often distinguish between parenteral and enteral administration of drugs and other xenobiotics. It shall not be out of place to mention that enteral administration includes all routes pertaining to the alimentary canal (sublingual, oral, and rectal), whereas parenteral administration involves all other routes (intravenous, intraperitoneal, intramuscular, subcutaneous) etc.

Overall, the absorption of xenobiotics may take place through 4 ways :

A. Absorption by the skin (Dermal absorption)

B. Absorption by the lungs (Pulmonary absorption)

C. Absorption by gastro-intestinal tract (Gastro-intestinal absorption)

D. Absorption through special routes.

A. **Absorption by the Skin** : The body's primary barrier to the toxic chemicals is the skin, which has a surface area of about 18,000 cm^2 in humans and constitutes about 10% of body weight. Thus, dermal absorption is very important in view of the surface area of skin. A xenobiotic entering through the skin would normally have to penetrate several layers of intact cells to reach the systemic blood circulation. Lipid-soluble molecules such as tetraethyl lead and benzene are more easily absorbed via the skin than water-soluble polar molecules and ions (e.g., inorganic leads, H_2SO_4). Solvents such as CCl_4, highly lipid soluble, absorbed percutaneously exert systemic toxic effect following absorption by this route. Small hydrophilic xenobiotics such as hydrazine is sufficiently absorbed through skin, causes local as well as systemic toxic effect.

B. **Absorption by the Lungs** : Humans breathe 22,000 times a day taking in 16 kg of oxygen. Thus pulmonary absorption can be the principal route of entry for gaseous and particulate air pollutants and volatile organic chemicals. The large surface area of lungs makes it particularly vulnerable to the toxic injuries caused by inhaled gases and particulates. The most frequent cause of death from poisoning by CO and occupational disease *silicosis* are the consequences and the results of absorption of air-borne poisons by the lungs. Bhopal Gas Tragedy may be considered as an extreme example of absorption of MIC gas through the lungs.

The air-borne particulate matters deposited in the lungs are absorbed by processes known as 'pinocytosis' (a special type of transport, in which cells engulf small droplets of extracellular fluid) and 'phagocytosis' (a specialized transport process that involves the engulfing of a particle or colloidal material by the cells) and moved by the action of cilia into the pharynx from where it may be swallowed in. But the soluble chemical molecules could penetrate the epithelium and enter the blood circulation directly. Pinocytosis and phogocytosis may also be referred to as cell-drinking and cell-eating, respectively.

C. **Absorption by the Gastro-intestinal Tract** : The oral uptake is the most important pathway at least for the water-borne and food-borne pollutants. The absorption of xenobiotic molecules along the gastro-intestinal (G.I.) tract (consisting of stomach, small intestine and colon) is characteristically due to the epithelial wall of the G. I. Tract, which exhibits the properties of the lipoid membrane. Hence, un-ionized polar toxicants are more readily absorbed, the absorption rates for these chemicals being influenced by their relative octanol-water partition coefficients. The substances ingested by oral route do not produce systemic effects unless they are absorbed. The stomach having a pH 1 to 3 represents the most significant site of absorption for xenobiotics that are actually acidic or near neutral. Along the small intestines and colon (whose pH lies in the range of 6 to 8), weak acids and bases are more efficiently absorbed, the rate of absorption being inversely related to their water solubilities.

D. **Absorption through special routes** : Generally the xenobiotics enter the blood stream following absorption through skin, lungs and gastrointestinal tract. But, sometimes, the toxicants are administered in the body of experimental animals through special routes such as (1) intra-peritoneal (2) subcutaneous (3) intra-

muscular, and (4) intravenous. The toxicants are directly administered into the blood stream through intravenous route. Administration of toxicants through intraperitoneal route results in rapid absorption of toxicants primarily through the portal circulation because of the large surface area and rich blood supply to the peritoneal cavity. Toxicants administered subcutaneously and intramuscularly are absorbed at slow rate. This can be altered by changing the blood flow to the area and the medium in which the toxicant is administered. Most of the toxicant administered intra-peritoneally enters the liver via portal circulation before it reaches the general circulation of the animals. Sometimes the xenobiotics may be completely biotransformed and eliminated into the bile and consequently it never reaches the target sites.

DISTRIBUTION

A xenobiotic after entering the blood by absorption or intravenous administration is ready for distribution throughout the body. Distribution usually occurs rapidly. The rate of distribution to organs or tissues is determined primarily by blood flow and the rate of diffusion out of the capillary bed into the cells of a particular organ or tissues. The final distribution depends largely on the affinity of a xenobiotic for various tissues. In general, the initial phase of distribution is dominated by the blood flow, whereas the eventual distribution is determined largely by affinity.

