SECTION A
GENERAL ASPECTS OF DRUG ACTION

1

General Introduction

1.1 DEFINITION AND HISTORICAL

Medicinal chemistry is difficult to define because it is an interdisciplinary science and touches upon various branches of chemistry and biology. It involves on one hand the isolation, characterisation and synthesis of compounds that can be used in medicine for the treatment and cure of disease, and on the other hand establish a link between chemical structure and biological activity.

Medicinal chemistry has also contributed indirectly to the development of organic chemistry in terms of designing routes of synthesis and to pharmacology in terms of spectrum of action of new compounds. The preparations of antibioties and natural products like peptides has lead to the development of new equipments etc. at the industrial level.

Research programmes in medicinal chemistry have created products like hormones, vitamins, biochemicals and also contributed in the development of drugs for veternary medicine.

The oldest historical records on therapeutics indicate that the early drugs were obtained from plants and originated from the ancient civilizations in India, China, in Latin American Mayas and in Mediterranian region. These civilizations used empirical methods for the collection, preparation and administration of herbs and herbal concoctions. Besides, herbs, some metallic drugs from copper, zinc, iron, cadmium were also used for different health problems.

As the scientific ideas on the laws of chemistry were laid and also when the physiological action of drugs became available around sixteenth century new drugs were formulated and the old ones were improved. The ninteenth century saw a great progress in the development in medicinal chemistry. Active principles were isolated and purified. Early synthetic agents were discovered and the foundation of chemotherapy was also laid. The introduction of pencillin produced a profound change in the medical practice and saved a great toll of human life.

However, it cannot be denied that in the beginning of twentieth century empirical ideas formed the basis of medicinal chemical research and it is during the past thirty years or, so that some of the theories of drug action based on sound logic have been proposed.

1.2 CLASSIFICATION OF DRUGS

Since there is an uncertanity 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. Alcohols are known to possess hypnotic, analgesic and antibiotic action. Phenolic group is present in antiseptics, estrogenic hormones,

vitamins, trypanocidal compounds and autonomic drugs. Similarly lactones are found in cardiotonic and anthelmintic drugs. Therefore it is advantageous to arrange the drugs according to their medicinal, use. Drugs which act on the various physiological functions of the body can be grouped together as (i) "pharmacodynamic agents" whereas those which are used to fight pathogenic organisms are grouped together as (ii) "chemotherapeutic agents".

1.3 NOMENCLATURE OF MEDICINAL COMPOUNDS

The common approach to the naming of medicinal compounds is to follow the system formulated for the nomenclature of organic compounds and these principles should be studied in any of the standard organic chemistry text books.

Normally, when synthetic compounds are prepared and sent to a pharmacologist for testing of their pharmacological activities, it is a general practice to identify the compound by means of a code name, the initials of the chemist or research team that prepared the drug are used. As the chemical name is long and cumbersome more easily pronounceable names are devised by the industrial laboratories when the drug has reached a marketable stage. A simplified contraction of the chemical name in which the name of the manufacturer is woven into the name is generally devised. Such names become trade marked names also called proprietary names and are published in Trade Mark bulletin of Pharmaceutical Manufacturers Association. The pharmaceutical literature also reports the establishment of generic names for pharmaceutical compounds. For example, 2, 4-diamino-5-(p-chlorophenyl) -6-ethylpyrimidine which is an antimalarial compound has a proprietary name of Daraprim while its generic name is pyrimethamine. For the compilation of scientific data on the chemistry of a drug, its synthesis, physical properties, reactions, analysis and metabolism, it is necessary to give it a rational name.

The world health organization has given the member countries specific guiding principles and rules for devising drug names for their national pharmacopoeias.

1.4 ECONOMIC ASPECTS OF MODERN DRUG RESEARCH

In the modern world of today the demand for the supply of drugs for the public has become very huge. The cost of synthesising and testing new drugs and introducing them into market has become astronomical. By a conservative estimate the total investment in the preparation of a drug and the demonstration of its efficacy and safety it may cost a pharmaceutical company up to four hundred thousand dollars or more prior to its actual announcement and production.

2

Chemical Structure and Biological Activity

2.1 GENERAL

The early important drugs, such as morphine, atropine, quinine etc, were obtained from plant sources. The study of the chemical structures of these and other natural product compounds with useful medcinal properties furnished the first useful ideas concerning the relationship between the chemical structure and biological activities of such substances. From these studies it became clear that certain structural units of molecules of biologically active compounds are also to be found in those of other compounds having similar properties. This observation was used as a guiding principal in determining the structures of other compounds with analogous activities possibly more specific or more potent and less toxic.

The molecular modification of natural *lead drugs* is still a major line of approach to the design of new drug compounds. It has been postulated that structural alternations produce changes in physical properties and reactivities of a molecule which in turn may cause variations in the distribution in cells and tissues, in access to their sites of action and excertion behaviour. A minor change in the chemical structure of a parent compound may uncover biological properities that might have remained dormant by side effects. The benefits of the use of molecular modification as a successful tool in the drug discoveries can be supported by the synthesis of sulphonamide derivatives with bacteriostatic, diuretic and antihyperglycemic actions.

Though based on empirical approach but from experience several structural units and fragments have been associated with particular type of pharmacological activity. Some of these structural moieties with pharmacological activities are listed in table 1.

TABLE 1

Type of structure	Chemical group	Examples of Drug Compound	Pharmacological Activities
R-COOH R-CH-OH-COOH HO-Ar-COOH	Acids	Propionic acid Chaulmoogric acid Mandelic acid Salicylic acid	Fungistatic, Mycobacteriostatic, Bacteriostatic, antipyretic, anti-rheumatic

(Continued)

ROH, R may be simple or complex	Alcohols	Benzyl Alcohol Ethyl Alcohol 2-propanol Propranolol	Local anesthetic, Sedative, Excitant Anticonvulsant Antihypertensive
$RCONH_2$	Amides	Hydantion Procaineamide Nikethamide Lidocaine Lysergic acid diethylamide (LSD)	Anticonvulsant Cardiotonic Analeptic Local anesthetic Psychotomimatic
R_2-$NHCH_2CH_2Cl$ $RN(CH_2CH_2Cl)_2$ RNHCl Heterocyclic amines $ArC(OH)CRNHR$	Amines	Dibenamine Nitrogen mustard Chlorpromazine Chloroquine Phenethylamine Amphetamine Serotonin	Sympatholytic Anticancer Antipsychotic Antimalarial Pressor CNS Stimultant Neuromodulator
$R_2CHO(CH_2)_2NR_2$		Diphenhydramine Methadone	Antihistaminic Analgesic
$ArCH(OH)(CH_2)_nNR_2$	Aminoal-cohols	Norepinephrine Ephedrine Quinine	Pressor Sympathomimatic antimalarial
$ROCH_2CH_2NR_2$	Aminoether	Phenoxybenzamine Dimenhydrinate	Sympatholytic Antimotion sickness
$Ar_2C(COR)(CH_2)_2NR_2$ N^+R_4	Aminoketone Ammonium compounds	Methadone Acetylcholine Tetraethyl Ammonium Decamethonium Hexamethonium	Analgesic Cholinergic Depressor Curarform Hypotensive
$RONO_2$ $H_2NArCOR$	Esters	Glycerol-Trinitrate Benzocaine	Coronary dilator Local anesthetic
R_2O	Ether	Ethyl Ether	Anaesthetic
RNHC = NHNHR	Guanidine	Chlorguanide, Guanethidine	Antimalarial Antihypertensive
R-Cl $CHCl_3$ Iodinated Compounds	Halogenated Compounds	Ethylchloride Chloroform	Anthelminitic anaesthetic Radiopaque
Fluoro-Compounds		Fluorocorticoids Trifluperazine	Antiinflammatory antipsychotic, antiemetic
RH	Hydrocarbons	Cyclopropane	Aneasthetic

(Continued)

(HO)ArCOR	Ketones	Acetophenone Phenylindandione Ketosteriods	Sedative anticoagulant hormonal
$ArNO_2$	Nitro compounds	Chloramphenicol Nitrofurans	Antibiotic bactericidal
ONNHCONHR	Nitroso compounds	Nitrosoureas	antineoplastic
ArOH	Phenols	Guaicol Hexylresorcinol Estradiol Amodiaquine	Expectorant anthelmintic estrogenic antimalarial
RNHCONHR'	Ureas and Ureides	Barbiturates Hydantoins	hypnotic anticonvulsant

2.2 BIOISOSTERISM

The synthesis of structural analogues of a *lead compound* has been carried out by the substitution of an atom or a group of atoms in the parent compound for another with similar electronic and steric characteristics. The rationale behind this procedure is the principle called *bioisosterism.*

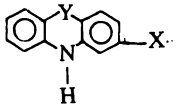
The principle of isosterism was formulated by langmuir, who postulated that two molecules (ions, radicals) containing an identical number and arrangement of electrons should have similar properties, therefore they should be *isosters.*

Accordingly the *isosters* should be *isoelectric* i.e. they should possess same total charge. Examples of such pairs of isosters are CO and NO_2, CO_2 and N_2O, N_3^- and NCO^- and CH_2N_2 and $CH_2{=}CO$. In the aromatic ring system the vinylene group (-CH = CH-) of benzene, the sulphur of thiophene (-S-) and nitrogen (-N=) of pyridine are examples of isosteric groups.

Although there was an extension of these ideas by picking other equivalent groups but no attention was paid to smaller atoms like hydrogen and also to differences in the hybridization of outer oribitals which produce variations in the size, shape and polarity of molecules. In order to widen the application of the principle of isosterism of biological systems, Friedman used the term *bioisosterism* to incorporate both the classical and non-classical isosters so that groups may be interchanged with retention of major degree of similarity in their steric and regional electronic configuration. Accordingly groups like F and H;CO and SO_2 can be considered biosteric pairs though it may be difficult for all molecules to match each other in all their physical, chemical and steric similarities.

The bivalent atoms and groups like -O-, -S-, -NH- and $-CH_2-$ have been interchanged in many types of biologically active compounds especially in anticholinergic and antihistaminic agents, $R_2NCH_2CH_2YCH(C_6H_5)_2$, Y = CH_2, O, NH. These bioisosters when placed adjacent to carbonyl groups give rise to esters ($-CO_2-$), thiolesters -C(= O)S-, amides (= CONH-) and Ketones ($-COCH_2$). Such types of bioisosteric compounds are commonly found in local anaesthetics like procaine and thiocaine, in antispasmodics like adephenine and analgesics like mepiridine.

Among the heterocyclic ring systems the inter-change of -O- or -S- by -NH- or $-CH_2-$ is a common practice and illustrations can be found among tranquilizers and antidepressants as indicated by the chemical structure I below.



X = Cl, CH_2

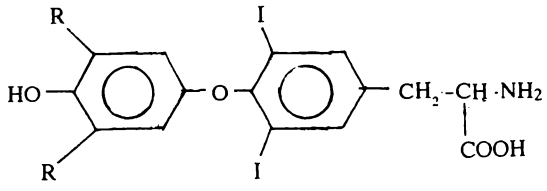
Y = O, S, CF_3

I

The bioisosterism has also been applied to the corresponding derivatives of benzene and thiophene respectively while furan and pyrrole do not show a close resembalance to benzene.

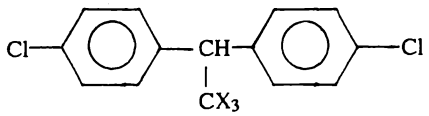
A close steric similarity for thiophene and benzene derivatives has been explained in terms of hybridization in sulphur atom which allows participation of pd^2-orbitals.

According to the definition of bioisosterism groups like halogens, OH, NH_2, and CH_3 can be interchanged in isosters with retention of biological activity. Examples of such molecules are found in thyromimetic compounds, (Levothyroxine, II) the insecticides (DDT, III) and in compounds with antihistamimic activities (tripelamine, IV).



