects on the heart and the blood vessels and also indirect effects through actions of CNS and autonomic reflexes. Ryall (1956) observed that CPZ has an antifibrillatory and quinidine-like action on isolated rabbit atria. Tachycardia develops after CPZ injection (due to lowered peripheral resistance and resulting hypotension; slight atropine like effect may also play role). In normal man, I.V. administration of CPZ causes orthostatic hypotension and tachycardia. Tolerance
develops to the hypotensive effect. According to Courvoiser et al (1955), vascular dilatation and increased capillary permeability due to application of skin irritants is prevented by CPZ.

iii) **Muscle relaxant Effect:**

CPZ causes skeletal muscular relaxation and since it has little effect at spinal levels, actions on motor activity are mediated in the medulla or in basal ganglia. A selective depression of the gama efferent system contributes to the muscular relaxation (Henatsch and Ingvar - 1956; as mentioned by Goodman and Gilman - 1970). Ryall (1956) concluded that CPZ diminishes the muscle contraction by blocking neuromuscular transmission and by a direct depressing effect on the muscle. Jindal and Deshpande (1961) described a nicotin-like blocking effect on the end plate region induced by CPZ, prochlorpromazine and promethazine in invivo experiments on dogs.

iv) **Effects on Kidney, Liver and Peripheral Nerves:**

CPZ may have diuretic effects in animals and man, due either to a depressant action upon the secretion of ADH or to inhibition of reabsorption of water electrolytes by a direct action on the renal tubule or both (Gaunt et al - 1963; as cited by Goodman and Gilman - 1970). It also has a diuretic
effect in patients with congestive cardiac failure. It may prevent the fall in the renal blood flow occurring in shock.

Besides hypersensitivity reactions which occur in the liver CPZ may produce an increase in bile viscosity unaccompanied by clinical signs.

The local anaesthetic effect of CPZ is pronounced (Courvoisier - 1953; Kopera and Armitage - 1954), but the drug has never been used for this purpose.

v) **Effects on Gastro-intestinal Tract**:

CPZ increases appetite, decreases gastric motility and gastric secretion and there occurs a tendency to constipate.

vi) **Effects on Blood**:

There is no significant changes in red blood corpuscles and haemoglobin concentration but there may be rise in the Erythrocyte Sedimentation Rate (ESR) and fall in W.B.C. by CPZ. Still there is no impairment of resistance.

vii) **Endocrine effects**:

Whitelaw (1956) observed the postponement of ovulation and menstruation and in large doses phenothiazine
may lead to amenorrhoea (Clark and Johnson - 1960). CPZ diminishes the excretion of gonadotrophines, estradiol, estrone, estriol and pregnanediol. The excretion of total 17-hydroxycorticoids is also reduced, whereas 17-ketosteroid excretion is unaffected. Since CPZ diminishes the gonadotrophin excretion even in pregnant women, its effect appears to be central (hypophysis) and peripheral (chorion). CPZ causes lactation in man (Hooper et al - 1961) and animals (Sulman - 1961). Many authors (Brucke et al. - 1970) consider the endocrine effects of CPZ to be a consequence of an inhibitory influence of this agent on the hypophysis and hypothalamus.

B. IMIPRAMINE (TOFRANIL):

Imipramine is one of the most widely used drugs for the treatment of depression. In 1989 it was first synthesized by Thiele and Holzinger. The pharmacological properties were not investigated until 1948, when Hafliger synthesized a series of more than forty derivatives which had antihistaminic, sedative, analgesic and anti-parkinsonic effects. During clinical investigation of this drug Kuhn (1958) found quite fortuitously that unlike Phenothiazines, Imipramine was relatively ineffective in agitated psychotic patients. Instead, it showed remarkable benefit
upon certain depressed patients. Subsequently, Kulm - (1958) administered imipramine to approximately 50 patients suffering from a variety of depressive syndromes and concluded that it was most useful in endogenous depression. Imipramine has become popular in the treatment of depression because it is relatively safer/MAO inhibitors, more acceptable to patients and easier to administer than E.C.T. (Goodman and Gilman - 1970).

