ABSORPTION OF TOXICANTS

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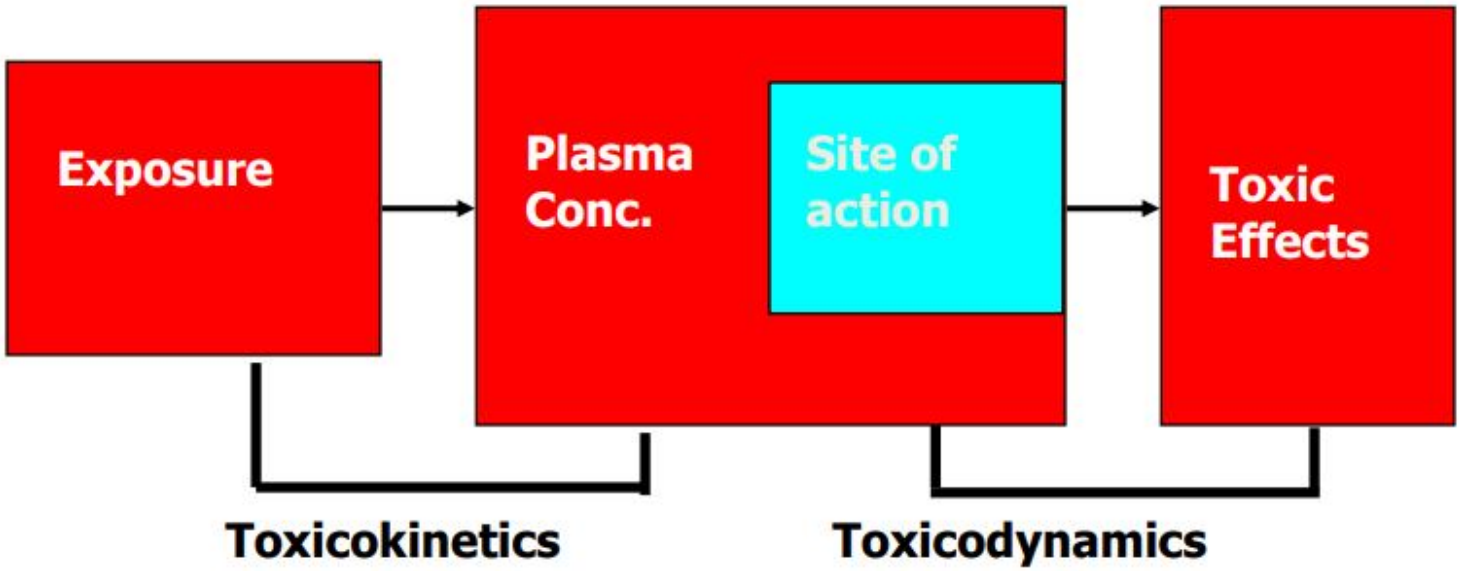
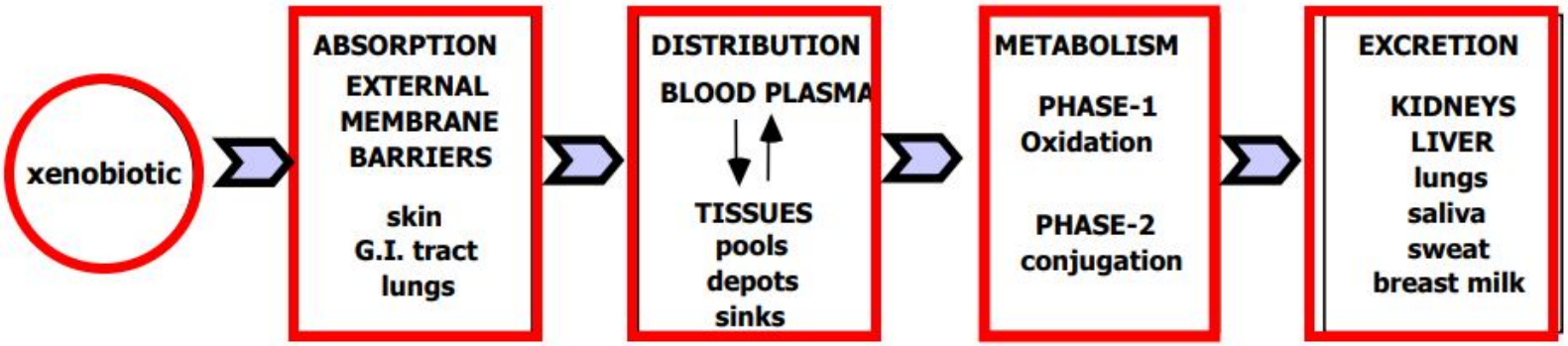
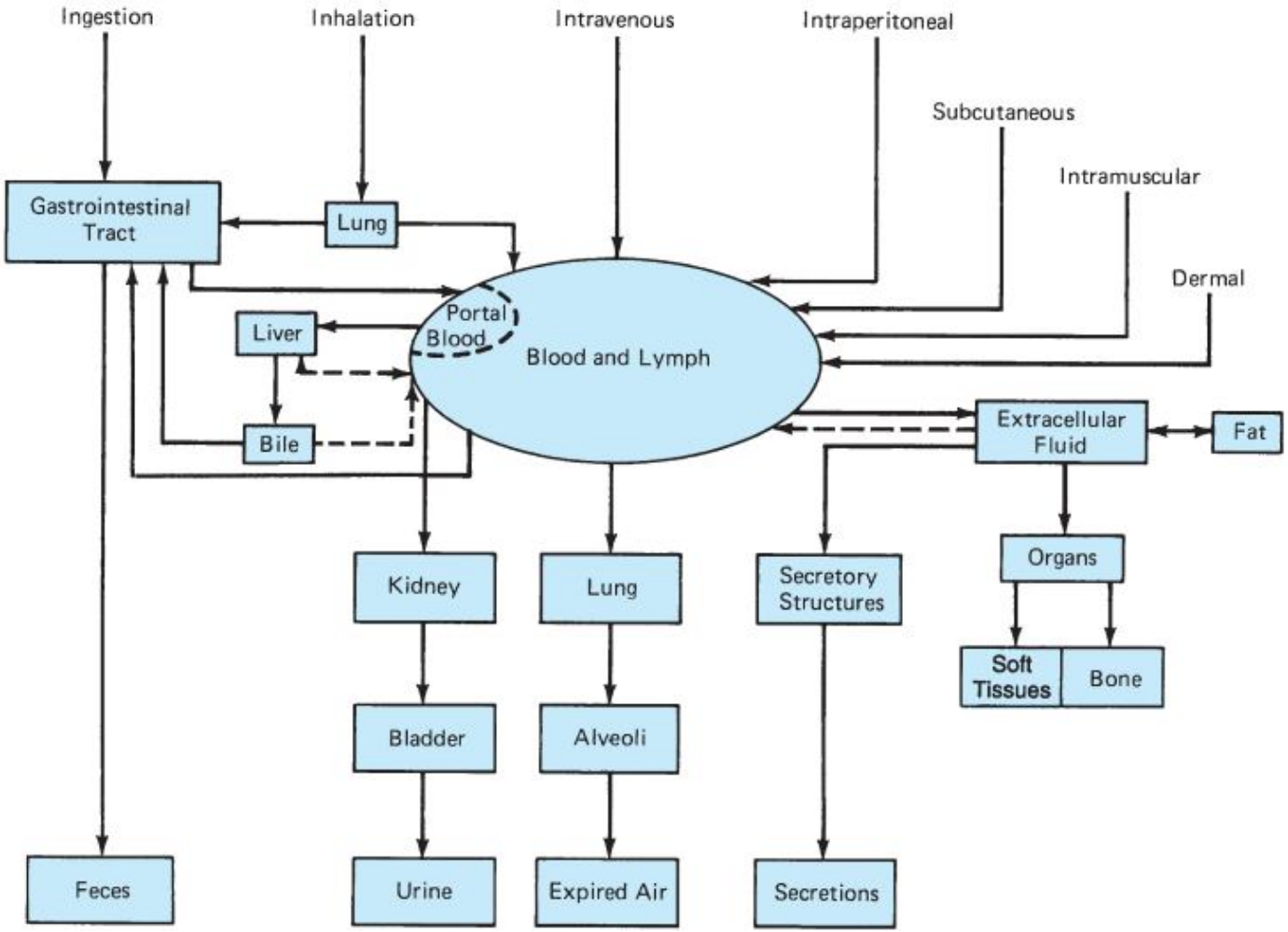