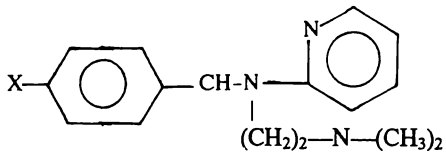
R = I
= $C(CH_3)_3$

II



X = Cl (DDT)
= CH_3

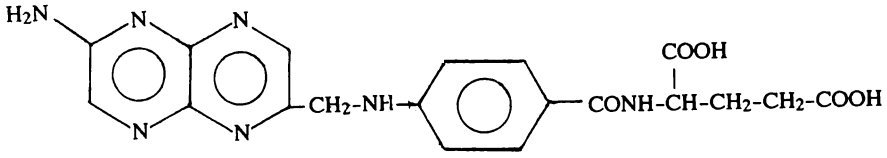
III



X = H

IV

The isosteric comparison of -OH-, $-NH_2$ and -SH groups has been rationalized on their ability to donate electrons and also to form hydrogen bonds. The antagonistic activity of $-NH_2$ and -OH has been reported among the derivatives of pteroylglutamic acid (PGA, V).



V

The non-classical bioisosters comprise groups which are structurally similar but do not meet the electronic and steric requirements in the rigorous sense. They are postulated to act by deforming the structure of macromolecules thus preventing the correct conformation of an active site. This view is based on the fact that a metabolite antagonism is commonly produced when a non-classical bioisoster is incorporated into the structure of a metabolite. Such examples are provided by cases of exchange of -CO- with $-SO_2-$ and $-CO_2H$ with $-SO_3H$.

2.3 QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP (QSAR)

In the original Overton-Meyer theory the biological activity of substances is related to oil water distribution coefficient, K (O/W). The partition coefficients were correlated with biological activity of hypnotic and narcotic agents. The efficiency as hypnotic or anaesthetic drug is dependent on the partition coefficient which measures the distribution of the compound between the aqueous and the lipid phases of the tissue.

The above theory was extended by Ferguson who postulated that drugs produce their effects by combining with a hydrophobic group of an enzyme or protein which he termed as *biophase*. Further, Ferguson proposed that it is not necessary to define the nature of the biophase or receptor or to find the concentration of the drug at this site. He assumed that under equilibrium conditions though the concentration of the drug in the biophase and in the extracellular fluids is different but their escaping tendency in each phase would be same. The degree of saturation of each phase was taken as a quantitative measure of the escaping tendency and he called it "thermodynamic activity".

In recent years, efforts have been made by chemists to establish more meaningful structure - activity correlations on a quantitative basis and it has been observed that the overall pharmacological action of a particular drug is due to the contribution of hydrophobic, electronic and steric factors.

The subject of quantitative structure activity relationships of medicinal compounds was extended by Hansch by investigating the effect of substituent groups of distribution between water and the non-polar solvent 1-octanol. For example the partition coefficient of Phenoxyacetic acetic acid and one of its derivative 3-trifluoromethyl phenoxy acetic acid are measured. A value called solubility constant π for the trifluoro methyl group is obtained by the difference between the logrithm of the partition coefficients and is represented by the equation:

$$\pi_{CF_3} = \log P_{CF_3} - \log P_H$$

where P_{CF_3} is partition coefficient of 3-trifluoromethyl derivative and P_H that of the unsubstituted parent compound. The π values are combined with the sigma (σ) values which give the electronic contribution of the substituent groups with respect to hydrogen.

According to Hansch the values of π and σ are approximately constant and can be combined in a number of different aromatic systems so long as no strong group interactions take place. Thus the substituent constant for a polysubstituted aromatic compound are approximately equal to the sum of the π and σ values for the individual substituent. The additive character of these constants have been demonstrated from correlations obtained for the action of polysubstituted phenols on gram-positive and gram negative bacteria, the carcinogenic action of aromatic hydrocarbons and benzacridines and the action of thyroxine analogs on rodents.

When the substituents are not attached to an aromatic nucleus, different sets of π values have been obtained. For example in a homologous series of compounds if the functional groups are removed by two or more methylene (CH_2) groups the inteaction is small and values can normally be determined additively. The methyl and the methylene groups have an additive π value of +0.50. The π values for various functional groups substituted in the 3-position of phenoxyacetic acid have been calculated as:

$$H = 0, CH_3 = 0.51; C_2H_5 = 0.97; n\text{-}C_3H_7 = 1.43; n\text{-}C_4H_9 = 1.90.$$

Relative to hydrogen = 0, a positive value for π indicates that the group increases solublity in non-polar solvents while a negative value indicates that solublity in polar solvents is increased. Similarly, a positive value for π denotes as electron attracting effect while a negative value dénotes an electron donation effect. For example, methyl group increases non-polar solubility therefore it has π value = + 0.51 and is electron donating its σ value = - 0.17, whereas acetamide (CH_3CONH-) group which increses water solubility has π value = - 0.79 and as a weak electron accepter has σ value = + 0.10. The trifluoromethyl group which has a very high lipohilic character has π value = + 1.07 and σ value = + 0.55.

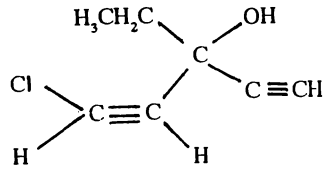
Corwin Hansch further advanced the application of the use of Pi (π) and sigma (σ) substituent constants to biological activities and correlating them to chemical structure. He developed an equation which is represented as:

$$\log (1/C) = - k\pi^2 + k'\pi + \rho\sigma + k''$$

where C is the concentration of the drug necesary to produce the biological response, k, $k'\pi$, $k'\pi'\pi$ are constants for the system under study, ρ is a reaction constant, π is the constant for solubility contribution and σ is the constant for electronic contribution as explained previously. In the above equation log (1/C) can be replaced by log A which stands for logarithm of relative biological activity and can be represented as:

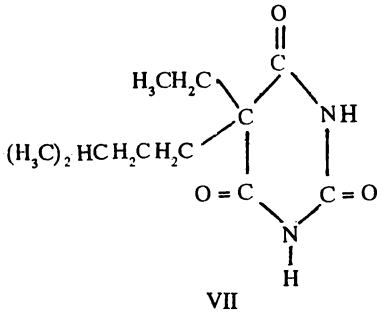
$$\log A = - k\pi^2 + k'\pi + \rho\sigma + k''$$

A very large number of examples of medicinal compounds are available in the literature which show the additive nature of the substituent constant (π) in estimation of the partition coefficient (log p) and closeness of this value to ideal coefficient in such compounds. Such calculations for two representative examples of ethechlorynol VI and amobarbital, VII are given below:



VI

Substituent	*π Value*
-C - OH	- 1.16
-C ≡ CH	0.84
$-CH_3$ - CH_2	1.00
ClCH = CH	1.32
	$\Sigma\pi$ = 2.00 = log P



VII

-C-CONCONHCO | -CH_3CH_2	- 1.35 1.00
$(CH_3)_2C$ $CHCH_2CH_2$-	2.30
	$\Sigma\pi$ = 1.95 = log P

In addition to the incorporation of solubility and electronic constants for functional groups contribution for steric constants (Es), molar refraction (MR) and molecular weight (MW), Van der Waals volume, Taft Polar constants (σ^*) an inductive constant σ_i, group dipole moments μ and many other physical quantities also have been incorporated to obtain correlation coefficients. A large volume of literature is available for these types of parameter correlations.

The quantitative structive-activity correlations can be used to predict the design of new compounds and also to deduce the types of chemical process involved in the biological activity. However, examples of predictions of drug activity from substituent effect analysis that have proved to be successful mainly through QSAR are rare or have not been reported.

The quantitative structure-activity relationship can do more than suggest molecules for study, the only way to determine their pharmacological activity is through synthesis and experimentation.

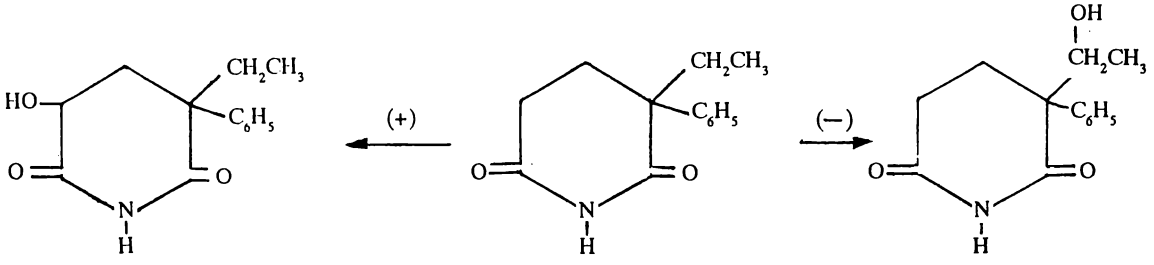
2.4 STEREOCHEMISTRY

Over many years of drug research it has been observed that enantiomorphic pairs of compounds show differences in their biological activity. The earliest case reported was by Louis Pasteur on the finding that

dextro-form of ammonium tartrate was rapidly destroyed by *penicillium glaucum* than the levo form. In a similar manner the levo and dextro forms of epinephrine were found to differ in their pressor effects.

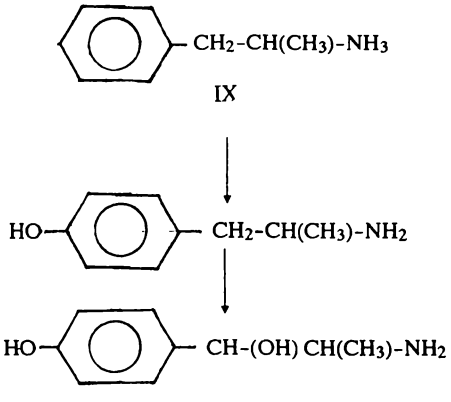
The main reason for studying the stereochemistry of drug molecules is the information that can be obtained concerning the nature of drug receptor interactions and also the characteristics of the different receptors. Before a drug molecule reaches its site of action it is subjected to different processes like the absorption, distribution, uptake at the storage sites and excertion. Some of these processes can be stereoselective in different degrees with the result that the isomeric concentrations at the receptor site will differ. In such cases there will be potency variations among the isomers and this difference will be due to their ability to concentrate at the site of action rather than related to the drug-receptor interactions. Many such examples, where the two isomers differ in their biological activity are: (i) natural R-amino acids are absorbed much more rapidly then the S-enantiomorphs; (ii) in the rat the brain/serum concentration ratio of dextro-hexobarbital exceeds that of levo isomer, which makes the (+) form more potent; (iii) (-) α-methyl dopa picks up higher concentration than the (+) form in most organs in accordance with the fact that only the (-) form has hypotensive activity.

The isomeric compounds also show differences in their metabolic conversions. For example, in the rat liver levo-isomers of 3-hydroxy-N-methtyl morphinan and methadone are 2-3 times rapidily N-demethylated than the corresponding dextro isomers. In the case of glutethimide (VIII) the two isomers have different metabolic fates. The d-isomer is metabolized by hydroxylation of the ring while the L-isomer undergoes hydroxylation of the ethyl group.



VIII

The metabolic break down of amphetamine (IX) involves p-hydroxylation of the phenyl ring in the first stage which is not stereoselective. The second p- hydroxylation occurs at the side-chain and is specific for the product of the first stage.



In line with the above metabolic fate when the rats were fed with (±), (+) and (-) isomers of amphetamine, they were found to excrete less of (+) isomer than (-) isomer indicating that the dextro isomer is more potent than the (-) isomer.

It is now well accepted that there are two aspects of drug receptor interactions, namely the degree of binding of the drug molecule to the surface called *affinity* of the drug and the ability of the drug to generate a stimulus once the drug-receptor complex is formed termed the *intrinsic activity* of the drug.

The differences in activities among the stereoisomers have been explained in terms of affinity, with the result that one form fits the receptor well while the other form fits badly. While in some cases the isomers may possess similar affinities but different intrinsic activities, e.g. (-) isoproterenol is a weak α-sympathomimatic agonist whereas the (+) form is an antagonist at the same site. In general, a three point fit has been postulated to be involved in binding a drug to a receptor surface (Fig. 2.1). Thus in an enantiomorphic pair, only one member will be able to present the required configuration to the receptor surface. In the less active form only two of the binding groups may be aligned correctly towards the receptor surface.