(a) **Central Effects**:

(1) **Interaction with central autonomic mechanism**:

According to Sigg (1959) imipramine interferes with central adrenergic events which may be the basis for its clinical effectiveness. The action of central stimulants like amphetamine, LSD are enhanced by imipramine, for instance, motor hyper-activity in rodents (Halliwell et al. - 1964) conditioned avoidance behavior (Carlton - 1961; Scheckel and Boff - 1964), hyperthermia (Jori and Garattini - 1965). Hyperpyretic responses and stimulated behavior induced by dopa in mice pretreated with a MAO inhibitor are also increased by tricyclic antidepressants (Sigg and Hill - 1966; Everett - 1967). MAO inhibitors combined with imipramine lead to flattening in mice (Sapoelli et al. - 1961) and to EEG arousal in dogs (Himwich and Peterson - 1961).
Such interactions are of clinical importance because combinations of MAO inhibitors with imipramine may result in serious central nervous systems side effects like hypertensive crises and hyperthermia.

Imipramine prevents the central depressant effects of reserpine like compounds. Imipramine does not prevent amine depletion induced by reserpine in brain (Garattini et al. - 1962; Pletscher and Gey - 1962). This indicates that imipramine does not interfere with loss of nor-epinephrine storage capacity in intraneuronal sites induced by reserpine.

Many investigators (Cairncross et al. - 1963) hypothesized that depressive states may be related to excessive cholinergic activity in the brain and that imipramine produces its effect by virtue of its anticholinergic action. It was recognised that depression frequently accompanies parkinsonism implicating the importance of cholinergic dysfunction in both of these conditions. That imipramine improves not only the depression but also the rigidity of patients suffering from parkinsonism is another point in favour of the anticholinergic property of this drug. The numerous atropine-like side effects that occur in the course of treatment with this drug are the most convincing evidences of the anticholinergic action of imipramine.
More recently direct evidence has been obtained that, while imipramine antagonizes the effect of adrenaline, it enhances the effect of nor-epinephrine. This effect is correlated with a decrease in biogenic amines stored in the brain which in turn is concomitant with a blockade in the uptake of the administered nor-epinephrine. Sulser and Dingell (1966), Gyermek (1966); Vernier (1966); Lehmann (1966); Efron and Kety (1966), found that the inhibition of the amine uptake mechanisms in the adrenergic neuronal cell membrane was the central mechanism of the antidepressant action of imipramine. The direct evidences of this are the findings that imipramine potentiates the central actions of dopa and amphetamine; potentiates the amine releasing action of reserpine and antagonizes other reserpine effects. Axelrod (1966) recognised that while imipramine inhibits nor-adrenaline uptake both centrally and peripherally, phenothiazines exert this effect only peripherally. Messerman (1970) postulated on the contrary to the currently held catecholamine theory of mood that nor-epinephrine was normally behavior depressing and the blocking of the access of nor-epinephrine to the post synaptic receptor was responsible, as was found on the basis of his experiment, for mood elevating effects of drugs.
Imipramine's effect on the Medulla oblongata is seen as a mild anti-emetic effect.

Systematic studies (Ban - 1969) revealed the influence of tricyclic antidepressants on the arousal reaction related to brain stem reticular formation function. On the basis of drug-induced changes of the arousal reaction, Himwich (1960) differentiated between two major groups of psychoanalectics: energizers and antidepressants (suppressant drugs). He calls energizers those drugs which have a stimulating influence on brain stem reticular formation functions, e.g., the amphetamines and methylphenidate, because they increase the electrical activity of the brain and antidepressants those drugs which have an inhibitory (suppressant) effect on the same structures, e.g., imipramine, benactyzine, orphenadrine, etc., because "they act primarily upon depressive affect," diminishing the response to "disturbing beliefs and unpleasant stimuli" (Ban - 1969). All known tricyclic antidepressants belong to this latter category. It has also been noted, however, that the two classical representatives of drugs which are beneficial in depression, the mono amine oxidase inhibitor iproniazid and the dibenzazepine imipramine, are placed in opposite categories, whereas neither benactyzine nor orphenadrine has a comparable antidepressant action with the tricyclic
preparations. This implies that the mode of action of these drugs is not exclusively in the depression of the arousal response of the reticular formation in the brain stem. The effect of tricyclic antidepressants was further qualified by psychopharmacological experiments which revealed that chlorpromazine is synergistic with imipramine, evoking a sleep-like brain wave pattern and preventing the alerting response on the electroencephalogram (Ban - 1969), while resepine is antagonistic to imipramine in the same areas.