Exposure
Plasma Conc.
Site of action
Toxic Effects
Toxicokinetics
Toxicodynamics

FATE OF A TOXICANT (XENOBIOTIC)



Routes of Absorption, Distribution and Excretion



<u>Routes of Absorption:</u>

1. Ingestion
2. Inhalation
3. Dermal
4. Inhalation
5. Intravenous
6. Intraperitoneal
7. Intramuscular
8. Subcutaneous

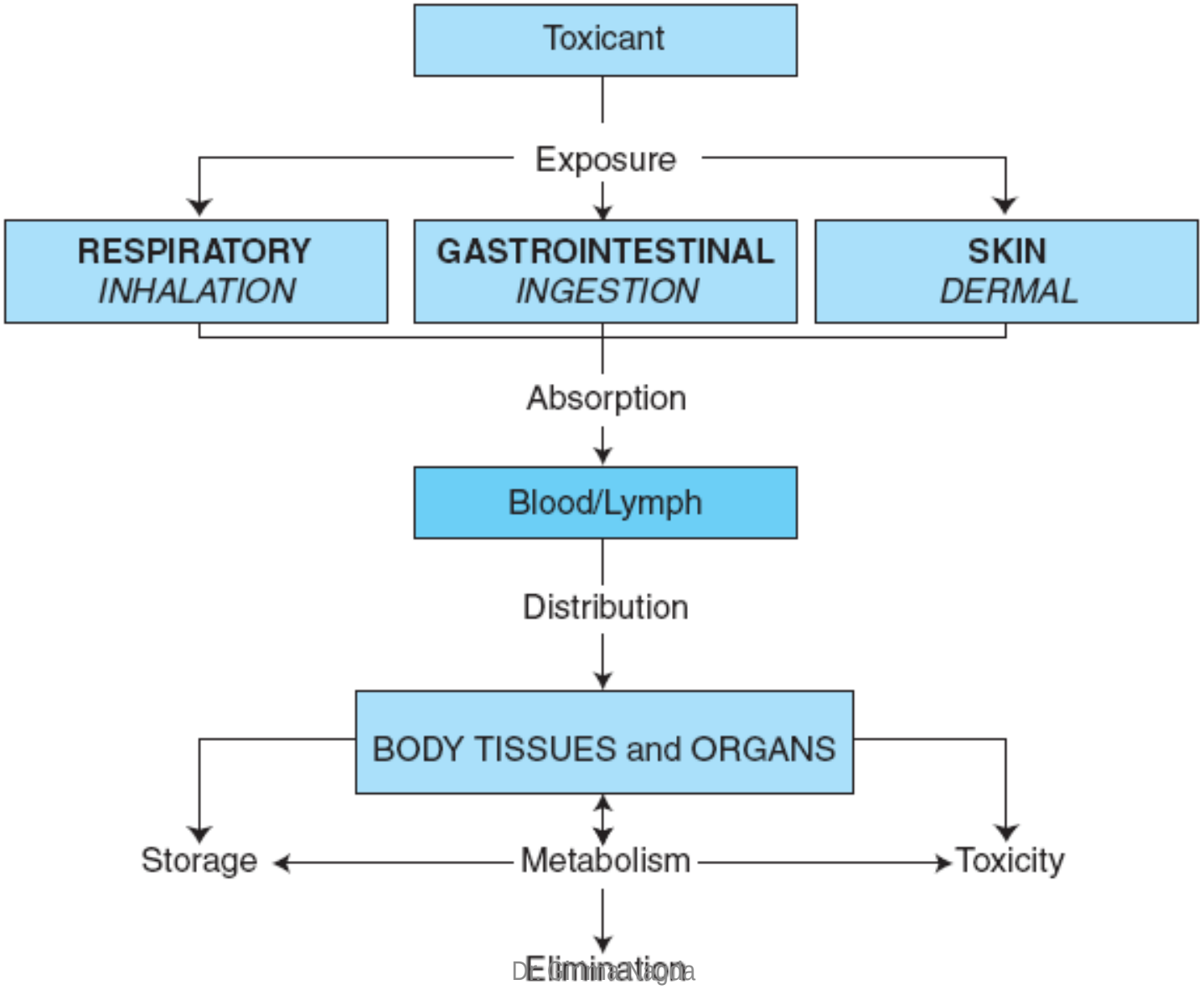
<u>Routes of Distribution:</u>

1. Systemic circulation
2. Portal circulation
3. Lymphatic system
4. Fat
5. Extracellular fluid
6. Organs

<u>Routes of Excretion:</u>

1. Feces
2. Urine
3. Expired air
4. secretions

Absorption and Fate of a Toxicant



Routes of exposure

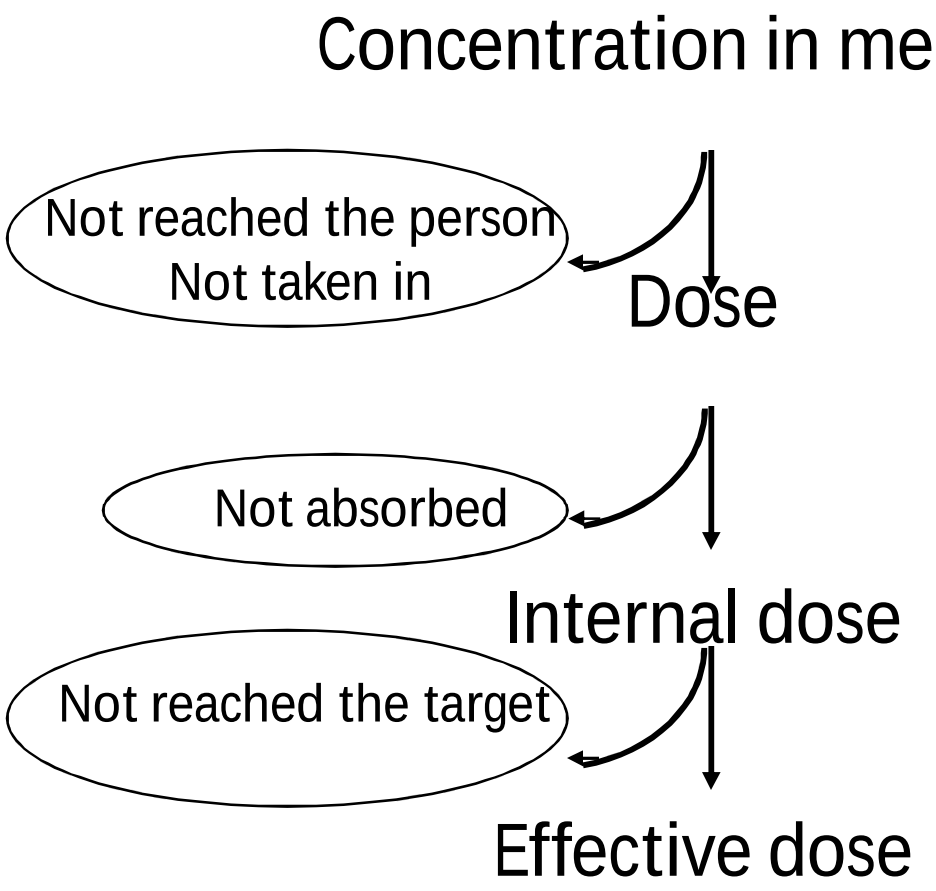
- Gastrointestinal
- Lungs
- Skin
- Mucosa
- Parenteral

Effectiveness

IV > inhalation > IP > SC > IM > intradermal > oral > dermal

Toxicity varies by route (curare)

Dose from exposure



ABSORPTION
DISTRIBUTION
METABOLISM-BIOTRANSFORMATION
ELIMINATION

- Absorption- xenobiotics gets into bloodstream
- Distribution - gets to site of action
- **Metabolism - is "changed" so that it can be excreted**
- Elimination - leaves the body

How toxicokinetics can influence the toxicity?

❖ *Absorption*

- A toxic xenobiotic which is poorly absorbed may not cause toxicity

❖ *Distribution*

- The distribution of a toxicant to a tissue other than the target organ decreases its toxicity.

❖ *Metabolism (Biotransformation)*

- Two substances with equal absorption rate may differ in toxicity depending on their biotransformation.

❖ *Elimination*

- The toxicity of xenobiotic depends on its elimination rate from an organism.

Toxicant Entry into the Body

- To produce a systemic effect, a toxicant has to defeat barriers to absorption and enter into the internal compartments of the body; otherwise, all effects are confined to the site of exposure, that is, all toxicity will be local (e.g., irritation to skin or respiratory tract).
- An orally consumed toxicant, or one that enters into the respiratory system, is not considered to be “internal” until it moves across the epithelial cellular membranes that line the respective systems, thus gaining entry into the internal fluid compartments of the body