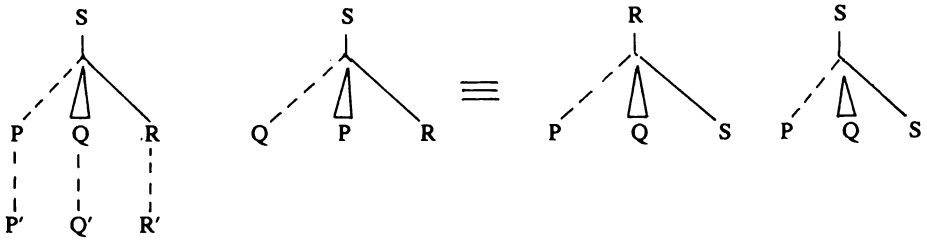


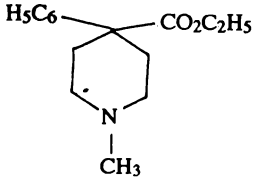
Fig. 2.1. Three point fit for receptor surface

However, the isomeric affinity differences are also possible to occur if only two groups of a molecule bind effectively to the receptor, while the third group may be contributing little or nothing to the affinity of the active isomer but may interfere in the close approach of the two binding functions to the receptor in the less active form.

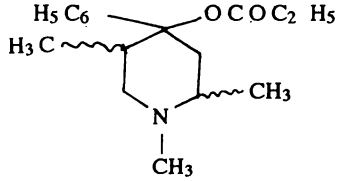
Among the three isomers of ephedrine namely (+), (-) and (+) ψ; (-) ψ ephedrine is most potent, whereas (-) ephedrine has a weak pressor action in the cat and a depressor effect in the dog. This difference in the activity in the two isomers has been explained by the fact that S-β-carbon configuration positions the hydroxyl group in such a way that it retards the uptake of the aminoalcohol molecule by the catecholamine storage sites. Whereas the deoxy compounds with an asymmetric center at the α-carbon atom are much less stereospecific.

In the studies on epinephrine and norepinephrine, the levo enantiomers are more active by factors of 15-40 over their dextro forms. Such stereospecificity of action has been also noted for N-isopropyl and N-t-butyl analogs of epinephrine and for monophenolic derivatives like Synphrine and phenylephrine. All the above described levo-isomers have been reported to have R-configuration.

In the case of an analgesic compound like meperidine (X) with an asymmetric N-substituent, the S(-) isomer is 4-times more potent than R(+) form. Whereas the diasterioisomeric reversed esters of meperidine (XI) which owe their asymmetry to the presence of one or more alkyl substituents in the piperidine ring show marked differences in their activities.



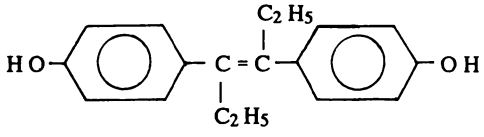
X



XI

Among the 4-phenylpiperidine analgesics it has been postulated that the conformation for the piperidine ring is a skew-boat with a phenyl group in the bowsprit position which is an optimal arrangement for drug-receptor association.

The variations in biological activity have been also reported among geometrical isomers, the cis-trans isomers show large differences in their physical properties. Among the estrogenic stilbenes, the trans form of stilbesterol (XII) is more potent.



XII

Similarly, the geometrical isomers of antihistaminic alkylamines and tranquilizing thioxanthenes show differences in their biological activities which may be due to their differences in their drug-receptor interactions.

2.5 PHYSICO-CHEMICAL PROPERTIES AND DRUG ACTION

In general when a drug molecule enters the body, it will interact with one or more biopolymers found in the extracellular fluid, in the cell membrane and within cells. The type and extent of this interaction will depend on the kind and number of chemically reactive functional groups and the polarity of the molecule. The drug-protein interaction does not involve covalent bonds which are relatively stable at body temperatures. Instead weak forces like ionic bonds, hydrogen bonds, Van der Waals forces, dipole-ion and dipole-dipole forces are involved. A consideration of some of these phsico-chemical forces is described below.

Van der Waals Forces: These are weak attractive forces between molecules and are electrostatic in origin. The physical properties which result from the existance of Van der Waals forces are adsorption to surfaces, solubility in lipids and chemical reactivity. The property of the looseness of the electronic cloud of the molecules is called polarizability which is related to the biological properties and can be obtained from Van der Walls expression for real gases.

The Van der Waals equation for 1 mole of a real gas is given by :

$$(P + \frac{a}{V^2})(V - b) = RT$$

Where P is pressure of a gas, V is the volume, R is the gas constant, T is the temperature (degrees Kelvin), a is a constant related to polarizability of the gas and b is a constant related to molecular volume. Therefore for a gaseous substance, in order to function as a general anaesthetic it must possess polarizability and size. In the case of liquids or solids the above expression has been extended in its scope by using Lorentz-Lorenz formula for molar refractivity.

$$Pr = \frac{n^2 - 1}{n^2 + 2} \cdot \frac{m}{d}$$

Pr is molar refractivity, n is the index of refraction, m is the molecular weight and d is the density of the substance. In this way the contribution of a chemical group to the total polarizability of a chemical compound can be obtained, e.g. in the case of antibiotics and antibodies, the polarizability is related to the binding of various foreign materials with them.

Dipole Moment: Whereever there is a separation of a positive and a negative charge in an atom or a bond, a dipole is produced. Dipole moment is defined as the product of the charge and the distance between the positive and the negative charges as shown by the formula below:

$$\mu = q/d$$

μ is the dipole moment, q is the electronic charge, d is the distance separating the two charges. The dipole moment has a magnitude of the order of 10^{-18} esu - cm because electronic unit charge is equal to 4.8×10^{-10} esu and the distance between the charge centers in a bond is 10^{-10} cm. The quantity of 10^{-18} esu - cm is called a Debye(D).

Dipole moment provides a measure of charge separation in a bond, and in a series of related compounds it can provide an indication as to the manner in which the substituents can affect the charge distribution of a bonded pair of atoms.

Hydrogen Bond : Among the secondary forces hydrogen bonding is one of the most important force that affects the physical property of a compound. The important hydrogen bonding groups are -OH, -NH and -SH through the last group is not very effective in such bonding. The -OH and -NH groups can form either inter or intromolecular hydrogen bonds. Some of the common examples are water, salicylic acid, nitrophenol, antipyrine etc. etc. (Fig. 2).

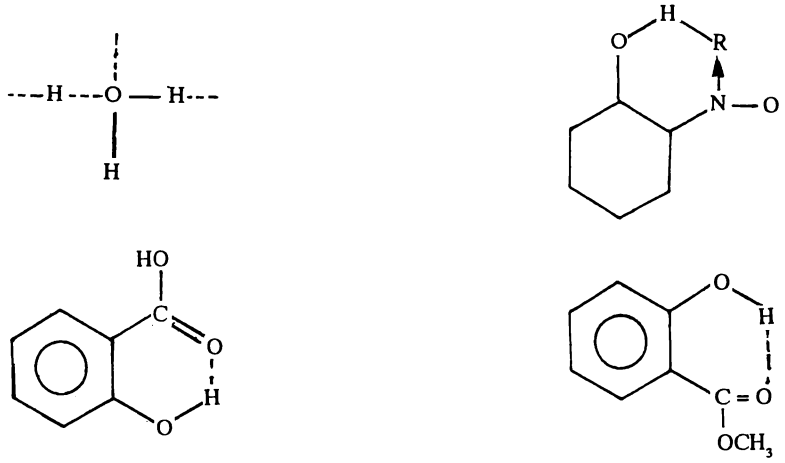


Fig. 2.2. Hydrogen Bonding.

Hydrogen bonding occurs over short distances. The distance between the electronegative elements in a hydrogen bond is in the range of 2.5 - 2.7 A° and beyond a distance of 3.0 A° there is little or no interaction. Maximum interaction is possible when hydrogen lies in a line joining the two electronegative elements in the bond. Though there can be deviation from the linearity but this is accompanied by a decrease in the strength of the bond. The heat of formation of a hydrogen bond is about 5 K cal/mole showing it to be fairly a stable bond. The stability of hydrogen bonds is represented in the following order:

$$OHO > NHO > NHN$$

$$FHF > OHN > NHF$$

Chelation : The compounds that are obtained by donating electrons to a metal ion with the formation of a ring structure are called *chelates* (Fig. 3). The compounds capable of forming a ring structure with a metal are termed *ligands*. If the metal is bonded to a carbon, the ring structure is not a chelate but an *organometallic* compound which has different properties. If the metal is not in a ring, the compound is called a *metal complex*. Most of the metals are capable of forming chelates or complexes, but the chelating property is restricted to atoms like N, O and S which are electron donating. If the complex forming ligand supplies both the electrons for chelation, then the bond is actually a 'coordinate covalent bond' and is represented as M ← X, where M is the metal and X is ligand. When a ligand molecule contains only 2-electron donating groups, it is called bidentate and can form only a single ring. If it contains 3-electron donating groups, it is tridentate and can from

2 rings in an interlocked complex and metals which can form a number of interlooked rings are called polydentate structures.

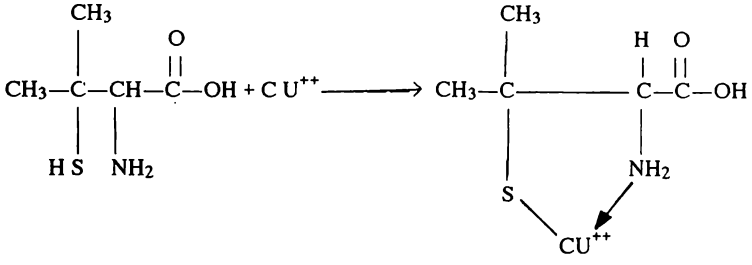


Fig. 2.3.1 Cu-chelate.

In the biological system the amino acids, proteins and acids of *Tricarboxylic acid Cycle* are the main ligands and the metals involved are iron, magnesium, manganese, copper, cobalt and zinc.

Dimercaprol is an effective antidote for the organic arsenical like ***lewisite***, but can also be used for poisoning due to antimony, gold and mercury.

Penicillamine is an effective antidote for the treatment of poisoning by copper. 8-Hydroxyquinoline and its analogs act as antibacterial and antifungal agents by complexing with iron or copper, while in the absence of these metals, it is non-toxic to microorganisms.

In general, chelation can be used for sequestration of metal ions, stabilization of drugs, elimination of toxic metals from intact organisms and also for the improvement of metal absorption.

Surface Activity: Four different types of surface active agents can be recognized: (a) anionic compounds, e.g. ordinary soaps, salt of bile acids, salts of sulfate or phosphate esters of alcohols, and salts of sulfonic acids; (b) cationic compounds, e.g. high molecular weight aliphatic amines and quaternary ammonium derivatives; (c) nonionic compounds, e.g. polyoxylene ethers and glycol esters of fatty acids; and (d) amphoteric surfactants.

The surface-active molecules can be formed at the surface of water or at the interface of polar and nonpolar liquids with the non-polar portion of the molecule oriented towards the non-polar liquid and the polar groups towards the polar liquids. Three different types of forces are involved in the orientations of surface active molecules namely Van der Waals,hydrogen bonds and ion dipoles.

A surfactant molecule which exhibits two distinct regions of lipophilic and hydrophilic character are called *amphilhillic* and differ from those which are predominantly lipophilic to predominantly hydrophilic depending on the ratio of polar to non-polar groups present.

The hydrophilic groups can differ widely in their degree of polarity e.g. $-OSO_3^-$, $-SO_3$, $-NR_3^+$ are more polar than $-NH_2$, -OH, -COOH, the latter being weaker polarizing groups.

The surface-active ions of intermediate to high molecular weight (150 - 300) show the same electrical and osmotic properties in dilute solutions and equivalent concentrations of inorganic electrolytes. Therefore, in dilute solutions, the ions are distributed in their monomeric state. But, with increasing concentration of the surfactant, a critical point will be reached at which the molecules will associate and become polymeric. Such polymeric molecules are termed *micelles* and the concentration at which they are formed is termed, "Critical micelle concentration" (CMC) and will be different for each surfactant (Fig. 4). At the critical micelle concentration large polymers (i.e. macromolecular state) will be formed and the solution will be colloidal in nature. This is a reversible process and a micelle on dilution will change back to the monomeric state. The solublisation of organic compounds begins at CMC and increases rapidly with increasing concentration of the solublising agent. A common example of micelle formation in sodium oleate solublising an insoluble

compound phenol is sketched here. When phenol is solublized by soap, mixed micelles are formed and the activity of phenol may be enhanced or reduced depending on the ratio of soap to phenol used.