Under the influence of imipramine an increase in self stimulation has been seen with electrodes implanted in the lateral hypothalamus, and an augmentation of the methamphetamine-induced increment in the rate of self stimulation has been found with the same method when electrodes were placed in the posterior hypothalamic region.

(ii) **Electrophysiological effects**

Electroencephalographic (EEG) studies in man, according to Fink (1961), show that imipramine decreases the percentage time alpha and total electrical activity, but increases both theta and fast-beta activities. The behavioral and EEG patterns of imipramine resemble those of centrally acting cholinergic blocking agents. Mercier et al.
(1963) (as cited by Brucke et al) found that imipramine and amitriptyline shorten after-discharges in the amygdala. Locally evoked amygdaloid potentials are diminished while at the same time evoked potentials in the mesencephalic reticular formation are increased (Guerrero-Figueroa and Gallant - 1967). Small doses of imipramine lower the threshold of the rage response to hypothalamic stimulation in cats (Penoloza - Rojs et al. - 1961).

(iii) Biochemical effects:

The psychoactive effects of imipramine and other tricyclic antidepressants cannot be reduced to a single chemical concomitant of drug action. There are a number of central and peripheral changes related to the actions of these drugs. While these drugs as a rule do not have an inhibitory effect on the monoamine oxidase enzyme, they do have an influence on the nervous system transmitter substances, i.e., acetylcholine, nor-epinephrine and serotonin.

(iv) Effects on Behavior:

Very high doses of imipramine and other antidepressants are required to impair locomotor activity and somatic reflexes. Marrriot and Spencer (1965) observed that the exploratory behavior of rodents placed in Y maze was not
affected by imipramine. According to Cook and Kelleher (1962); Morpurgo (1965); Owen and Rathbun (1966), experiments involving operant techniques also indicate that imipramine and other tricyclic antidepressants do not cause significant avoidance failures except in very high doses. Even though it helps depressed patients, imipramine does not produce euphoria in normal human volunteers rather it engenders feeling of fatigue accompanied by atropine like symptoms (dryness of the mouth, palpitations, urinary retention etc.). Grunthall (1958) (cited by Goodman and Gilman) found that on repeated administration for several days these symptoms accentuate giving rise to difficulty in concentration and thinking. Imipramine seems to produce greater impairment of cognitive and affective processes and lesser reduction in physical movement, than does chlorpromazine. Similar findings were reported by Dimascio and associates (1964). The manner in which imipramine relieves the signs and symptoms of depression is not clear. Its effect has been described as a dulling of depressive ideation (Cole et al. - 1962) rather than as the euphoric stimulation produced by MAO inhibitors, but a definitively discriminative experiment is yet to be performed. However, frequent reports of manic excitement as well as of euphoria and insomnia in psychiatric patients indicate that imipramine
does have a stimulant action under certain circumstances. Lehmann et al. (1958) reported similar findings.

(v) Other Central effects:

Imipramine lowers body temperature in several species but does so to a considerably lesser extent than the phenothiazines (Sigg - 1959; Herr et al. - 1961; Theobald et al. - 1965). It lacks any antiemetic effect against apomorphine and does not offer significant protection against electroshock strychnine seizures (Theobald et al. - 1965).

(b) Peripheral Effects:

(i) Cholinolytic, Antihistaminic, Antiserotonin and Adrenolytic Effects:

Imipramine possesses distinct cholinergic blocking properties, particularly against the masarkin actions of acetylcholine. In vivo the cholinolytic effects as evidenced by the antagonism of the hypotensive response to acetylcholine and vagal stimulation, as well as to pilocarpine induced salivation, seem to be somewhat more pronounced (Theobald et al. - 1965; also mentioned by Goodman and Gilman).

The peripheral antihistaminic properties of
imipramine in vivo (Metysova et al. - 1963; Theobald et al. - 1964; also mentioned by Goodman and Gilman) led to the belief that central antihistaminergic properties might contribute to the clinical effectiveness of these agents.

Imipramine blocks the spasmogenic effects of both histamine and 5-hydroxytryptamine on the isolated guinea-pig ileum. Sigg et al. (1963) found that imipramine enhances some peripheral effects of serotonin. On the other hand, many other serotonin actions are diminished specially after administration of large doses. Thus, the rat paw oedema, gastric ulcer and the increased capillary permeability induced by 5-HT are reduced by imipramine (Theobald et al. - 1964).