Some toxicants do not readily cross plasma membranes and, therefore, have restricted distribution; whereas other xenobiotics rapidly pass through plasma membranes and are distributed throughout the body. During the course of distribution, the xenobiotics may get concentrated in a particular tissue or organ and such tissues or sites are termed *storage depots*. The site of accumulation of toxicant may be its site of major toxic action, but more often it is not. Actually xenobiotics (toxicant) accumulate at a site other than the target organ or tissue. The accumulation may be viewed as a protective process. Xenobiotics enter the systemic blood circulation as a result of the absorption processes. Since the blood-stream passes through all the body tissues, it can distribute the chemical throughout the body. Among the body fluids, plasma water is relatively more important than the interstitial or intra-cellular water. In humans, the blood plasma accounts for 4% of the total body weight and for about 53% of the total blood volume.

The concentration of a chemical (xenobiotic) in blood plasma, is very important since it determines the amount of the chemical (1) that can reach the site of toxic action (i.e., target organ), (2) that might be directed to a storage depot (e.g., bone, adipose tissue) and (3) that is transported to the liver where the process of biotransformation to activate or inactivate an organic pollutant occurs. The concentration of a toxicant in blood is primarily dependent on its volume of distribution. The volume of distribution can be quantified by the following formula :

$$VD = \frac{\text{Dose (mg)}}{\text{Plasma concentrat ion (mg/l)}}$$

The volume of distribution sometimes indicates that the xenobiotic compound is localized in a particular tissue or is mainly confined to the plasma.

Various factors influence the distribution of toxicants from the blood stream; of prime importance is the binding of chemical molecules in blood to the plasmatic proteins, particularly, the serum albumins. The chemical molecules that are bound to the plasmatic proteins are rendered unavailable for distribution or for immediate toxic action (until dissociated, or competitively displaced by another chemical molecule). Only the free and unbound chemical forms are susceptible for metabolic alterations and are responsible for the elimination of toxic effects.

Several organophosphorus insecticides and also the organo-chlorine insecticides, dieldrin, for example, are known to be firmly bound to plasmatic proteins. Problems could emerge when a second substance is introduced into the blood-stream, especially if the latter replaces the previously bound substance(s) from the binding sites on the plasma proteins. This can result in unpredictable increase of the unbound fraction of the first substance in the plasma, leading to serious toxicological consequences.

Storage-depots or store — house (Storage of toxicants in certain tissues)

Xenobiotics often are concentrated in a specific tissue. Some xenobiotics attain their highest

concentrations at the site of toxic action and in fact such situations prove to be highly deleterious. For example, CO which keeps a high degree of affinity for haemoglobin and paraquet shows high affinity for the lungs, hence it accumulates in the lung. Other xenobiotics get concentrated at sites other than the target organ. For example, lead is accumulated in bone but its poisoning appears in soft tissues.

Likewise, organochlorines, which are well known neurotoxicants, accumulate in tissue having high lipid content. The compartments where xenobiotics get concentrated or accumulated are denoted as *storage depots* or *storehouse* of toxicants. As mentioned earlier, the storage may be viewed as a protective device, which prevents the deposition or accumulation or storage of xenobiotics (toxicants) at the site of their action, and consequently minimize their toxic actions. Elimination of the toxicants of storage depots takes place through biotransformation and excretion.

The principal storage sites for xenobiotics are :

1. Plasma proteins as Storage Depot

Several plasma proteins — for example albumin, transferring, ceruloplasmin, α & β lipoprotein etc.— may bind some xenobiotics (toxicants). The extent of plasma protein binding varies considerably among xenobiotics. For example, antipyrine is not bound. Others such as secobaribital are bound to about 50% and some, like warfarin, are about 99% bound. Plasma proteins are capable of binding various acidic compounds such as phenylbutazone, basic compounds such as imipramine, and netural compounds such as digitoxin. Most xenobiotics that are bound to plasma proteins bind to albumin. The principal metal binding protein in plasma is ceruloplasmin. The binding of xenobiotics with plasma protein is of special significance in toxicology. Because of their binding with high molecular weight plasma protein, they cannot cross capillary walls and other plasma membranes. Consequently, the bound form of toxicant may not enter the target site to produce injury. However, addition of another toxic agent can displace the first one from the plasma proteins, thus making it available in free form. For example, if a sulphonamide drug is provided to a patient already taking any diabetic drug, the former replaces the latter and induces hypoglycemic coma.

2. Body Fat as Storage Depot

Tissues and areas in the body rich in fat tend to store some xenobiotics that are highly soluble in lipids. These chemicals tend to localize in adipose tissues by partitioning between intracellular lipids and body water. Such accumulation in adipose tissue has been demonstrated for a number of xenobiotics, including chlordane, DDT, and polychlorinated and polybrominated biphenyls. Storage lowers the concentration of the toxicants in the target organ and serves as protective mechanism. Following starvation, the fat mobilization leads to a sharp rise in the plasma concentration of the stored xenobiotics.

Age, sex and race play an important role in the storage (accumulation) of lipid soluble xenobiotics. For example, males accumulate more of organochlorie insecticides than females, older people accumulate more OCIs than young people and Afro-Americans accumulate more of these insecticides than white men.