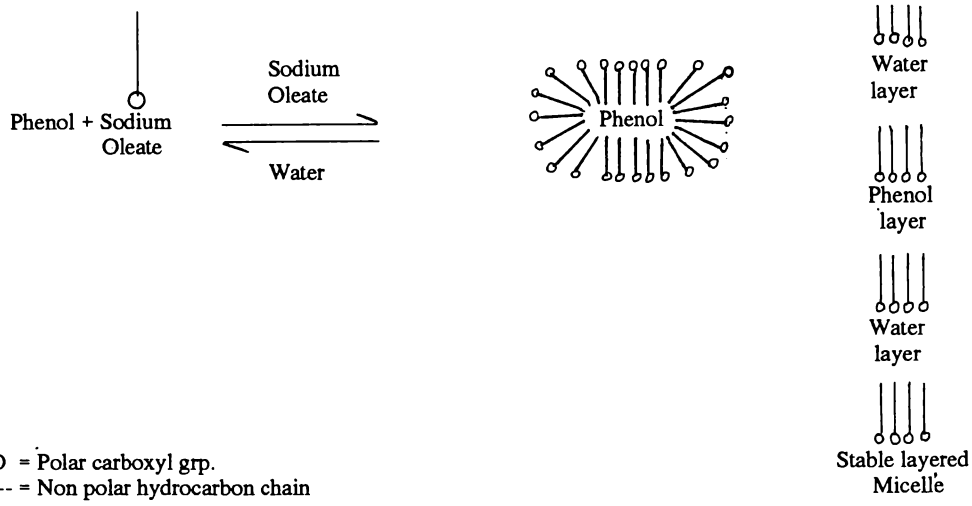


Fig. 2.4. Critical micelle formation

The substances which show high surface activity are unsuited for use in animal body because these are lost through adsorption on proteins and disorganize the cell membrane and also cause haemolysis of red blood cells.

The anthelmintic activity of hexylresorcinol has to be explained in terms of its surface active property.

The quaternary ammonium compounds form micelles and their bactericidal activity is due to hydrophilic-lipophilic balance to impart optimum surface activity.

The neuroleptic compounds have been reported to be highly surface-active in nature that accumulate readily at interfaces and cell membranes and their pharmacological action involves stabilization of biological membranes, e.g. chlorpromazine, haloperidol etc.

Steroid hormones have also been reported to be surface active and get highly oriented at Phase-boundaries but their action is not primarily due to their association with cell surface.

In a similar manner, barbiturates and several other drug compounds have been described to have surface-active properties.

Charge Transfer Interactions : In charge transfer interactions electrons are not fully transferred, rather electron density is distributed between molecules the same way as in a covalent bond. The molecule that accepts electron density is called the *acceptor* and the molecule that donates electron density is called the *donar*. The charge transfer interactions are weak in comparison with the covalent bonding because each of the molecules involved in the interaction already has its primary valence requirements satisfied. The reacting molecules can be recovered from the reaction mixture unchanged. The commonly known examples of charge transfer comlexes are met with among aromatic molecules. The interaction is produced from the overlap of the π -frame work of an electron-deficient aromatic molecule with a π -framework of an electron-rich aromatic compound, Maximum overlap between the π -framework is possible if the aromatic rings are parallel and are oriented with their centres directly over one another. The best known example is that of 1:1 adduct of p-benzoquinone with hydroquinone.

The contribution of charge transfer interactions to drug activity has been computed in terms of molecular orbital calculations. It is possible to obtain a value for the energy of the highest and the lowest empty molecular

orbitals. The calculation for highest occupied molecular orbital (HOMO) and lowest empty molecular orbital (LEMO) of actinomycin and of various purines have shown them to be in accord with observed electron accepting and electron donating properties of the respective compounds. The interaction of Cu, Pd and Ni chelates of 8-hydroxyquinoline with various electron acceptors support charge transfer as a possible mechanism of action for these compounds.

3

RECEPTOR THEORIES

3.1 MEMBRANES IN THE BODY

In order for a drug to reach its site of action it must pass through a number of complex membranes. Membranes play an important role in determining the manner by which drugs are distributed or in some cases may serve as the site of action, therefore, an understanding of their structure and properties is necessary for the study of drug action.

Although there are a large variety of complex membranes in the body, but the plasma membrane surrounding the individual cells seem to be similar for a wide variety of tissues. A study of a plasma membrane should provide with enough insight of the properties of membranes in general.

1. The Davson-Danielli-Robertson model of plasma membrane consists of ordered arrangement of lipid and protein molecules in the bulk membrane with ionic and polar heads of phospholipid submerged under a monolayer of protein at the surface of membrane (Fig. 3.1).

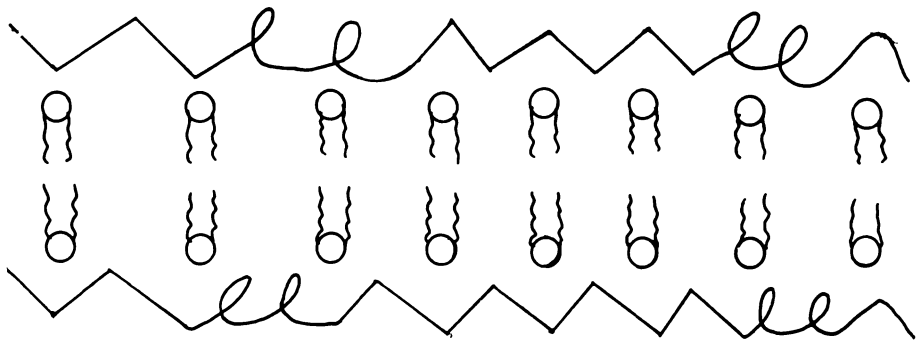


Fig. 3.1. Davson-Danielli-Robertson model

2. Another view is that the membrane consists of hydrophobic helical coils of peptides and hydrocarbon portions of lipid arranged in the bulk of the membrane. The ionic and polar heads of phospholipids together with the charged heads of proteins are at the surface of the membrane (Fig. 3.2).

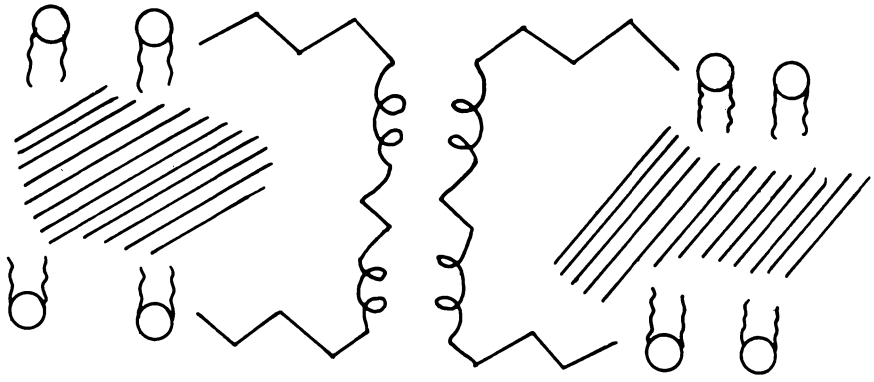


Fig. 3.2. Lenard and Singers Model

In short a plasma membrane of a cell is considered to consist of 2 layers of lipid molecules oriented with their water soluble polar groups facing outward and their non-polar groups held together on the inside by Van der Waals forces. The lipids include lecithin, sphingomyelin, cephalin and cholesterol. The bimolecular lipid layer is thought to be stabilized by a layer of unfolded protein molecules. The total thickness of the unit membrane is about 75 A^{o}.

3. The present day model for biological membrane structure is that of singer and Nicholson. The model is named as *fluid mosaic model* and consists of a repeating unit of phospholipid molecule in a bilayer arrangement with a thickness of 50 A^{o} (Fig. 3.3). Integral membrane proteins are dissolved in bilayer in a random fashion. Some proteins like mitochondrial cytochromes are located at one or the other of the two surfaces of the bilayer while other proteins like glycophorin and anion channel may pass from one side of the membrane to the other. Still other proteins are embeded in the hydrophobic matrix. The membrane proteins and lipids diffuse laterally, parallel to the plane of the bilayer and a flip-flop or transverse motion does not occur. The other important property proposed for the biological membranes is the asymmetric partitioning of the lipids between the bilayer leaflets.

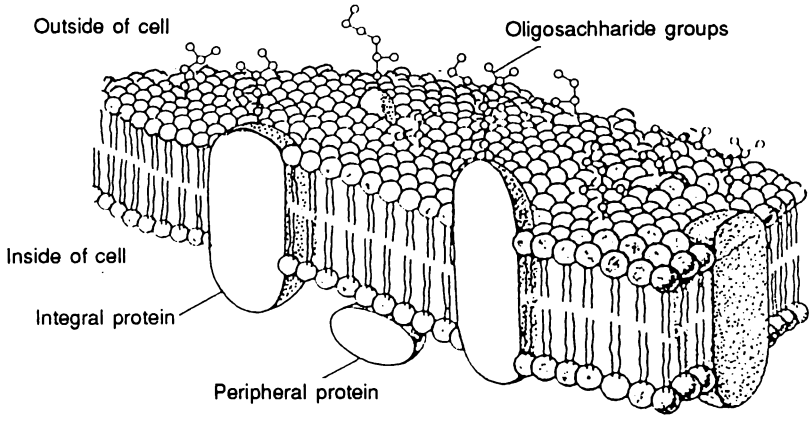


Fig. 3.3. Singer and Nicholson Model

It is obvious that a cell will present a liphophilic barrier to the external substances. A complex membrane which is a combination of a number of cells stocked one on another will present a similar barrier to the entry of the drugs. The mechanisms of transport of molecules across these complex membranes probably involves a conformational change of the protein-lipid aggregates in the membrane. The properties of a membrane varies

according to the function performed by it. Thus the capillaries in the circulatory system of the body allow the passage of ions, neutral molecules and proteins, while the vessels of CNS are more selective and allow the passage of liphophilic substances but not ions. The glomerulus of the renal system functions like a filtration unit allowing the passage of polar molecules and small proteins but not of large proteins like albumin. Plasma membrane contains pores that allows the passage of water, ions and water soluble species not greater than 4 A° in diameter.

3.2 THE DRUG RECEPTOR

The desire to understand the drug action in molecular terms has existed for a long time. The site in the biological system where the drug exerts its characteristic effects is called the *receptor*. In the study of various autonomic drugs and their antagonists Langley proposed the presence of "specific receptive substance" with which the competing drugs were supposed to react. The concept of *receptors* was again put forth by Erlich in connection with his work on *immunology* whereby he postulated that receptors were small discrete areas from which a biological response was produced following an interaction with a complementary foreign molecule.

The thought that there is a *structural complementarity* between the drug molecule and the receptor has dominated the minds of many scientists and in the last several years different receptor theories have been proposed.

Clark's Theory : A.J. Clark was the first to present a quantitative approach to receptor theory. He assumed that one molecule of drug occupies one receptor and that the drug is present in sufficient excess so that its concentration remains effectively unchanged during complex formation. Then if [D] is the concentration of drug and [R] is the equilibrium concentration of free receptors the drug-receptor interaction may be written as [D] + [R] ⇌ [DR]. This expression means that drug molecules combine with receptors at a rate proportional to the concentration of the drug in solution and to the number of unoccupied receptors and that the drug receptor complex dissociates at a rate proportional only to the number of such complexes. The affinity constant K for the drug-receptor complex is defined by the mass-action law as:

$$K = \frac{[D.\,R.]}{[D]\,[R]}$$

Since the total receptor concentration always equals [R] + [D, R.] it follows that the fraction of receptor occupied at equilibrium by a given concentration of drug [D] is:

$$\frac{[D.\,R.]}{[R] + [D.\,R.]} = \frac{1}{1 + \dfrac{1}{K\,[D]}}$$

Accordingly if one makes a further assumption that the observed biological response produced by a given concentration of active drug is directly proportional to the fraction of receptors occupied at that drug concentration it may be determined that K equals the concentration of drug that produces a response exactly half the size of the maximum one obtainable. This means that K can be estimated from the dose-response curve. This theory was widely used and applied for some 20 years following its acceptance.

Occupation Theory : The occupation theory was proposed by Ariens, Stephenson and Furchgott in 1950s when they showed that different agonists action on the same receptor system do not give identical maximum effects. This theory lead to the introduction of the terms like *intrinsic activity* and *affinity* as two different parameters for drug action unlike that just *affinity* as proposed in Clark's view.

A third term like *partial agonist* was used to describe compounds that gave any dose less than maximal response against another agonist at the same receptor site while antagonists would have no interinsic activity at all by definition.