ABSORPTION OF TOXICANTS

- Process by which toxicants cross the epithelial cell barrier.
- Depending on the nature of the toxicant, dose, duration, and type of exposure, a toxicant may limit its contact to the outer surface of the epithelial cell barrier, or cross the cell membrane, enter the cell, and possibly move completely through the cell and into the underlying tissues.

I. ABSORPTION

Absorption is the transfer of a xenobiotic from the site of exposure into the systemic circulation. During this process, xenobiotics cross body membranes and enter the bloodstream.

It is ***the first rate limiting step*** in the toxicokinetics of a xenobiotic.

No absorption, no toxicity

ABSORPTION

Factors involved in absorbing a chemical:

1. Physicochemical properties of your chemical
    1. Hyrdrophobic? Hydrophilic?
    2. Ionized? Nonionized? Weak acid/base?
    3. Molecular weight? Volatility?
2. Route of exposure
3. Getting chemicals across cell membranes
    1. Diffusion/Passive transport
    2. Active transport

Factors affecting absorption

1. Factors related with chemical.

a. Physiochemical properties

b. Concentration at absorption site

c. Physical form

2. Factors related with site of exposure

a. Blood flow

b. Surface area and permeability

1. Factors related with chemical

a. Physiochemical properties

i. Mol. weight: Small molecules are readily absorbed.

ii. Lipid solubility: Lipid solubility increases the absorption.

Lipid solubility is determined by lipid/water partition coefficient (log P). Octanol and water mixture is used to determine this value.

Positive log P value = high lipid solubility
Negative log P value = water solubility

iii. Ionization degree of a chemical

The ionized form usually has low lipid solubility and thus does not cross *readily through the lipid domain of a membrane*.

The degree of ionization of a chemical depends on its pK_a and the pH of the solution.

The pH at which a weak organic acid or base is 50% ionized is called its pK_a or pK_b.

pH of the medium:

Effects ionization of xenobiotics.

Weak acids → best absorbed in stomach.