3. Liver as Storage Depot

Actually liver may be regarded as a principal storage organ. Since it performs variety of functions viz., storage of glycogen, deamination of amino acids, production of bile, synthesis of blood proteins, synthesis of urea through ornithine cycle and biotransformation, it receives all kinds of molecules from GIT through portal circulation and houses a large amount of all types of xenobiotics as well as proteins, bile and glycogen. The xenobiotics, entering liver for the process of biotransformation, bind with different constituents or groups and with other molecules present in the liver, according to their solubility and affinity. Thus liver acts as storage depot for various xenobiotics.

A protein in the cytoplasm of liver cells called ligandin, a Y protein, has been identified which shows a high affinity for many organic acids. Researches reveal that this protein may play a key role in the transfer of organic anions from plasma into liver. This protein also binds azo dye carcinogens and corticosteroids. Metalothionin, another binding protein of liver, binds to the cadmium. Liver is capable of binding lead 50 times greater than plasma within 30 minutes after single administration.

4. Kidney as Storage Depot

Like liver, kidney has a high capacity for binding multitude of xenobiotics. Since kidney is the principal excretory organ, all kinds of xenobiotics reach kidney glomeruli for filtration. The glomerular

basement membrane restricts excretion of protein and lipid molecules, stores various metalloprotein molecules and chlorinated hydrocarbon contaminated fat molecules. These go on accumulating at this site and cause extensive damage to the kidney glomerular basement membrane. It shall not be out of place to mention that liver and kidney probably concentrate more xenobiotics than do all the other organs combined.

5. Bone as Storage Depot

Bone is known to serve as a major storage site for some xenobiotics viz., lead, fluoride, and radioactive strontium. Of these xenobiotics, accumulation of lead in skeletal tissues is more pronounced, as it comprises of about 90% of the total lead in the body. Actually, skeletal uptake of xenobiotics is essentially a surface chemistry phenomenon, with exchange taking place between the bone surface and the fluid in contact with it. Deposition and storage of toxicants in bone may or may not be detrimental. For instance, lead is not toxic to the bones whereas the accumulation of fluoride for long term exposure causes skeletal flurosis. Likewise, long term storage of radioactive strontium produces osteosarcoma and other neoplasma. Xenobiotics may be released from the bone by ionic exchange at the crystal surface and dissolution of bone crystals through osteoclastic activity.

6. Brain and Nervous Tissues as Storage Depots

Some xenobiotics have high affinity for the brain tissues. For example, CNS drugs like thiopentone, barbiturates and psychotropic drugs, chlordiazepoxide and chlorpromazine enter the brain tissue rapidly after intravenous administration in experimental animals.

The myelin sheath of axon also accumulates lipid-soluble xenobiotics and acts as storage depot. The axon sheath accumulates a large amount of lipophilic chlorinated hydrocarbons and retains them for long time. Likewise, mercury also accumulates in myelin sheath and produces *Hatter's Shake.*

7. Erythrocytes as Storage Depot

Pharmacological agents, viz. nitroalamine, becomes localized in the R. B. C. by binding with hemoglobin. Similarly, other xenobiotics, viz. triethyltin (TET) has been reported to bind rapidly with rat hemoglobin. Arsenic, cadmium and lead also localize with erythrocytes for short time.

8. Gonads as Storage Depot

Researches reveal that epididymal fat of testes and of prostate gland accumulate and store lipid-soluble xenobiotics, example — DDT.

9. Respiratory Tract as Storage Depot

Xenobiotic molecules may get deposited on the mucosal lining of the respiratory tract and remain trapped there for short time.

10. G.I.T. as Storage Depot

Various lipid soluble xenobiotics and metals like mercury get deposited and remain trapped in the G.I.T. and accumulate. Also intestinal mucosal lining absorbs lipid soluble xenobiotics and retains them.

11. Gall Bladder as Storage Depot

Gall bladder acts as storage organ of bile. It also receives and accumulates all kinds of fat-soluble xenobiotic molecules that come from liver and finally pours them into the intestine. In this way, gall bladder also acts as a temporary storage depot.

12. Spleen as Storage Depot

Spleen being the principal organ for the removal of dead RBCs, also collects large number of RBCs from blood; and along with them, it collects protein binding as well as –SH group binding toxic molecules and stores them for considerable time.

13. Fetus as Storage Depot

Various lipophilic and hydrophilic xenobiotic molecules cross the placental barrier and reach the fetus. The lipophilic xenobiotics get absorbed in the fat content and accumulate, while hydrophilic molecules get absorbed in the fluid compartments of the fetus and are released slowly.

Effect of Accumulation and Retention of Xenobiotics

Some xenobiotics (toxicants) do not readily cross plasma membrane and, therefore, have restricted distribution. Whereas, other toxicants rapidly pass through plasma membrane and are distributed