Large doses of imipramine tend to have adrenolytic effect. The difference between imipramine and phenothiazines is in this respect only quantitative since a catecholamine potentiating effect can, under special circumstances also be observed with low doses of phenothiazines (Martin et al. - 1960). In isolated tissues, only adrenolytic effects are observed with imipramine and other tricyclic anti-depressants. Imipramine does not inhibit the uptake of catecholamines into storage granules but appears to inhibit solely the uptake from the extraneuronal space.
into the terminal adrenergic nerve fibres (Carlsson and Waldeck - 1965).

(ii) Effects on Cardiovascular systems:

Imipramine lowers the blood pressure in anaesthetised dogs (Sigg et al. - 1963) and obtunds various cardiovascular reflexes including carotid occlusion reflex and postural reflexes. Orthostatic hypotension is commonly observed with therapeutic doses, and myocardial infarction and the precipitation of congestive cardiac failure during the course of treatment have been attributed to imipramine administration. Toxic doses of imipramine produce cardiac arrhythmias and tachycardia. E.C.G. changes observed following the use of imipramine consist in inversion or flattening of T waves.

(iii) Effects on Respiration:

Imipramine in clinical doses produces little effect on the respiration. Respiratory depression has been observed following poisoning with imipramine (Goodman and Gilman - 1970).

C. DI______

This compound belongs to the benzodiazepine
group and has been initially synthesized in 1933. The reviews on the pharmacology of diazepam have been written by Randall et al. (1961), Zbinden (1967). Diazepam, a minor tranquilizer is distinctly different from either rauwolfia alkaloids or the phenothiazines in that it is not effective in treatment of psychoses. In contrast to the neuroleptic agents it exerts little effect on the peripheral autonomic nervous system and does not, as a rule, produce extra-pyramidal effects. It is distinguished by its anti-convulsant properties and its depressant effects on spinal reflex activity.

(a) Central Effects:

(1) Spinal Cord:

Randall et al. (1961), Klupp and Kahling (1965), (also mentioned by Brucke et al. - 1970), Gluckmann (1965) observed that disruption of coordinate motor behavior with diazepam, might be due to the marked muscle relaxant effect of this compound. Diazepam diminishes polysynaptic reflexes (Hendly et al. - 1954; also cited by Brucke et al. - 1970), Wilson and Talbot - 1960; Randall - 1961). According to Tardiue et al. 1964; also mentioned by Brucke et al. - 1970), Jimenez - Pabon and Nelson (1965), and Ngai et al. (1966), the muscle relaxant effect of diazepam is particularly
pronounced in decerebrated animal. Recent evidence indicates (Schmidt et al. 1967; also mentioned by Brucke et al. - 1970) that the reflex depressant effects of diazepam stems chiefly from an intensification and prolongation of presynaptic inhibition of proprio- and exteroceptive afferents in the spinal cord.

(ii) **Effects on Medulla oblongata, hypothalamus and thalamus:**

Diazepam is ineffective in apomorphine induced vomiting on medullary centres but chlordiazepoxide in high dosages inhibits it.

Diazepam has an inhibitory effect on the sympathetic nuclei of the hypothalamus and also on the hypothalamic centers which control pituitary prolactin secretion. This is responsible for the mammotrophic effects of this drug described in rats.

On thalamic structure it has also inhibitory actions. This is manifested primarily by a raised threshold to stimulation and in a diminished responsivity.

(iii) **Effects on hippocampus and amygdala:**

Hippocampus is more sensitive to diazepam activity.
Even low dosages slow down the spontaneous electrical activity and depress after discharges to direct stimulation in these structures (Ban - 1969).

Diazepam increases the threshold of the amygdala to direct stimulation. It has a controlling effect on cocaine-induced seizures which spread from the amygdala to other central nervous system structures (Ban - 1969).

(iv) **Effects on Autonomic system**:

The slight sympatholytic action of diazepam, is seen in minimal ptosis, lacrimation and lowering of blood pressure and pulse rate.

(v) **Effects on brainstem reticular formation**:

The sensitivity of the brain stem reticular formation structures to diazepam and its analogues is relatively low (Ban - 1969).