Weak bases → best absorbed in intestine.

b. Concentration at exposure site

Generally high concentration results with higher absorption.

c. Physical form

Solid chemicals are absorbed slowly, as they have to be dissolved first.

MAIN ABSORPTION ROUTES/BARRIERS ARE;

1. **ORAL-GASTRO INTESTINAL TRACT (GI)**
2. **INHALATION-LUNG**
2. **DERMAL-SKIN**

Xenobiotics must cross one of these barriers to exert their toxicities in the body. However during this process they usually pass through various cell membranes.

TRANSMEMBRANE TRANSPORT OF XENOBIOTICS

Xenobiotics must pass a number of cell membrans to enter systemic circulation, to move within and leave the body.

Structure of a cell membrane

- ✓ The basic unit of the cell membrane is a ***phospholipid bilayer***
- ✓ Different proteins are inserted or embedded in membrane.
- ✓ Some of these proteins serve as **important biological receptors** or **aqueous pores** and **ion channels**.

BASIC MECHANISMS OF XENOBIOTIC TRANSMEMBRANE TRANSPORT

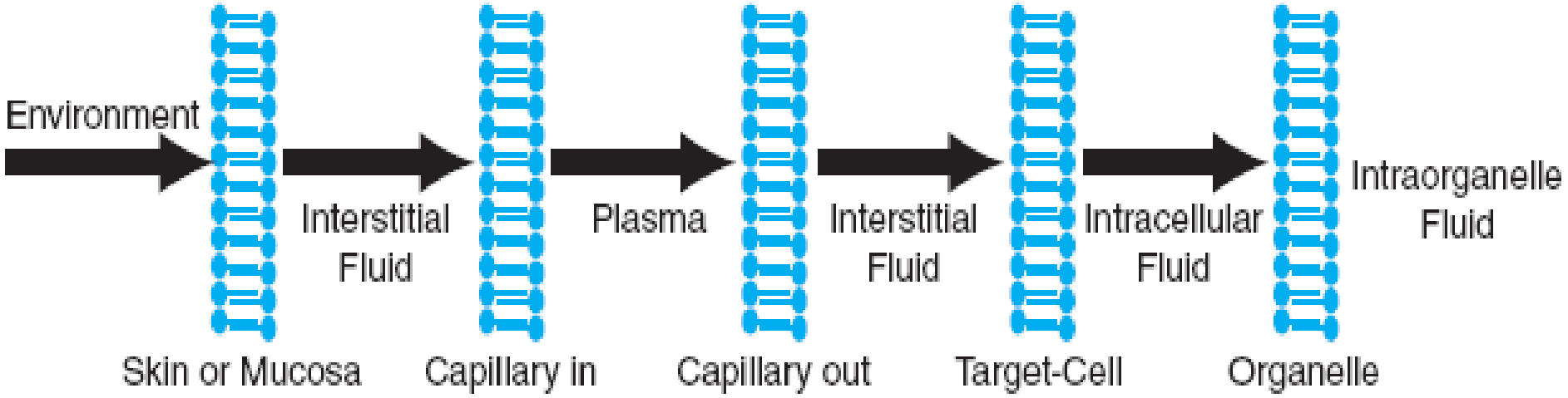
A xenobiotic may pass through a membrane by;

1. Passive transfer (simple diffusion)
2. Facilitated diffusion
3. Active transport
4. Endocytosis (phagocytosis and pinocytosis)

Cell Membranes

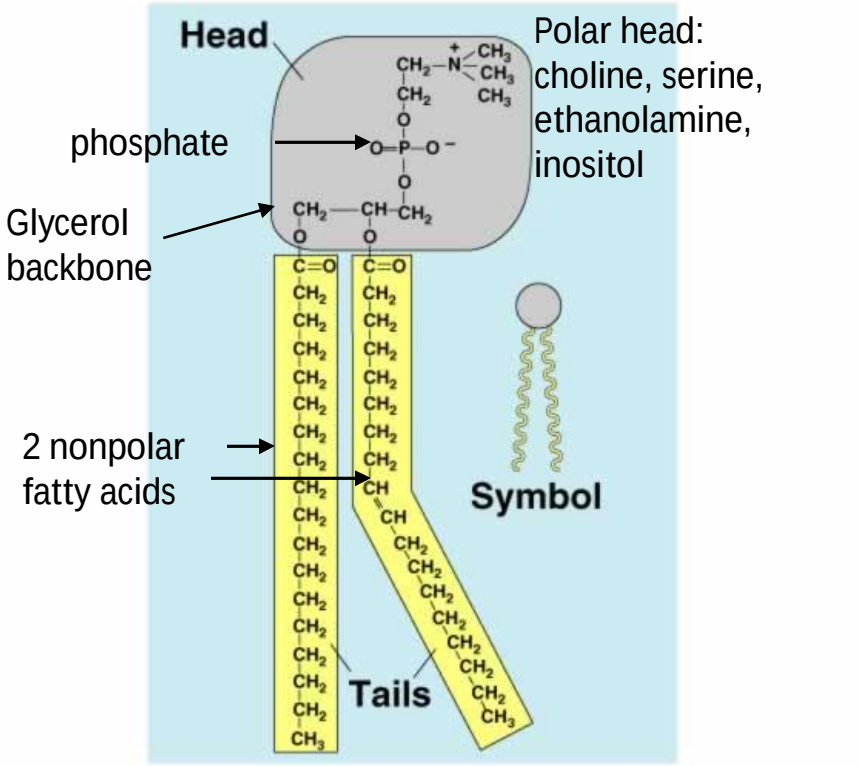
- Contained within the phospholipid bilayer are proteins that may assist in the movement of chemicals (e.g.,some proteins form aqueous pores, whereas others serve as transport proteins for chemicals).
- For a toxicant to enter into the internal body fluid compartments or to enter, leave, or move to other cells requires passage across several cell membranes.