According to Ariens, one could stipulate that:

Biological effect = intrinsic activity *X* (drug-receptor complex)

However, Stephenson and Furchgott abondoned the above stated assumption of linear proportionality and introduced the term *efficacy* to replace intrinsic activity. Thus we can write: Biological effect = f [efficiency *X* (drug-receptor complex)]. The above experiment was substantiated by experiments on dose-response curves produced by agonist drugs under condition in wich a certain fraction of receptor population was inactivated by treatment with large amounts of antagonists of the type of β-haloalkylamines.

This theory was also found to be limited in explaining the true nature of drug-receptor interactions inspite of improvements made in mathematical procedures.

Rate Theory : Paton, who criticized receptor theory, postulated that biological effect produced by an agonist is proportional to the rate at which drug and receptor molecules combine rather than to the extent of receptor occupancy. Further, he explained that the type of drug action produced is solely determined by the rate at which *drug-receptor complexes* are formed and broken, consequently *antagonist-receptor complex* would dissociate only slowly, while *agonist-receptor complex* would dissociate rapidly like *hit and run.*

For the support of the rate theory evidence has been collected which shows that agonist drugs possess lower affinities than antagonists, however other views on the nature of drug action especially that drugs are capable of *exciting* a given receptor has not been accepted by all.

Macromolecular Perturbation Theory : Belleau has proposed a generalized theory based on the principle that the primary action at its receptor site involves an induced *conformational* perturbation. He has based the theory extensively for the acetylcholine estrase and muscarinic-cholinergic receptor and has also extended it to adrenergic receptors. Belleau explains that the natural hormone like acetylcholine and structurally related compounds can form an addition complex at regulatory site of the receptor protein, which transforms the macromolecule from a resting state to a conformationally altered active site, in which it becomes an effective enzyme. The product of this enzymatic reaction is supposed to be stimulus for the biological effect of the drug. Whereas the competitive antagonists are assumed to bind to the regulatory site in a manner that induces a conformational change yielding a catalytically ineffective enzyme. Two types of conformational changes have been postulated, these being termed *specific* and *non-specific* perturbations respectively. The partial agonists are assumed to induce an equilibrium mixture of both types of conformations of enzyme which infact limits the maximum attainable enzymatic activity.

Belleau and his associates carried out lot of experimentation to support their theory, He attempted to build correlations between entropies of binding to acetylcholine estrase for a homologous series of alkyl-trimethylammonium ions and their pharmacological properties at the cholinergic receptor. The conformational perturbation of the enzyme protein has been suggested to arise due to the loss of structural water and occurs during *drug-receptor complex* formation as well as more directly from the entropy driven interaction of the protein with certain lipophillic groups of the drug.

Other workers in an attempt to extend this theory suggested, that substances like acetycholine induces conformational changes in its receptor protein that leads directly to changes in cell membrane ion premeability. The increased permeability is brought about from structural change in the membrane rather than from catalysis of an enzymatic reaction.

3.3 FORCES BETWEEN DRUGS AND RECEPTORS

The drug compounds get absorbed to the complementary receptor surfaces and in the process of this interaction requirements such as size, shape, stereochemistry, electron distribution and distribution of groups has to be met. It was initially felt that drugs acted upon cells by chemical reaction but infact many types of physical and chemical interactions are involved e.g. Van der Waals forces, dipole-dipole interactions, dipole-ion interactions, hydrogen bonds, coordinate covalent bonds, covalent bonds and ionic bonds (Fig. 3.4).

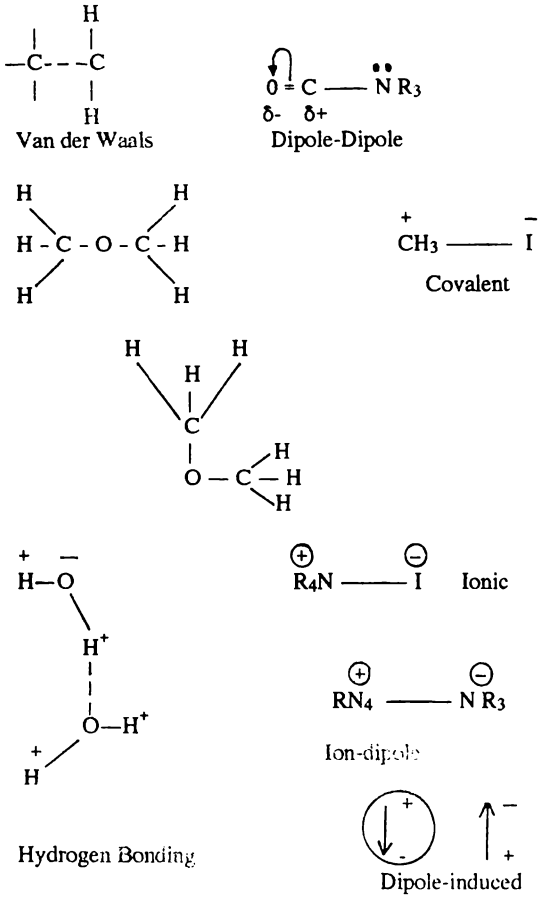


Fig. 3.4. Different types of Physico-chemical forces

The majority of drug compound are absorbed reversibly and are in equilibrium with the surrounding medium indicating that strong bonds are usually not involved.

3.4 INTERMOLECULAR DISTANCES AND BIOLOGICAL ACTIVITY

Almost all drugs combine at some stage with a receptor and most of the receptors are proteins. The important structural feature of proteins is their polypeptide nature. The space between a polypeptide bond is very regular because all the aminoacids are linked through their α-amine and α-carboxyl groups. The distance between the peptide bonds is known as the *identity distance* and is equal to 3.16 A^{o} in a maximally extended peptide (Fig. 3.5).

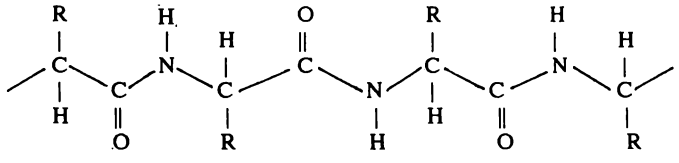
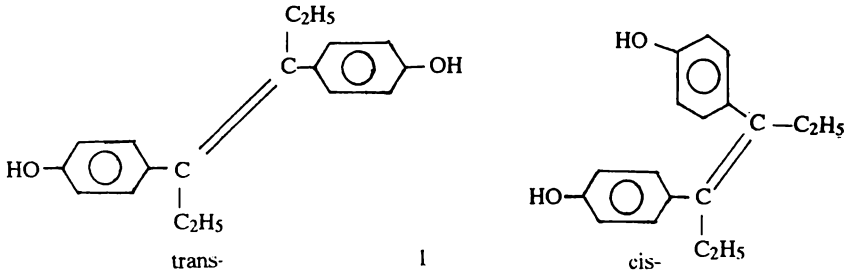
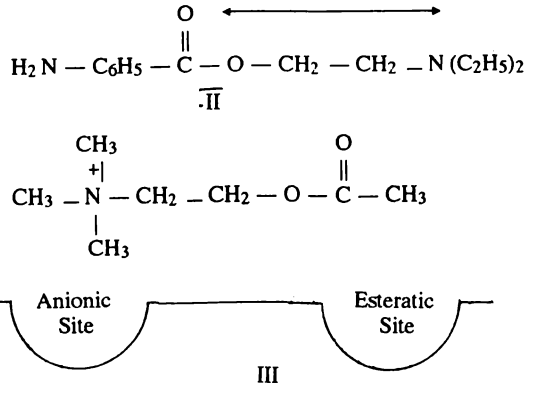


Fig. 3.5. Extended Polypeptide

Different series of drugs have revealed a relationship between the pharmacological activity and the intramolecular distance between groupings. This identity distance or a some whole number multiple thereof is required as the spacing for optimum biological activity; e.g. in trans stilbesterol (I) the two hydroxyl groups are 14.5 A° (4 × 3.61) apart and is a potent estrogen whereas in the cis-compound the hydroxyl groups are closer and cannot participate in hydrogen bonding with the receptor and therefore shows weak activity.



In general, it can be said that receptors at which the drugs are absorbed to produce the pharmacological actions must have appropriate absorption sites which correspond to the distance separating the carbonyl and nitrogen groups. The distance between the functional groups of many types of drugs appear to be about 5.5 A° (e.g. Procaineamide, II; acetyl Choline, III) and this corresponds to the distance between two turns of an α-protein helix.



3.5 STRUCTURALLY NON-SPECIFIC AND SPECIFIC ACTIVITY

Drug Activity can be classified as (a) structurally non-specific or (b) structurally specific.

Structurally non-specific activity is dependent on physical properties like solubility, partition coefficients and vapour pressure and not on the presence or absence of some chemical group. Substances such as alkanes, alkenes, alkynes, alcohols, amides, ethers, ketones and chlorinated hydrocarbons exhibit narcotic activity and potency of each substance is related to its partition coefficient. Structurally non-specific action results from accumulation of a drug in some vital part of a cell with lipid characteristics.

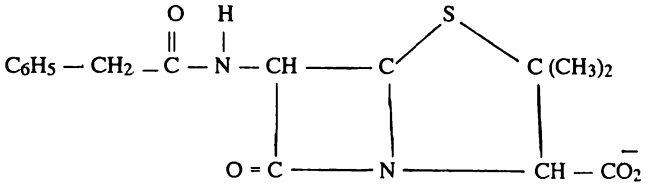
On the otherhand structurally specific activity is dependent upon factors such as the presence or absence of certain functional groups, intramolecular distance, and shape of the molecule.

Activity is not easily co-related with any physical property and small changes in structure often lead to changes in activity. Structurally specific activity is dependent upon the interaction of the drug with a cellular receptor.

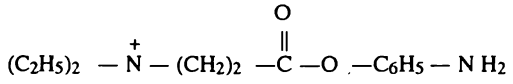
3.6 SOLUBILITY IN WATER

The solubility of substances in water controls the distribution of the substance and determines whether or not a substance can be biologically active. Because water is the solvent found in the transport system of living organisms the water solubility of a substance will determine how readily a compound is dissolved and transported.

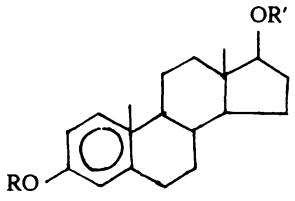
Sometimes, it is required that a drug be slowly absorbed. In such a case the water solubility can be lowered through chemical medification. The modified drug must retain the original biological action or it must be possible for the living system to change it to a compound with original biological action. A good example is that of injections of penicillin which are readily distributed throughout the animal. Because penicillin is excreted quickly in the kidneys, injections must be repeated every 3-4 hours in order to maintain therapeutic blood levels. However, this difficulty can be solved by using relatively insoluble depot salts with various amines which dissolve fast enough to maintain therepeutic levels. Such an example is Procain Penicillin (IV).



IV

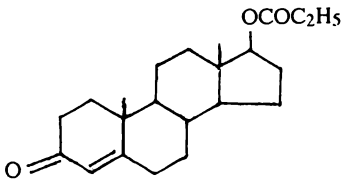


Similarly in case of estrogens and androgens absorption and metabolic degradation occurs immediately after i.m. injections. In order to prolong their duration of action less soluble derivatives such as estradiol benzoate (V), estradiol cyclopentyl propionate (VI) and testosterone propionate (VII) are used.



(i) R = C_6H_5CO
R′ = H
(ii) R = $CO(CH_2)_2$
R′ = H

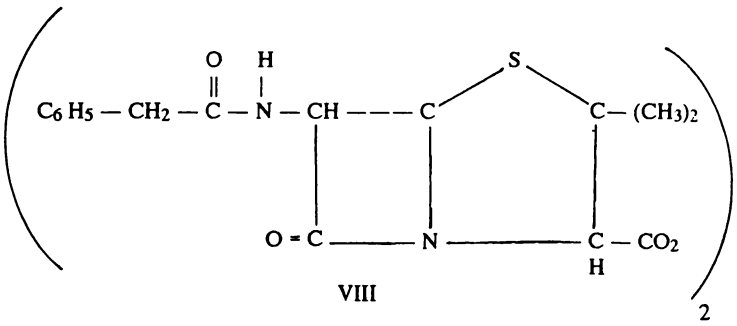
VI



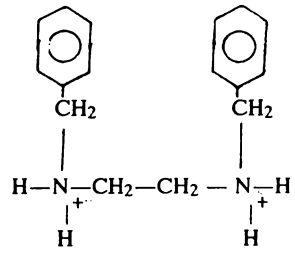
VII

3.7 ABSORPTION IN FAT DEPOTS

Substances which possess high partition coefficient are rapidly concentrated in the fat deposits of an animal. They are slowly released from the fat depots and low blood levels are maintained for longer periods of time. If these blood levels are sufficient to produce the desired pharmacological action the drug will have a long duration of action unless it is metabolized soon. However, if a high concentration of a drug is needed to produce a desirable pharmacological response the duration of action will be shortened by rapid absorption by fat depots. For example Benzathine penicillin G (VIII) has a prolonged duration of effect because it is slowly released from fat depots.



