MECHANISMS OF TOXICITY

- A common course is when a toxicant delivered to its target reacts with it, and the resultant cellular dysfunction manifests itself in toxicity.

- An example of this route to toxicity is that taken by the puffer fish poison, **tetrodotoxin**. After ingestion, this poison reaches the voltage-gated Na" channels of motoneurons (step I). Interaction of tetrodotoxin with this target (step 2a) results in blockade of Na" channels, inhibition of the activity of motor neurons (step 3), and ultimately skeletal muscle paralysis. No repair mechanisms can prevent the onset of such toxicity.

- Sometimes a xenobiotic does not react with a specific target molecule but rather adversely influences the biological (micro) environment, causing molecular, organellar, cellular, or organ dysfunction leading to deleterious effects.

- For example, 2,4-dinitrophenol, after entering the mitochondrial matrix space (step 1), collapses the outwardly directed proton gradient across the inner membrane by its mere presence there (step 2b), causing mitochondrial dysfunction (step 3), which is manifest in toxic effects such as hyperthermia and seizures. Chemicals that precipitate in renal tubules and block urine formation represent another example for such a

course (step 2b).

- The most complex path to toxicity involves more steps First, the toxicant is delivered to its target or targets (step I), after which the ultimate toxicant interacts with endogenous target molecules (step 2a), triggering perturbations in cell function and/or structure (step 3), which initiate repair mechanisms at the molecular, cellular, and/or tissue levels as well as adaptive mechanisms to diminish delivery, boost repair capacity and/or compensate for dysfunction (step 4). When the perturbations induced by the toxicant exceed repair and adaptive capacity or when repair and adaptation becomes malfunctional, toxicity occurs.
- Tissue necrosis, cancer, and fibrosis are examples of chemically induced toxicities whose development follow this four-step course.

STEP 1-DELIVERY: FROM THE SITE OF EXPOSURE TO THE TARGET

- Theoretically, the intensity of a toxic effect depends primarily on the concentration and persistence of the ultimate toxicant at its site of action.
- The ultimate toxicant is the chemical species that reacts with the endogenous target molecule (e.g., receptor, enzyme, DNA, microfilamental protein, lipid) or critically alters the biological (micro)

environment, initiating structural and/or functional alterations that result is toxicity.

- Often the ultimate toxicant is the original chemical to which the organism is exposed **(parent compound**).
- The ultimate toxicant is a metabolite of the parent compound or a reactive oxygen or nitrogen species (ROS or RNS) generated during the biotransformation of the toxicant.
- Occasionally, the ultimate toxicant is an unchanged or altered endogenous molecule.
- The concentration of the ultimate toxicant at the target molecule depends on the relative effectiveness of the processes that increase or decrease it's concentration at the target site .
- The accumulation of the ultimate toxicant at its target is facilitated by its absorption, distribution to the site of action, reabsorption, and toxication (metabolic activation).
- Conversely, presystemic elimination, distribution away from the site of action, excretion, and detoxication oppose these processes and work against the accumulation of the ultimate toxicant at the target molecule.

Absorption versus Presystemic Elimination

- Absorption is the transfer of a chemical from the site of exposure, usually an external or internal body surface (e.g., skin, mucosa of the alimentary and respiratory tracts), into the systemic circulation.
- Whereas transporters may contribute to the gastrointestinal absorption of some chemicals (e.g., salicylate and valproate by monocarboxylate transporters, some ,B-Iactamantibiotics and ACE inhibitor drugs by peptide transporters),
- the vast majority of toxicants traverse epithelial barriers and reach the blood capillaries by diffusing through cells.
- The rate of absorption is related to the concentration of the chemical at the absorbing surface, which depends on the rate of exposure and the dissolution of the chemical.
- It is also related to the area of the exposed site, the characteristics of the epithelial layer through which absorption takes place (e.g., the thickness of the stratum corneum in the skin), the intensity of the subepithelial microcirculation, and the physicochemical properties of the toxicant.
- Lipid solubility is usually the most important property influencing absorption.