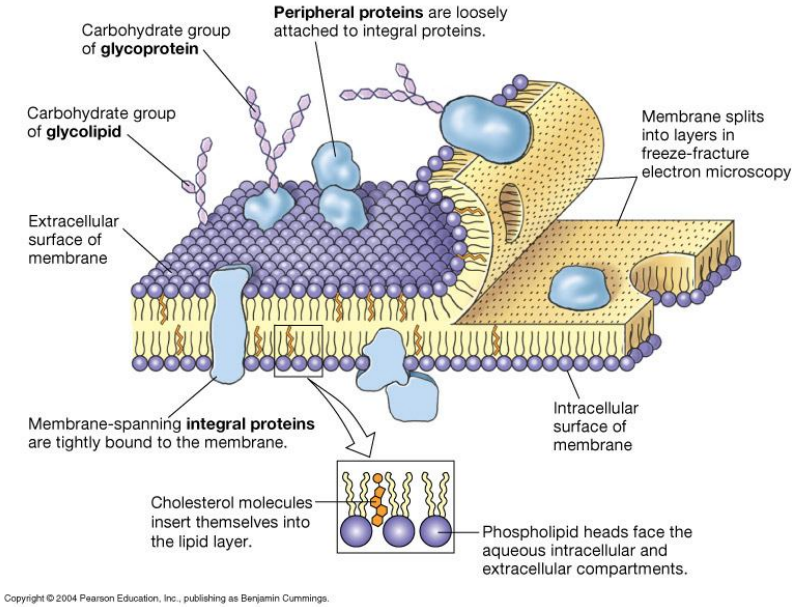
Cell Membranes

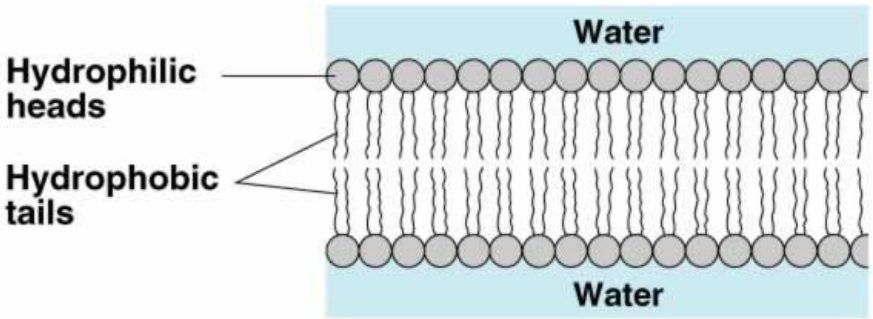


Cell membrane crossings for a toxicant from exposure site to target

Absorption Across Membranes





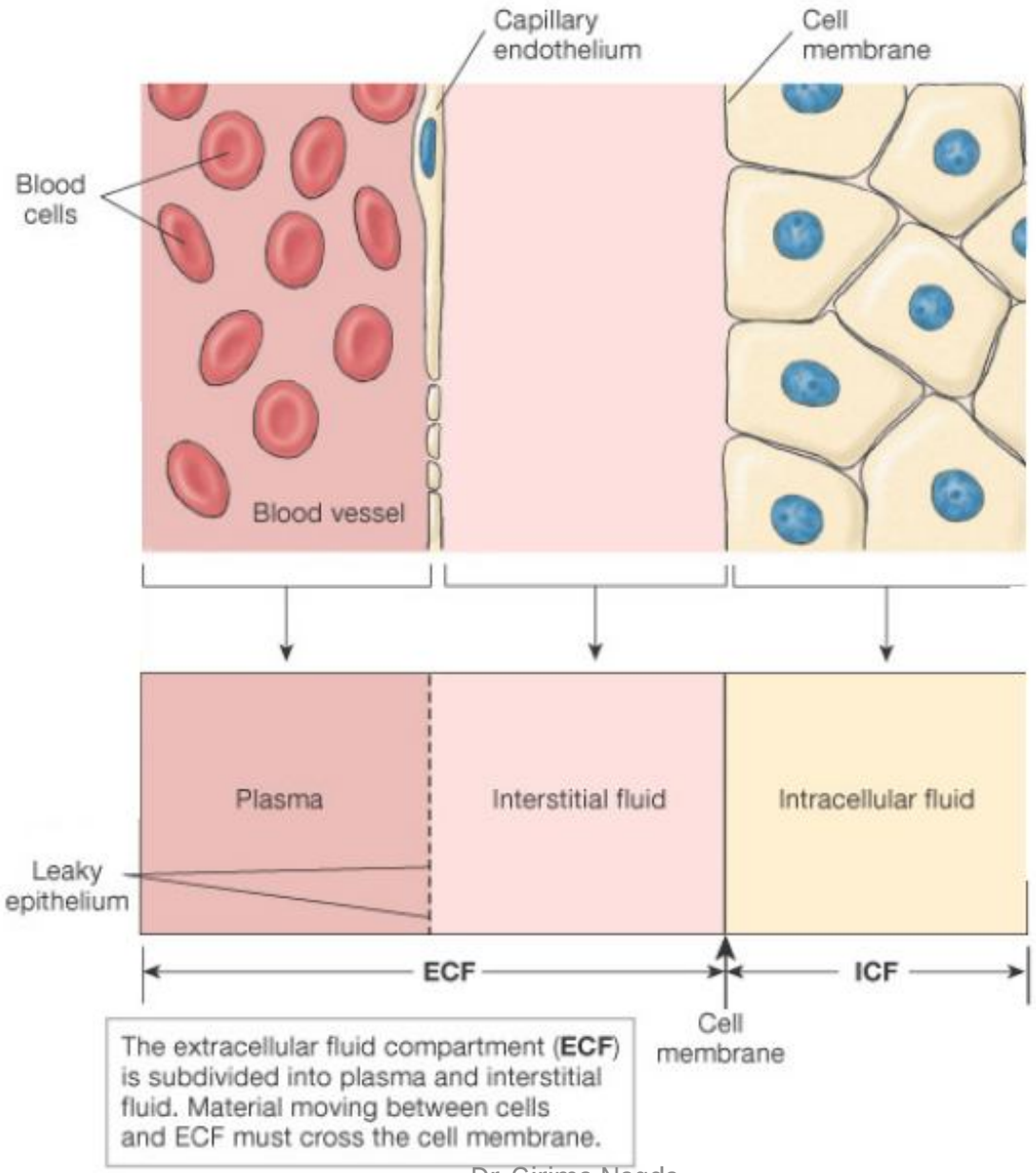


•The membrane is a phospholipid bi-layer consisting of a polar head group, phosphate, glycerol backbone and 2 fatty acid molecules esterified to the glycerol backbone.