(vi) **Biochemical effects**:

In contrast to neuroleptic agents, diazepam and other benzodiazepine derivatives do not significantly change the cerebral metabolism of catecholamines in vivo (Laverty and Sharmann - 1965; Rods - 1965; Daprada and Pletscher - 1966; also mentioned by Brucke et al. - 1970). Moreover,
diazepam and other minor tranquillizers, unlike antipsycho-
tic agents have little effect on the spontaneous release of
epinephrine from adrenal medullary granules or the 5-HT
outflow from the blood platelets (Pletscher et al. - 1967;
also mentioned by Brucke et al. - 1970).

(vii) Electrophysiological changes:

It is generally assumed that the minor tranquili-
lizers act predominantly on sub-cortical areas. The limbic system seems to be particularly sensitive and a signifi-
cant slowing in the electrical activity of the septum,
hippocampus and amygdala for diazepam (Schallek et al. - 1962;
Kletzkin and Sean - 1959; Randall et al. 1961; also mention-
ed by Brucke et al. - 1970), minor tranquilizers, e.g.,
diazepam, chlordiazepoxide and meprobamate shorten electro-
cal after discharges in the limbic system (Kletzkin and
Berger - 1959; Schallek et al. - 1962; Horovipz et al. -
1963; Requin et al. - 1963). Seizures induced chemically
by implanting acetylcholine into the amygdala are blocked
by diazepam (Hernandez - Peon et al. - 1964).

(viii) Anti-convulsant effects:

Diazepam and the other minor tranquilizers have
marked anti-convulsant properties. Whereas the seizures
induced by maximum electroshock and strychnine are diminished only after doses already causing muscle relaxant effects, pentamethylenetetrasole-induced convulsions are antagonized by vary low doses of chlordiazepoxide and diazepam (Randall et al. - 1961; Bastian - 1961; Lanoir et al. - 1965; also mentioned by Brucke et al. - 1970). Diazepam and other benzodiazepines also effectively block cocaine-induced seizures in rats in contrast to diphenylhydantoin and phenobarbital which are ineffective in this respect (Eidelberg et al. - 1965).

(ix) Behavioral Effects:

Diazepam and other benzodiazepine tranquilizers reduce aggressive behavior in monkeys (Randall et al. - 1960, 1961). These tranquilizers also inhibit the irritability of rats with lesions in the septum (Hunt - 1957; Raitt et al. - 1961; Schallek - 1962). In rats and squirrel monkeys submitted to continuous avoidance procedure small doses of diazepam cause avoidance failure as indicated by the increase in shock rate, whereas meprobamate causes loss of both avoidance and escape responses indicative of the inability to respond (Heise and Boff - 1962).

In human pharmacological studies diazepam was
given in dosages from 15 to 40 mg. a day over a period of a month. With increase in dosages, drowsiness, slurring of speech and ataxia were seen; and with the increase of time, there was an increase in slowness of mentation with apathy and pronounced impairment of memory functions (Ban - 1969). This reverted to normal only six to eight days after diazepam was withdrawn. (Ban - 1969).

(b) Peripheral effects:

Diazepam is capable of lowering the blood pressure in anaesthetized dogs and cats. Vaso depression is accompanied by bradycardia. However, no significant cardiovascular effects are seen in patients receiving therapeutic doses (Murray E. Jarvik - 1968; also cited by Goodman and Gilman - 1970).

DOSAGE AND ROUTE OF ADMINISTRATION:

Chlorpromazine:

Dosage varies within somewhat narrow limits between one patient and another. In general, the dosage is raised as quickly as possible until all symptoms are reduced to a minimum which will prevent the emergence of symptoms (Dally - 1967).
The usual starting dose of chlorpromazine in the treatment of schizophrenia is 300 mg. a day, given in three divided doses and increased progressively by 150 - 300 mg. a day up to a maximum of 1,500 mg. a day until symptoms and disturbed behavior are controlled or side effects become too troublesome. Doses up to 3,000 mg. a day have been used (Sargant and Slater - 1969). Once symptoms have disappeared or come under control the dose of chlorpromazine should be progressively lowered to the minimum needed to maintain improvement. This is in practice, usually between 150 to 300 mg. a day, although higher doses are sometimes needed (Dally - 1967; Sargant and Slater - 1969).

The clinician exercises considerable judgement in initiating chlorpromazine therapy for psychotic patients. Therapy may begin with 25 or 50 mg. three times daily by mouth if the patient is sufficiently cooperative (Goodman and Gilman - 1970). In addition to the oral tablets, chlorpromazine can be given by the intramuscular route when the patient is not cooperative to reduce quickly the excitement (Goodman and Gilman - 1970).