- In general, lipid-soluble chemicals are absorbed more readily than are water-soluble substances.

Presystemic Elimination

- During transfer from the site of exposure to the systemic circulation, toxicants may be eliminated.
- This is not unusual for chemicals absorbed from the gastrointestinal (GI) tract because they must first pass through the GI mucosal cells, liver, and lung before being distributed to the rest of the body by the systemic circulation.
- The GI mucosa and the liver may eliminate a significant fraction of a toxicant during its passage through these tissues, decreasing its systemic availability.
- For example, **ethanol** is oxidized by **dehydrogenase** in the gastric mucosa
- **morphine** is glucuronidated in intestinal mucosa and liver, and manganese is taken up from the portal blood into liver and excreted into bile.
- Such processes may prevent a considerable quantity of chemicals from reaching the systemic blood.
- Thus, presystemic or first-pass elimination reduces the toxic effects of chemicals that reach their target sites by way of the systemic circulation.
- In contrast, the processes involved in presystemic

elimination may contribute to injury of the digestive mucosa, liver, and lungs by chemicals such as ethanol, iron salts, o-amanitin, and paraquat because these processes promote their delivery to those sites.

Distribution to and Away from the Target

- Toxicants exit the blood during the distribution phase, enter the extracellular space, and may penetrate into cells.
- Chemicals dissolved in plasma water may diffuse through the capillary endothelium via aqueous intercellular spaces
- Lipid-soluble compounds move readily into cells by diffusion.
- In contrast, highly ionized and hydrophilic xenobiotics are largely restricted to the extracellular space unless specialized membrane carrier systems are available to transport them.
- During distribution toxicants reach their site or sites of action usually a macromolecule on either the surface or the interior of a particular type of cell.
- Some mechanisms facilitate whereas others delay the distribution of toxicants to their targets.
- Mechanisms Facilitating Distribution to a Target
  Distribution of toxicants to specific target sites may be enhanced by

(I) the porosity of the capillary endothelium,
(2) specialized membrane transport,
(3) accumulation in cell organelles,
(4) reversible intracellular binding.

- Mechanisms Opposing Distribution to a Target
Distribution of toxicants to specific sites may be hindered by several processes. The processes include
(1) binding to plasma proteins,
(2) specialized barriers,
(3) distribution to storage site such as adipose tissue,
(4) association with intracellular binding proteins,
(5) export from cells.

Excretion versus Reabsorption

Excretion is the removal of xenobiotics from the blood and their return to the external environment.

- Excretion is a physical mechanism whereas biotransformation is a chemical mechanism for eliminating the toxicant.
- The major excretory structures in the body are
1; the renal glomeruli; which filters small molecules through their pores
2; hepatocytes which actively transport chemicals from the blood into the renal tubules.

- The route and speed of excretion depends on the physic-chemical properties of the toxicant.
- The major excretory organs- kidney and liver can efficiently remove only highly hydrophilic, usually ionized chemicals such as organic acids and bases. The reasons for this are as follows:
- (1) in the renal glomeruli, only compounds dissolved in plasma water can be filtered;
- (2) transporters in hepatocytes and renal proximal tubular cells are specialized for secretion of highly hydrophilic organic acids and bases;
- (3) only hydrophilic chemicals are freely soluble in the aqueous urine and bile; and
- (4) lipid-soluble compounds are readily reabsorbed by transcellular diffusion.
- Their are no efficient elimination mechanisms for nonvolatile highly lipophilic, hydrophobic, chemicals such as polyhalogenated biphenyls and chlorinated hydrocarbon insecticides.
- If they are resistant to biotransformation, such chemicals are eliminated very slowly and tend to accumulate in the body upon repeated exposure. Three processes are available for the

elimination of such chemicals:
(1) excretion by the mammary gland after the chemical is dissolved in the milk lipids;
(2) excretion in bile in association with biliary and/or phospholipid vesicles;
(3) intestinal excretion, an incompletely understood transport from blood into the intestinal lumen. Volatile, nonreactive toxicants such as gases and volatile liquids diffuse from pulmonary capillaries into the alveoli and are exhaled.