VIII



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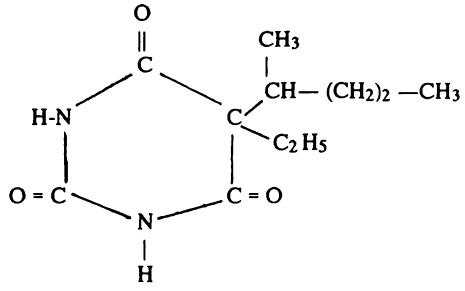
Thiopental (IX) is an ultrashort acting hypnotic because it is rapidly removed from the fat depots.



IX

4

TRANSPORT OF DRUGS

4.1 DRUG TRANSPORT

As explained in the previous chapter, the present view is that most cellular membranes are mosiac containing bi-molecular layers of phospholipid and intrinsic globular proteins. The hydrophobic groups of the phospholipids face towards the interior of the membrane while the hydrophilic groups face the aqueous phase on both sides of the membrane. The intrinsic proteins exist in conformations in which hydrophilic and hydrophobic groups are localized on different parts of protein surface. Further, they sink into the interior of the membrane depending on the distribution of hydrophobic and hydrophilic groups and the size of the protein itself. The properties of the membrane vary widely depending upon the function and location of the membrane. The mechanisms by which drugs are transported through membranes appear virtually the same in the cases. Drugs can pass through membranes by (i) Simple diffusion (ii) Filtration through pores or by (iii) Specialized transport system. These three processes are discussed below.

Simple Diffusion : Majority of drug substances pass through membranes by simple diffusion, the speed of the passage depending on the solubility of the drug in lipid or lipid/water partition coefficient. Most of the drug are weak electrolytes and exist in aqueous solutions as a mixture of ionized and unionized forms. The cell membranes are permeable to the lipid soluble unionized forms of weak acids and weak bases, and at equilibrium the concentration of the unionized form is identical on the two sides of the membrane. The lipid solubility of the ionized form of drug is low and its passage across the membrane is negligible. The fraction of the total drug present in the ionized form is given by the dissociation constant, which is expressed for both acids and base as a pK_a. The relationship between the pK_a and the concentration of ionized and unionized drug is given by Henderson-Hasselbalch equation indicated below:

$$\text{for weak acids : } pK_a = pH + \log \frac{C_u}{C_i}$$

$$\text{for weak bases: } pK_a = pH + \log \frac{C_i}{C_u}$$

where C_u and C_i are the concentrations of unionized and ionized form of drugs respectively. Because the ionized form of a weakly acidic and basic drug does not penetrate the lipid membrane, its concentration in each compartment in the body is a function of the pK_a of the compound and the pH in the compartment.

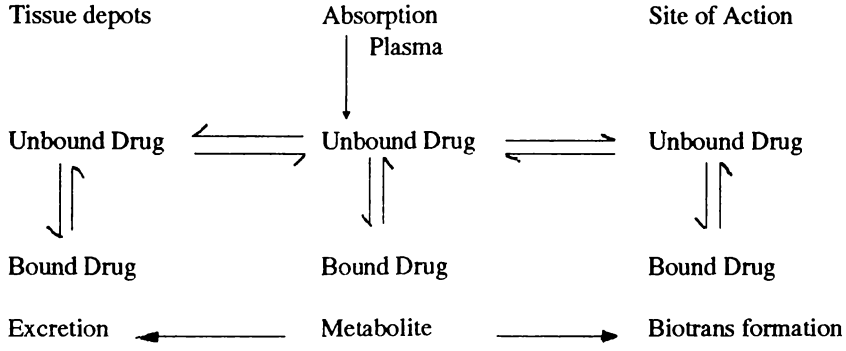
Filtration: It has been suggested that the lipoprotein membrane is not continuous but punctured by a series of water filled pores whose effective radius is about 4 A° and therefore small drug molecules can be transported by pore filtration. However, the epithelial cells of capillaries and the glomeruli of the Kidney do not fit and

the effective pore size may be as large as 40 A^{o} in radius, hence filteration of larger molecules can occur in such membranes. Plasma albumin being of a large size, is excreted only in very small amounts.

Specialized Transport : It has been proposed that certain organic and inorganic ions as well as certain large lipid insoluble molecules like monopolysarcharides can be transported by special carriers. The ions or molecules to be transported get attached to the carrier at one surface of the membrane and is released at the other surface while the carrier returns to the original surface to complete the cycle. The above process is called *special transport*, however if the substrate molecule is moved agajnst a concentration gradient, energy will be needed and the process may be termed *active transport*. For example, 5-fluorouracil and 5-bromouracil are transported by active transport.

4.2 ABSORPTION

When a drug is introduced into the body, it can produce its characteristic pharmacological properties only when a sufficient number of molecules reach its particular site when the response to triggered. Following its administration, its concentration in the body at any time is governed by three interacting processes namely absorption, distribution and elimination. The various factors which influence the concentration of the active drug in the plasma are shown in the following diagram;



Medicaments are presented for administration in different dosage forms, such as in tablets, capsules, powders, suspensions and solution etc. to be given by different routes like oral, intravenous, intramuscular, subcutaneous, intraspinal or intracerebral, implantation and so on. The rate of drug absorption will be influenced by the properties of the dosage form which in turn in influenced by particle size because the dissolution rate is directly related to the surface area of the drug exposed to the medium in which it dissolves. The chemical nature of the drug also influences the dissolution rate. For example, the salt of a weak acid dissolves faster than weak acid itself. For example, the crystalline form of novobiocin dissolves very slowly whereas its amorphous form dissolves readily and produces adequate concentration in the plasma.

4.3 ELIMINATION

Drugs can be eliminated by different routes, mainly through lung, Kidney and liver.

Lungs : The important class of drugs eliminated by this route is gaseous anaesthetics. The rate of elimination of drugs from the lungs is based on blood/air partition coefficient. For example when a drug is administered intravenously, a high plasma concentration is obtained immediately and absorption is not a factor modifying the pharmacological response. Further, the injected drug does not pass directly to the liver which is the major site for drug metabolism. Administration by other means like oral, rectal, mucous membrane, intramuscular etc. influences the rate of drug absorption and therefore the concentration of the drug in the plasma. Drugs, that are absorbed from GI tract enter the portal circulation and are passed immediately to the liver where their concentration may be greatly decreased by biotransforming systems. Thus different routes

of administration of a drug can produce both quantitative and qualitative differences in pharmacological response. Among the different oral dosage forms following order of decreasing rate of drug release is obtained: aqueous solution, suspension, powder, capsule, compressed tablet and coated tablet.

The most important factor regulating drug absorption from different dosage forms is the rate at which the drug goes into solution called "dissolution rate". The dissolution rate of inhalation anaesthetics in the brain approaches closely to that of the concentration in arterial blood. Thus anaesthetics like cyclopropane and nitrous oxide which have low blood/air partition coefficient recovery after administration is very rapid whereas for a drug like ethyl ether with high blood/air partition coefficient recovery after administration is slow.

Kidney : The glomerulus which is a membrane similar to capillary wall allows the passage of all solutes. Plasma is filtered here and the filterate flows down the tubules which have a lipoid nature. In its transport through the tubules and collecting ducts, 99% of water filtered in the glomerulus is reabsorbed, whereby organic solutes are concentrated and a concentration gradient is established between the tubular urine and the plasma. The passage of the organic molecules dissolved in the filterate across the tubular membrane is governed by properties like the molecular size and the lipid water partition coefficient.

The amount of the drug eliminated in the kidney is affected by the pH of the tubular contents in accordance with Henderson-Hasselbalch equation. Drugs which are weakely basic, their urinary excertion is increased when urine is more acid and decreases when urine is made more alkaline.

Further, it has been suggested that foreign molecules are removed from plasma, into the urine by two specialized transport mechanisms operating in the proximal tubules. One of the such mechanisms transports the ionized form of acidic drugs like salicylic acid, penicillins, probenecid, thiazide, diuretics, p-amino hippuric acid, acetylated sulfonamides, glucuronides and sulfate esters. The other mechanisms transports the ionized form of the basic compounds like histamines, thiamine and also hexamethonium and quaternary ammonium compounds.

In general, the transport mechanisms for acids and bases in the kidney have some characteristics of active transport especially that the drugs are transported against a concentration gradient and therefore require a supply of energy. However, the specialized transport systems are not as selective as active transport mechanisms for naturally occuring substances.

Liver : The elimination of drugs via bile into the intestine has not been studied extensively, however it has been observed that it is done largely in the form of conjugates like glucuroniders, glycine conjugates, and ethereal sulfates, the most important being glucuronides. In the intestine the conjugates may be reabsorbed unchanged into the plasma or excereted unchanged into the faeces, or hydrolysed by enzymes before their subsequent excertion.

4.4 BINDING CHARACTERISTICS OF DRUGS

Because of the presence of a large variety of functional groups on macromolecules, there exist sites on them that will interact with any foreign molecule. Proteins, which form a major tissue constituent have been studied extensively in regard to their ability to bind to drugs which has been postulated to be a reversible process.

$$\text{Drug} + \text{Protein} \rightleftharpoons \text{drug - Protein complex}$$

Further, because a drug will bind to different proteins to different degrees, its distribution will vary from one tissue to another. The average drug-protein interaction is supposed to involve weaker forces like ionic bonds, hydrogen bonds and short range Van der Waal's forces. The proteins in the primary structure are more exposed for possible binding with drugs.

Some drugs bind selectively to the retina of the eye, adrenal cortex, uterus, placenta, heart etc but these are not the sites where drugs produce their pharmacological action.

Many drugs bind reversibly to the DNA, RNA and nucleic acids in the nucleus of the cells. The antimalarial drug quinacrine binds to nucleic acids to such a great extent that a large primary dose has to be given to produce a quick constant chemotherapentic concentration in the plasma.

Drugs have been reported also to bind to mineral structures and accumulate in the bones and teeth.

Lipid soluble drugs bind to neutral triglycerides of number of fatty acids, to polar phospholipids like lecithin and cephalin, to sterols like cholesterol and to glycolipids like cerebrosides.

4.5 PHARMACOKINETICS

After a drug has been introduced into a biological system, it is subjected to a number of processes whose rates control the concentration of drug at the site of action thus affecting its onset, its duration of action and also intensity of action. Therefore, a study of these processes which are involved in determining the fate of a drug is necessary and this can be achieved by "pharmacokinetics". The pharmacokinetic parameters consist of items like the determination of the biological half-life, the apparent volume distribution, the rate constants for absorption and elimination for a drug. The investigation of these parameters comprises in the use of techniques of "compartmental analysis" which defines quantitatively what has become of a drug as a function of time from the moment it is administered untill the time it is no longer in the body.

With the increased interest in the understanding of drug action, various types of models have been applied in the pharmacokinetic analysis of many drugs. All the different models describe the distribution of drugs within "compartments". In humans, the compartments include the blood and urine which are analysed for both drug and drug metabolic products. The dosage regimen for a new drug can also be based on pharmacokinetic data and it may or may not involve a comparison with a standard drug.