Imipramine:

Dosage schedules for administration of imipramine
are adjusted in individual cases. It usually begins with 75 or 100 mg. given orally in divided doses, increasing progressively to 75 mg. three times a day (Sargant and Slater - 1969). The majority of patients who fail to respond to 150 mg. imipramine a day will not improve if the dosage is doubled (Dally - 1969). However, there are a few patients whose symptoms will only respond completely to 225 mg. or 300 mg. imipramine a day (Dally - 1969; Goodman and Gilman - 1970). Once the symptoms disappear the dosage is to be adjusted by trial and error to a level just sufficient to prevent any return of symptoms (Sargant and Slater - 1969) and this dose may vary from 50 - 150 mg. a day.

In severely depressed patients or extremely uncooperative patients quicker initial results may be obtained by giving 150 mg. a day intramuscularly for the first four days followed by oral administration of the same (Dally - 1967; Goodman and Gilman - 1970).

**Diazepam:**

The dosage depends upon the severity of the symptoms to be treated. It ranges from 2 mg. per day to 10 mg. three times a day given orally (Dally - 1967; Goodman and Gilman - 1970). Dosage varies according to the severity of anxiety.
SIDE EFFECTS:

Chlorpromazine:

Side effects are related not only to the dosage, but also to the personality of the patient (Sargant and Slater - 1969). Autonomic and endocrine effects are more frequent with chlorpromazine. Side effects of chlorpromazine can be described under the following headings:

**Autonomic Effects**:

Postural and orthostatic hypotension may occur and produce unpleasant effects like tiredness, weakness, fainting and dizziness. Tachycardia, blurring of vision, paralytic ileus, fecal impaction, dry mouth, facial pallor, lachrymation, aggravation of glaucoma, disturbance of micturition like - urgency, frequency, hesitancy, incontinence, rarely anuria; nasal congestion and inhibition of ejaculation are the important autonomic side effects.

**Endocrine Effects**:

Menstrual irregularities including amenorrhoea, lactation, gynaecomastia can occur. Weight increase is marked sometimes, although this may be partly the result of water retention. False positive reaction to pregnancy

**Central Nervous System Effects**:

Parkinsonism is common after large doses of chlorpromazine. Dyskinetic-dystonic reactions are the results of sudden usually short lived, tonic contractions of localized group of muscles. Acute dystonic (torticollis, oculogyric spasms, opisthotonous etc.) reactions usually affect younger patients, men more often than women. Epileptic fits may occur when large amounts of chlorpromazine are first given, or if the dosage is suddenly increased (Sargant and Slater - 1972), or in previously brain damaged patients (Caffey, E.M. (Jr.) et al - 1970-71). Disturbed body temperature, respiratory depression, other neurological manifestations like akathisia (an unpleasant form of restlessness often localized by the patient to his legs, which makes it difficult or impossible for him to sit still) are the other side effects of chlorpromazine.

**Behavioral Effects**:

Over sedation, impaired psychomotor functions, toxic confusional states, aggravation of schizophrenic

**Allergic or Hypersensitivity Effects:**

Jaundice sometimes occurs with chlorpromazine, usually within first two months of treatment. It is unrelated to the dosage and the obstructive type of jaundice is associated with eosinophilia. This type of jaundice is twice as common in women as in men. In majority of cases, withheld of the drug is followed by full recovery, although jaundice may take as long as six months to disappear completely (Dally - 1967).

Agranulocytosis is rare but occasionally fatal reactions to chlorpromazine occurring between the sixth and the tenth week of the treatment (Dally - 1967).

Leukocytosis, leukopenia and eosinophilia commonly occur with chlorpromazine and other phenothiazines (Goodman and Gilman - 1970). Dermatitis, photosensitivity, contact dermatitis, granular deposits in the cornea and in the lens may occur with chlorpromazine therapy (Sargant and Slater - 1967; Goodman and Gilman - 1970).
Miscellaneous Effects:

These include sudden death (due to dose, previous brain damage, seizures, induced ventricular tachycardia), hypostatic pneumonia, local inflammation, gangrene due to injection at site or perivenous leakage, potentiation of the effects of alcohol (Caffey, E.M. (Jr.) et al. 1970-71).