• hydrophobic compounds can diffuse across the membrane

• hydrophilic compounds will not diffuse across the membrane

Physical Barriers to Absorption



Process of Cellular Absorption

Types of transport mechanisms by which a substance enters a cell:

1. **Simple Diffusion:**
    - Passive
    - Most Common
    - Concentration Gradient

2. **Faciliated Diffusion:**
    - Passive

3. **Active Transport:**
    - Active (use of ATP)

4. **Macromolecules**
    - Phagocytosis

Types of Transport

1. Passive Diffusion—no ATP required; gradient driven

a. Simple Diffusion—hydrophobic molecules passively diffuse across the membrane. Rate of transport proportional to the octanol/water partition coefficient or logP.

b. Facilitated Diffusion—saturable carrier-mediated transport (e.g. glucose transporter)

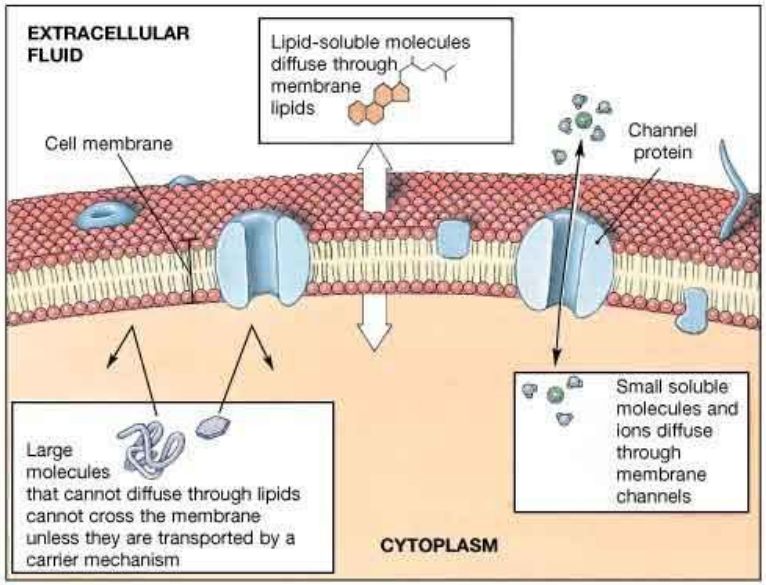


FIGURE 3-6 Diffusion across the Cell Membrane

Octanol/Water Partition Coefficients (*P*) of Different Molecules Expressed as log P

COMPOUND	LOG *P*
Paraquat	Charged molecule
Sulfobromophthalein	Charged molecule
Cephalosporin C	−4.72
Cystine	−4.45
Glycine	−3.21
Glutathione	−3.05
Gluconic acid	−2.89
Cysteine	−2.35
Glucose	−2.21
Edetic acid	−1.93
Ethylene glycol	−1.37
Lead acetate	−0.63
Ouabain	−0.35
p-Aminohippuric acid	−0.25
Dimercaprol	0.18
Scopolamine	0.30
Sarin	0.45
Aspirin	1.02
Colchicine	1.19
Atropine	1.32
Benzoic acid	1.88
Benzene	2.14
Salicylic acid	2.19
Digoxin	2.27
Methyl salicylate	2.34
2,4-D	2.73
Warfarin	2.89
Digitoxin	3.05
Parathion	3.47
DDT	6.76
TCDD	7.05

Movement of Toxicants Across Cell Membranes

- Toxicants move across cell membranes by either simple diffusion or specialized transport.
- Specialized transport mechanisms included active transport, special transport (facilitated or carrier-mediated diffusion and active transport), and endocytosis.

Movement of Toxicants Across Cell Membranes

- The primary mechanism is simple diffusion. Several primary factors determine net diffusion (amount of chemical moved) and the diffusion rate:
  - Size of the molecule
  - Molecular charge and degree of ionization
  - Water solubility
  - Concentration differences across the cell membrane

Passive transfer (simple diffusion)

Most xenobiotics cross membranes by passive transfer.

*It does not need cellular energy or assistance.

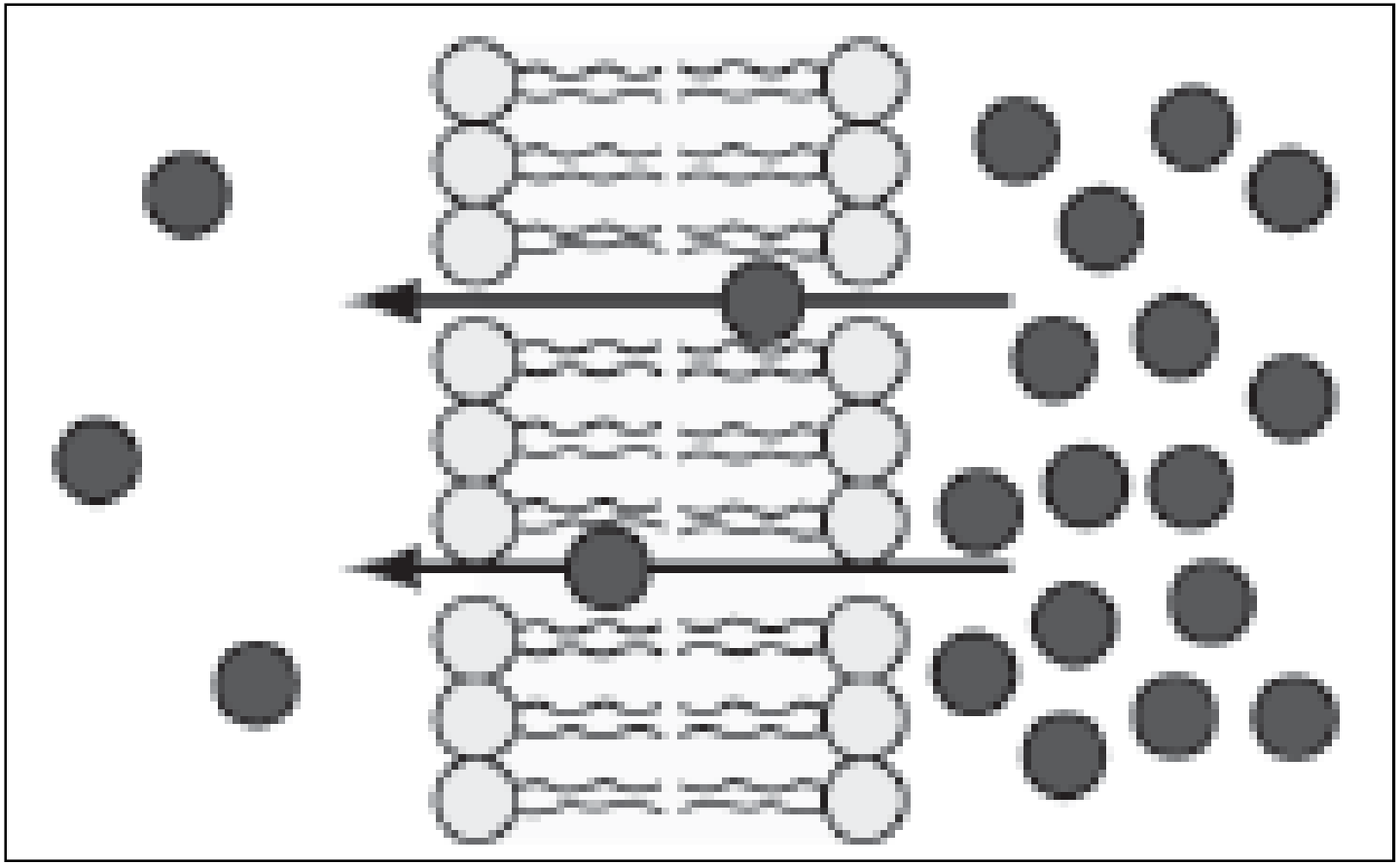
*The driving force force for the transport across the membrane is the concentration gradient (from higher to lower concentration) between the two compartments.