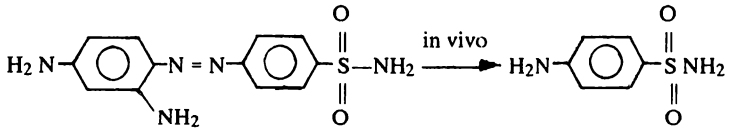
5

METABOLISM OF DRUGS

5.1 GENERAL

The pathway by which drugs and foreign compounds are chemically altered in the body is called the process of detexication or *metabolism*. Some of the compounds are excreted partially unchanged and some are known to be converted to products which may be more active or more toxic than the original compounds. A general view is that drug metabolism involves the conversion of relatively nonpolar lipophilic compounds which the body cannot excrete into more polar hydrophillic compounds which can be exerted over a short period of time. If the lipid soluble nonpolar compounds were not metabolized to the relatively polar water soluble compoundss, they would tend to remain in the blood and tissues and maintain their pharmacological effects for an indefinite time. some compounds are insoluble in body fluids and are resistant to chemical and enzymatic influences of the gastrointestinal tract (GI) and are eliminated in faeces and show no biological action. e.g. mineral oil, barium sulfate. Some compounds which are freely soluble in body fluids and resistant to chemical change are relatively non-toxic and rapidly excreted, e.g. aromatic and aliphatic sulfonic acids, mandelic acid etc.

It may be pointed out that the studies on metabolic changes that the drugs undergo have been of practical value in the search and development of new drugs. Examples are that of prontosil (I) which is inactive invitro but converted in the body to the active sulfanilamide which led to the development of sulfanomides (II) as therapeutic agents.



I II

Likewise, studies on the absorption of sulfonamides in the intestines led to the introduction of N^4 -acetylated derivatives for the treatment of intestinal infections. Chloroguanide, produces its antimalarial action through its metabolic product which also led to the preparation of pyrimethamine type of derivatives for the prevention of malaria. Other examples of such drug discoveries are the study of the metabolism of phenacetin, imipramine and amitriptyline etc.

In the recent years the metabolic data has become a requirement in the preclinical and clinical testing and evaluation of new drugs. The metabolic information required for drugs can be grouped under the following headings:

(a) Rates and site of absorption of both the drug and its metabolite.

(b) Plasma and tissue levels.

(c) Plasma protein binding.

(d) Rate of metabolism and half-life of the drug in blood and tissues and

(e) rates and routes of excertion.

5.2 SITES OF METABOLISM

The liver is the primary site of metabolism of all substances entering the blood stream especially through the G.I. The capilaries and blood vessels which absorb nutrients and other substances through the Waals of stomach and intestines deliver the blood to the larger vessels which empty into portal vein leading into liver. The liver also receives oxygenated blood from the heart through hepatic artery. The blood perfuses through the liver cells where nutrients are removed or stored for later utilization.

Foreign compounds such as environmental pollutants and drugs are metabolized into water soluble derivatives and returned to circulation for excertion by the kidneys. The liver also produces bile and emties through bilary duct into small intestine where it serves as a medium for the excretion of metabolic products in faeces.

The metabolism of drugs and foreign substances in the liver is carried out by a number of specific and non-specific enzymes situated in the membranes of the endoplasmic reticulum present in the cytoplasm of the liver cells.

In general, drug metabolism may involve the following types of transformations:

(a) a single step conversion of biologically active compound to an inactive compound which is excreted;

(b) a two step conversion, in which there is first inactivation followed by conjugation with glucuronic acid;

(c) a two step process in which an inactive compound is converted to a biologically active compound followed by inactivation and excretion;

(d) a two step process in which there is first a change in activity of an active compound followed by inactivation.

5.3 TYPES OF METABOLIC CONVERSIONS

The chemical reactions drugs and other organic substances undergo in the body are placed in the following classes:

(i) Oxidations

(ii) Reductions

(iii) Replacement Reactions

(a) Hydrolysis, (b) Acetylation, (c) Methylation (d) Conjugation reactions.

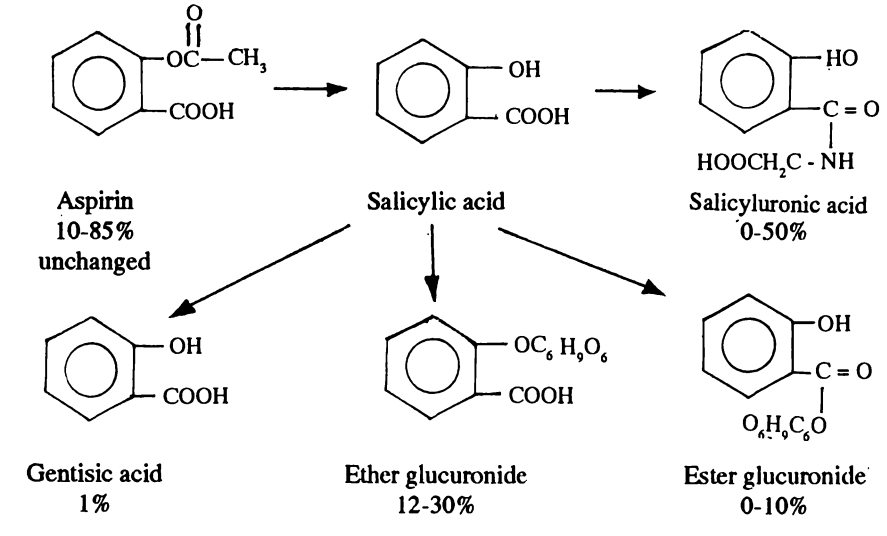
The metabolic pathways which involve the transformation of specific groupings in a substrate molecule are known as *phase I reactions*. The products of Phase I reactions acquire chemical groups to be coupled during phase II reactions. The products of *phase II reactions* are conjugates and are true detoxification reactions.

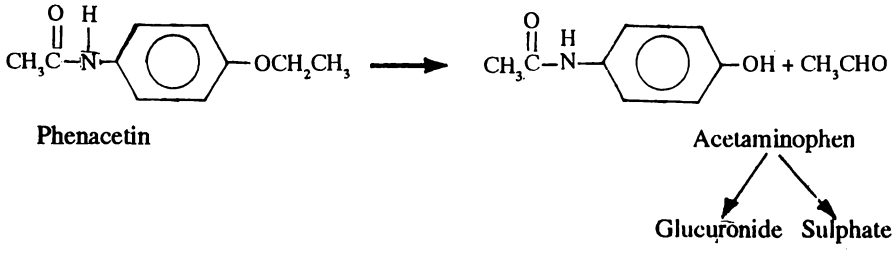
Oxidation : Oxidation is normally the first step involved in the drug metabolism unless the drug compound possesses such functional groups like -OH, -SH, $-NH_2$, $-CO_2H$ which are capable of conjugation. A complex of non-specific microsomal enzymes present in the liver catalyse metabolic oxidation of a large variety of compounds both endogenous substances like steroid hormones and exogenous substances like drugs and pollutants. The most important enzyme involved in this type of oxidation is cytochrome P-450.

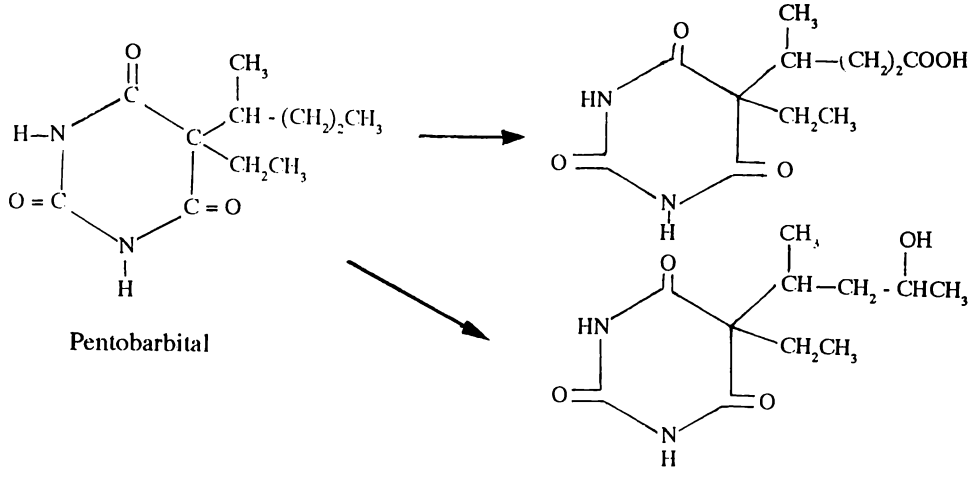
Reduction : Metabolic reductions are carried out by enzyme systems which make use of NADPH as a hydrogen doner.

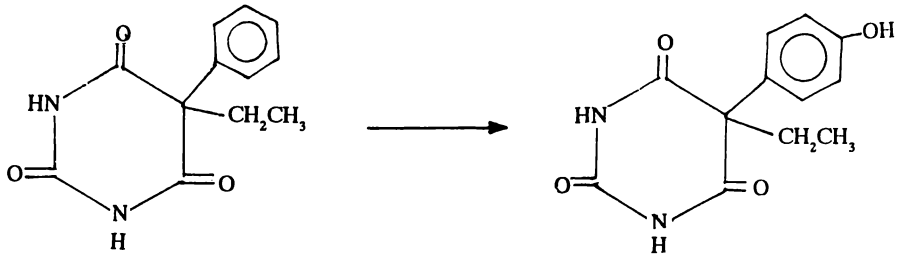
Hydrolysis: Esterases such as pseudocholine esterase present in plasma will catalyse the hydrolysis reactions of drug substances.

Conjugation Reactions : In the case of drugs and other molecules containing groups like -OH, -SH, $-NH_2$ or $-CO_2H$ conjugation with glucuronic acid, sulfate, amino acids and peptides is the major pathway for metabolic elimination. However, in the absence of such reactive groups, oxidation, reduction, hydrolysis etc. proceeds the conjugation reaction. The metabolism of various common types of drug compounds is shown below:

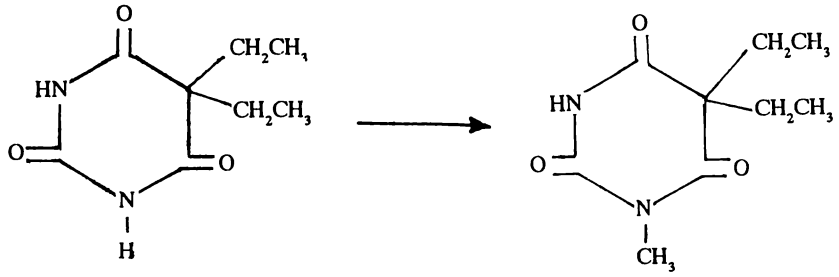




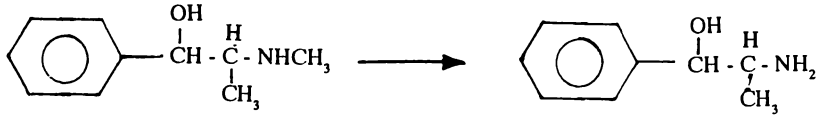




Phenobarbital

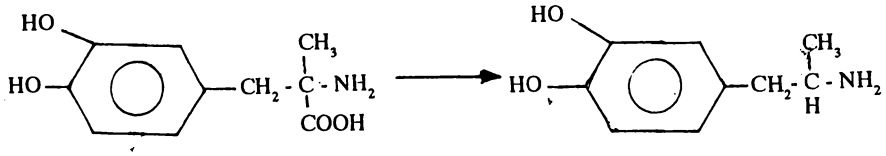


Metharbital

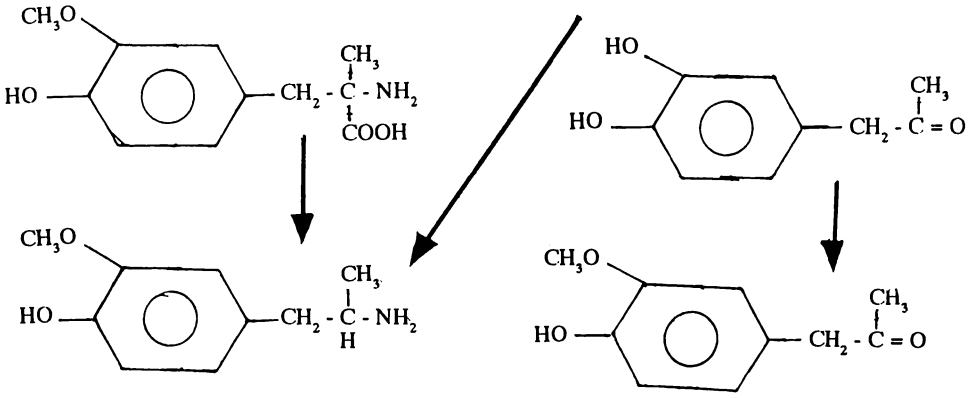


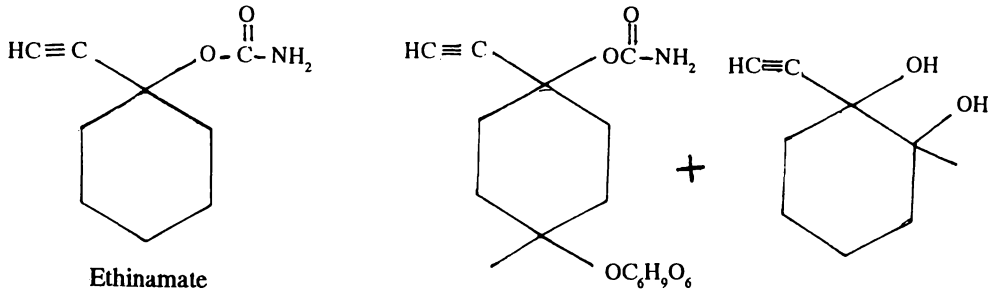
Ephedrine → p-Hydroxyephedrine → o-Glucuronide/Sulphate