Side Effects:

Imipramine:

Autonomic Effects:

The most frequent untoward reactions caused by imipramine are those attributed to atropine-like effects, including constipation, drymouth, dizziness, blurred vision, tachycardia, palpitations, urinary retention, aggravation of glaucoma (Goodman and Gilman - 1970).

Central Nervous System Effects:

Neurological symptoms are common. Tremulousness can vary from a vague sensation of restlessness and twitching to uncontrollable violent shivering. Difficulty in speaking, weakness of legs and pains in the limbs may also occur.
with high dosage epileptic fits occasionally occur (Dally - 1967). Parasthesiae, mainly of prickling or burning in nature in the limbs, or/and unpleasant cold feeling in the legs, are experienced sometimes (Dally - 1967). Fasciculation, ataxia, hyper-reflexia, increased tonus, peripheral neuropathy are also known to occur with imipramine (Caffey, E.M. (Jr.) - 1970-71). Rarely extrapyramidal symptoms do occur, although occasionally tremors and choreiform hyperkinesias are noted (Brucke et al. - 1970).

Behavioral Effects:

Imipramine may produce an acute toxic confusional state specially in the aged. Visual hallucinations are particularly vivid and frightening (Dally - 1967). Another undesirable effect of imipramine is a transition from depression to hypomanic or manic excitement in a pre-disposed individual (Dally - 1967; Goodman and Gilman - 1970). Schizophrenic symptoms may also be brought out or/acerbated.

Difficulty in sleeping may result if imipramine is given too late at night (Dally - 1967).

Allergic or Hypersensitivity Effects:

Hypersensitivity effects include jaundice, blood changes like agranulocytosis, eosinophilia, skin reactions
(allergic dermatoses, photosensitivity, pruritus, urticaria, angioneurotic oedema). These reactions generally disappear within few weeks of withdrawing the drug (Dally - 1967).

**Gastro-intestinal Effects**:

In addition to constipation, nausea and vomiting are uncommon but it is quite frequent to have an unpleasant burning sensation beneath the sternum or epigastrium, while taking imipramine (Dally - 1967; Sargant and Slater - 1967). Though there is suggestion that imipramine might be useful in the treatment of peptic ulcer because of their ability to reduce gastric secretion, a number of alcoholic patients have developed peptic ulcers while taking imipramine (Dally - 1967). Abdominal distension may occur which may progress to paralytic ileus (Gander, D.R., Devrin, H.B. - 1963).

**Miscellaneous Effects**:

Slight oedema of ankles and puffiness of face may occur in patients treated with imipramine (Dally - 1967; Sargant and Slater - 1967; Caffey, E.M. (Jr.) et al - 1970 -71). Weight gain can occur with imipramine. The drug causes a patient not only to feel excessively hungry but also it appears to cause gain by affecting central weight regulating mechanisms.
Impotence is unusual but delay in ejaculation can occur during first few weeks of treatment (Greenberg, H.R. - 1965). After large doses of imipramine, coma, shock, respiratory depression, fever, dysrhythmias and successful suicides have been observed (Brucke et al. - 1970).

**SIDE EFFECTS:**

**Diazepam:**

Side effects of this compound appear to be relatively low but somewhat greater than that of meprobamate (Goodman and Gilman - 1970).

**Autonomic Effects:**

Blurred vision, hypotension, difficulty in micturition particularly in older patients have been reported (Dally - 1967).

**Central Nervous System Effects:**

Signs and symptoms of C.N.S. depression, including drowsiness and lethargy are common side effects (Goodman and Gilman - 1970). Dizziness and ataxia have been reported (Dally - 1967).
Behavioral Effects:

Abrupt cessation of a high or prolonged dosage may precipitate the similar withdrawal pattern (depression, agitation, insomnia, aggravation of the psychopathological state, loss of appetite) in patients observed with barbiturates, chlordiazepoxide or meprobamate (Krantz and Carr - 1965; Goodman and Gilman - 1970). Elderly patients are particularly sensitive and in severe poisoning or suicide attempts. Coma and hypotension may occur (Brucke et al. - 1970).

Allergic or Hypersensitivity Effects:

Allergic reactions of diazepam are comparatively less than chlordiazepoxide and leukopenia has been reported (Ban - 1969).

Miscellaneous Effects:

Impairment of sexual functions, headache have been sporadically noted.