Reabsorption

- Toxicants delivered into the renal tubules may diffuse back across the tubular cells into the capillaries.
- This process is facilitated by tubular fluid reabsorption, which increases the intra tubular concentration as well as the **residence time** of the chemical by slowing urine flow.
- Reabsorption by diffusion is dependent on the lipid solubility of the chemical.
- For organic acids and bases, diffusion is inversely related to the extent of ionization, because the nonionized molecule is more lipid-soluble.
- The ionization of weak organic acids, such as salicylic acid and phenobarbital, and bases, such as

amphetamine, is strongly pH-dependent in the physiologic range.

- Therefore their reabsorption is influenced significantly by the pH of the tubular fluid.
- Acidification of urine favors the excretion of weak organic bases, whereas alkalinization favors the elimination of weak organic acids.
- Some organic compounds may be reabsorbed from the renal tubules by transporters. For example, peptide transporters (PEPT) can move some antibiotics across the membrane.
- Carriers for the physiologic oxyanions mediate the reabsorption of some toxic metal oxyanions in the kidney.
- Chromate and molybdate are reabsorbed by the sulfate transporter,
- whereas arsenate is reabsorbed by the phosphate transporter.
- Toxicants delivered to the GI tract by biliary, gastric, and intestinal excretion and secretion by salivary glands and pancreas may be reabsorbed by diffusion across the intestinal mucosa.
- Because compounds secreted into bile are usually organic acids, their reabsorption is possible only if they are sufficiently lipophilic or are converted to more lipid-soluble forms in the intestinal lumen.

Toxication versus **Detoxication**

Toxication

- A number of xenobiotics (e.g., strong acids and bases, nicotine, aminoglycosides, ethylene oxide, methylisocyanate, heavy-metal ions, HCN, CO) are directly toxic, whereas the toxicity of others is due largely to metabolites.
- Biotransformation to harmful products is called *toxication* or *metabolic activation*.
- With some xenobiotics, toxication confers physicochemical properties that adversely alter the microenvironment of biological processes or structures.

- For example, **oxalic acid** formed from **ethylene glycol** may cause acidosis and hypocalcaemia as well as obstruction of renal tubules by precipitation as **calcium oxalate.**

- Occasionally, chemicals acquire structural features and reactivity by biotransformation that allows for a more efficient interaction with' specific receptors or enzymes

➢ For example,

- ✓ the organophosphate insecticide parathion is biotransformed to paraoxon, an active cholinestrase inhibitor;
- ✓ the rodenticide fluoroacetate is converted in the citric acid cycle to fluorocitrate, that inhibits aconitase;
- ✓ the general anesthetic meth oxy flurane releases fluorideion which inhibits several enzymes and which contributes to renal injury after prolonged anesthesia;
- ✓ some cephalosporin antibiotics may cause hemorrhage because they undergo biotransformation and thus impairs activation clotting factors;
- ✓ This increased reactivity may be due to conversion into;
  (1) electrophiles,
  (2) free radicals,
  (3) nucleophiles, or
  (4) redox-active reactants.

Detoxication

- ✓ Biotransformation that eliminates an ultimate toxicant or prevents its formation is called *detoxication.*
- ✓ In some cases, detoxication may compete with toxication for a chemical.
- ✓ Detoxication can take several pathways, depending on the chemical nature of the toxic substance.
- ✓ Detoxification of toxicants with no functional groups
    1. Detoxication of nucleaphiles
    2. Detoxication of electrophiles
    3. Detoxication of free radicals
    4. Detoxication of protein toxins

When Detoxication Fails; Detoxication may be insufficient for several reasons:

1. Toxicants may overwhelm detoxication processes,
2. Occasionally, a reactive toxicant inactivates a detoxicating enzyme.
3. Some conjugation reactions can be reversed. For instance antidots are used against any toxication

4; Sometimes detoxication generates potentially harmful by- products, such as cadmium in the kidney form complexes.