Norephedrine → p-Hydroxy-Norephedrine → o-Glucuronide/sulphate



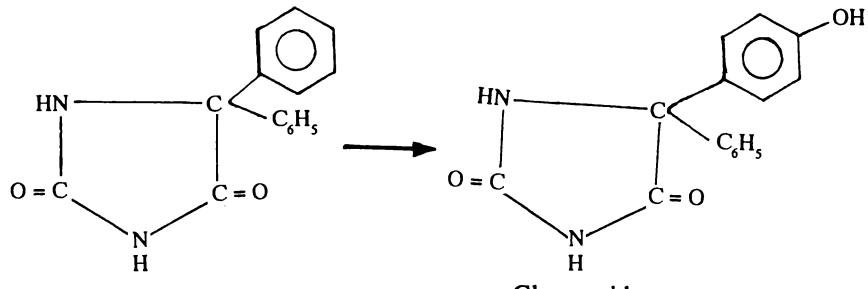
Methyl Dopa





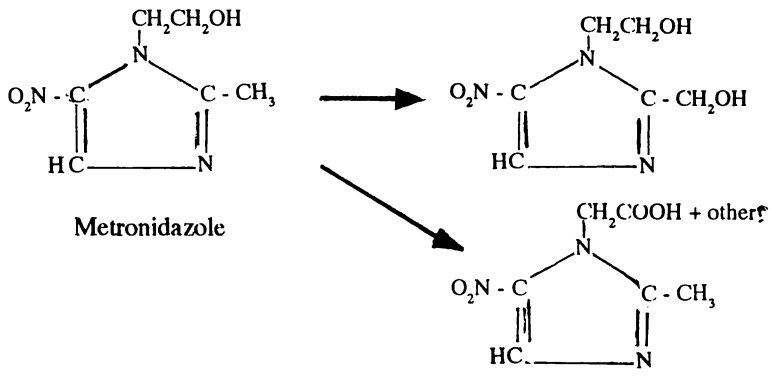
Ethinamate

Glucuronide

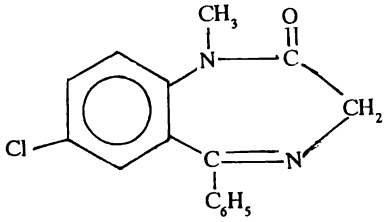


Phenytoin

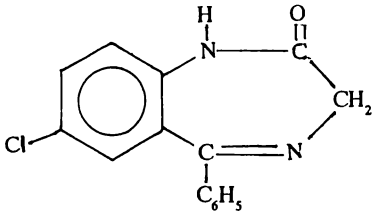
Glucuronide



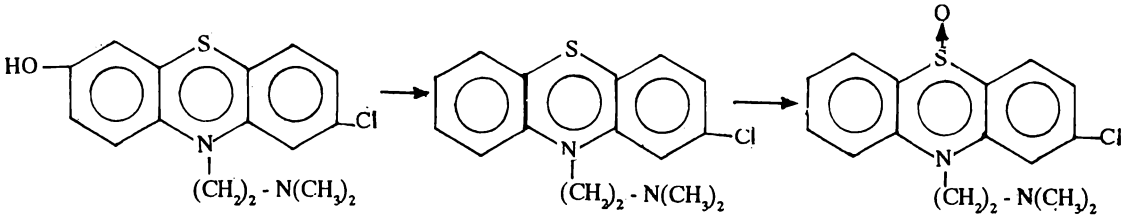
Metronidazole



Diazepam



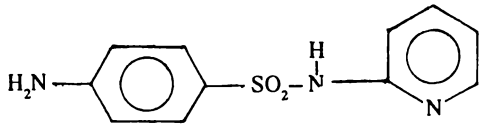
Desmethyl diazepam



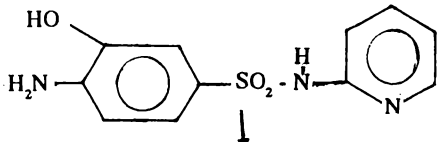
7-hydroxy → 7-hydroxy desmethyl → 7-hydroxy nor-methyl → Conjugates

Chlorpromazine → Desmethyl → Nor-methyl → N-Glucuronide

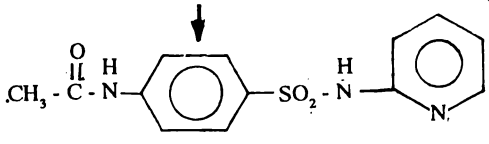
Sulpoxide → 7-hydroxy Sulphoxide → 7-hydroxy desmethyl → Conjugates



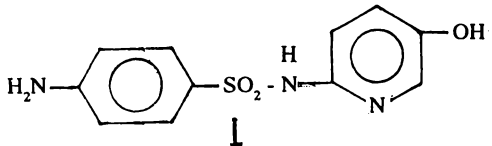
Sulphapyridine



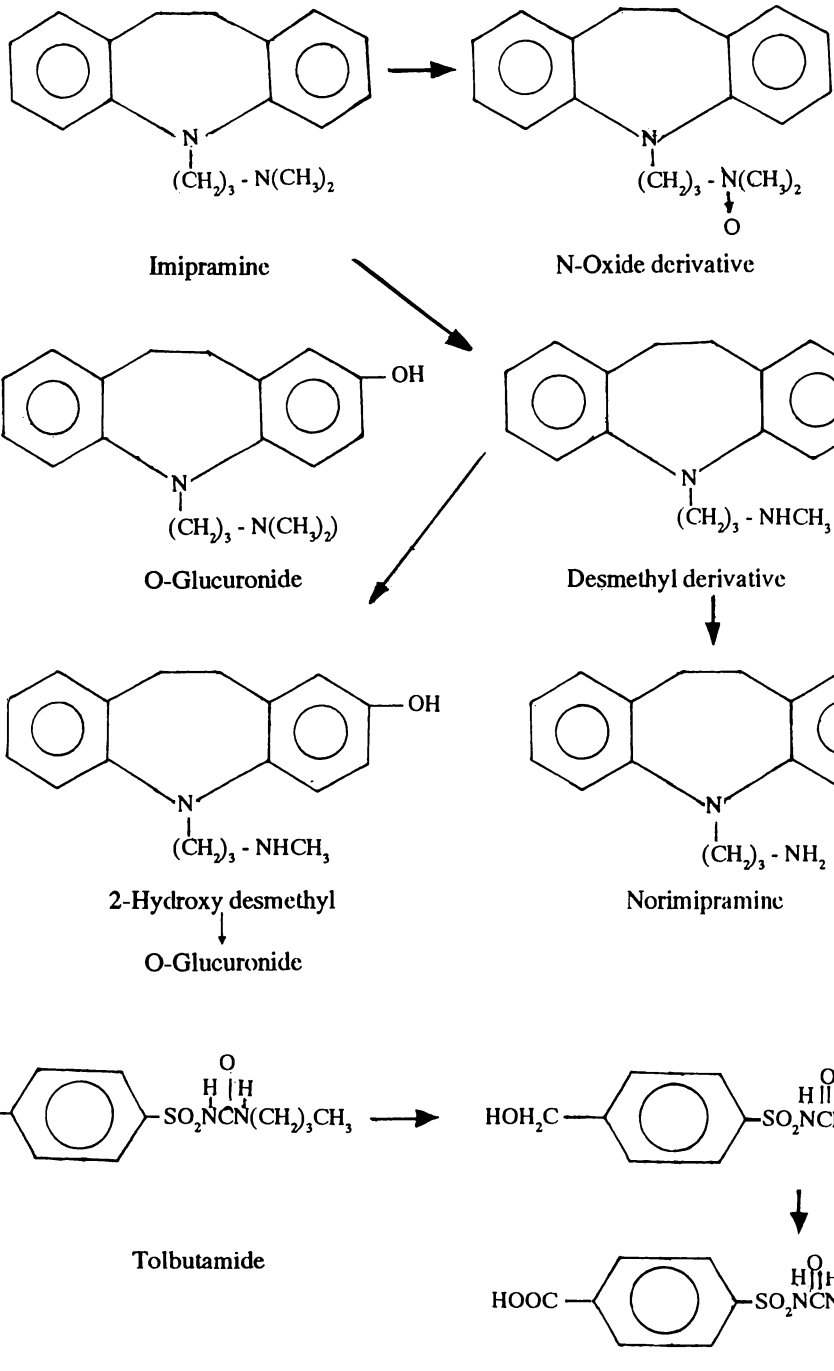
O-Glucuronide/Sulphate

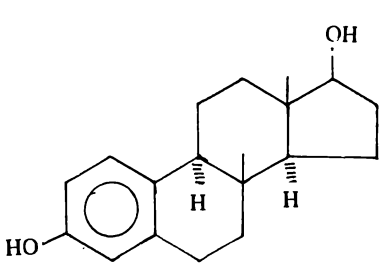


N^4-Acetyl derivative

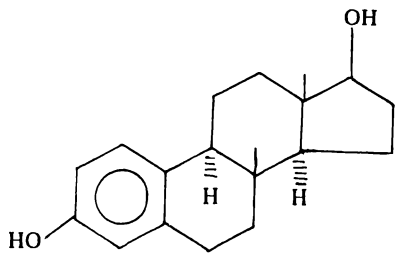


O-Glucuronide/Sulphate

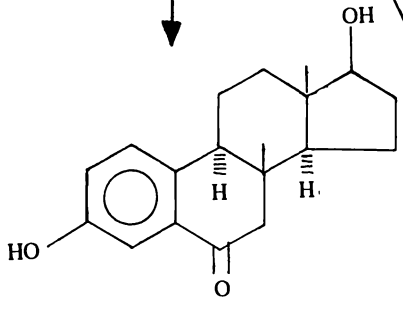

Imipramine
N-Oxide derivative
O-Glucuronide
Desmethyl derivative
2-Hydroxy desmethyl
O-Glucuronide
Norimipramine
Tolbutamide



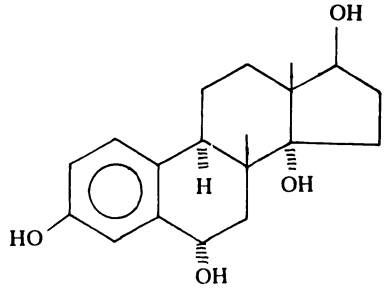
β-Estradiol



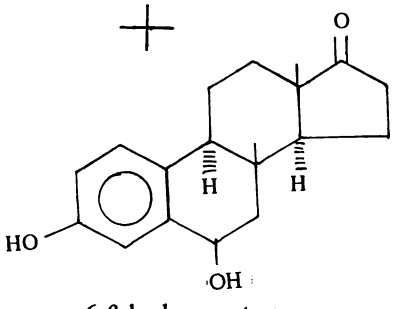
6 β-hydroxy derivative



6-oxo derivative

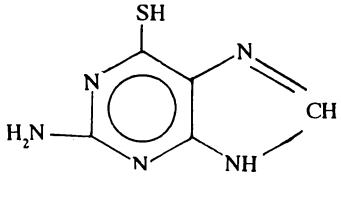


6α-hydroxy derivative

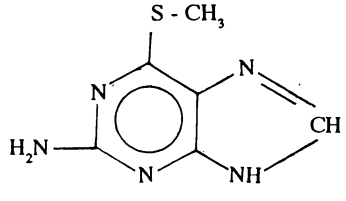


6-β-hydroxy estrone

Sulphate and
Glucuronide
Conjugates



Thioguanine



6-methyl derivative