*Lipid soluble chemicals diffuse across the lipid domain of membranes.

*Small hydrophilic molecules (up to m.w. 600) cross membranes through aqueous pores.

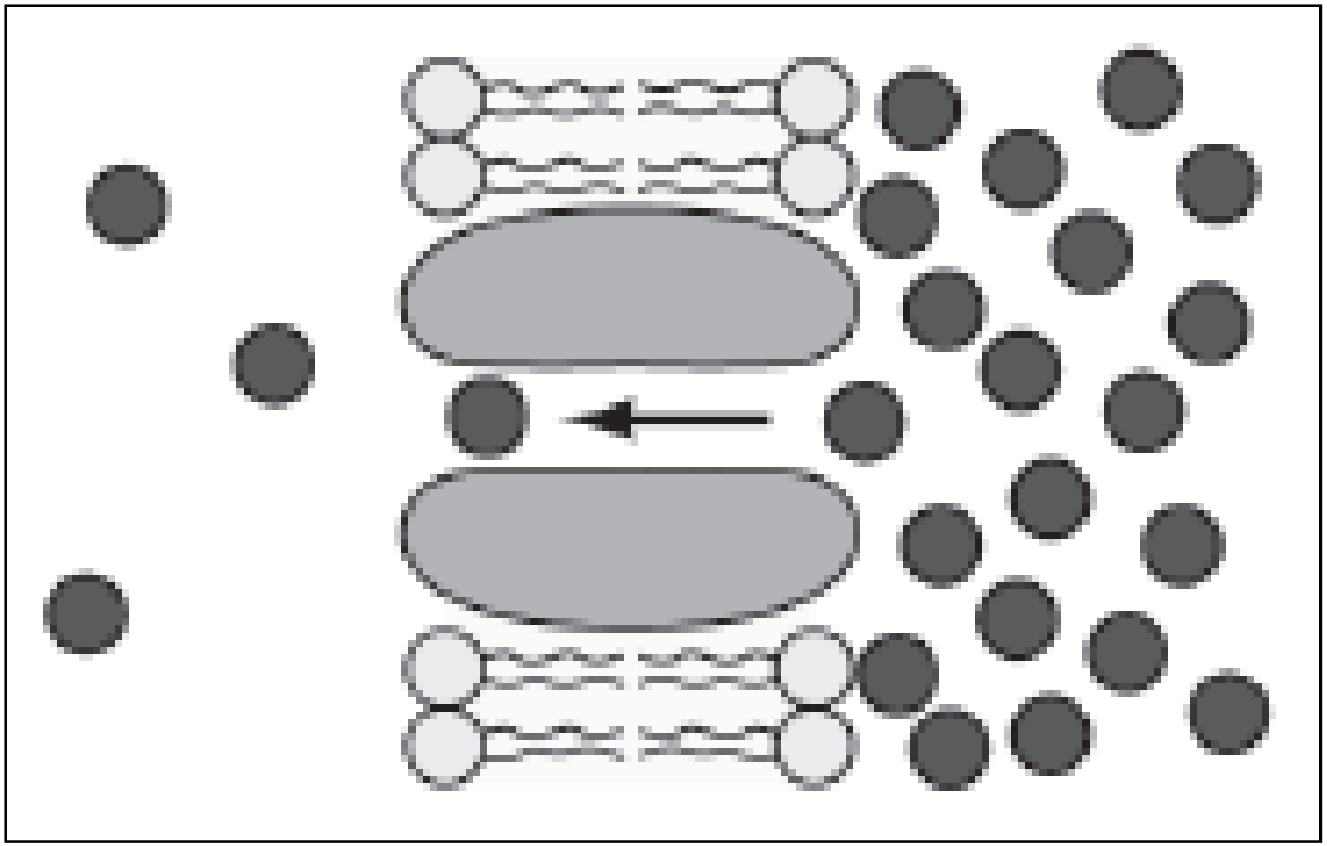
Modes in which a toxicant can cross a cell membrane:

(a) Simple diffusion



Modes in which a toxicant can cross a cell membrane:

(b) Diffusion through protein pores



Facilitated diffusion

* Similar to active transport, but

*Xenobiotic does not diffuse against a concentration gradient,

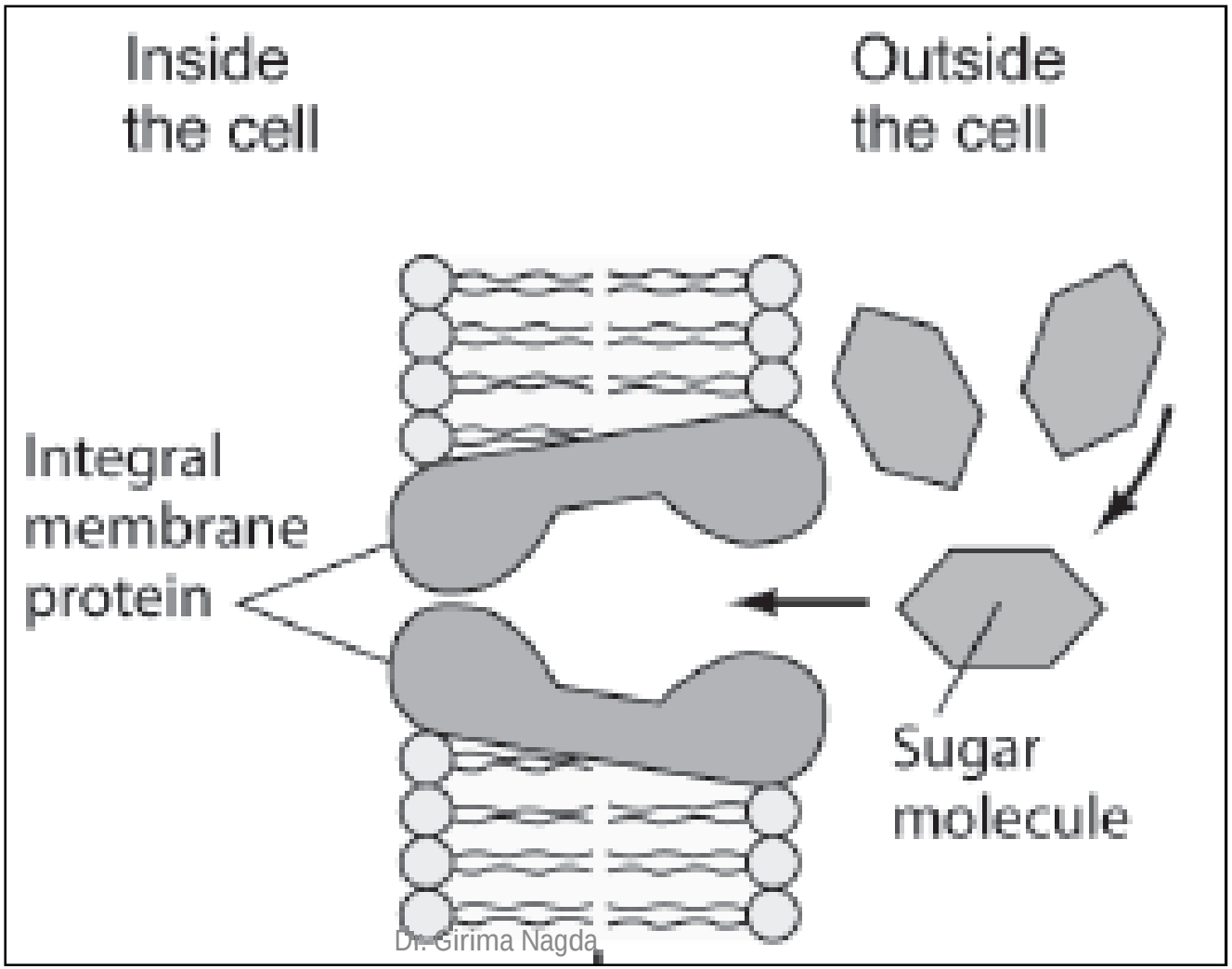
* No energy is needed and

* Protein carrier is used.

Modes in which a toxicant can cross a cell membrane: **(c)**

facilitated diffusion

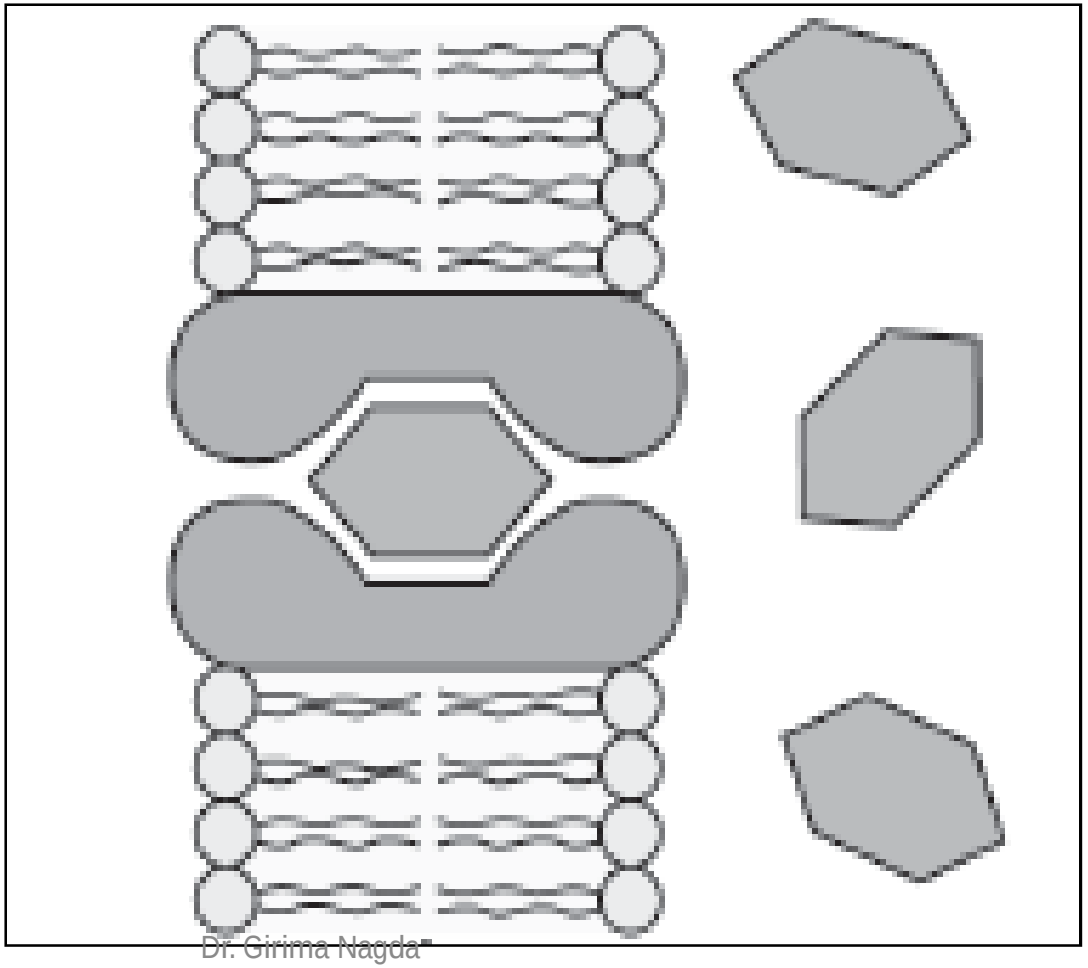
Step One



Modes in which a toxicant can cross a cell membrane: **(c)**

facilitated diffusion, cont.

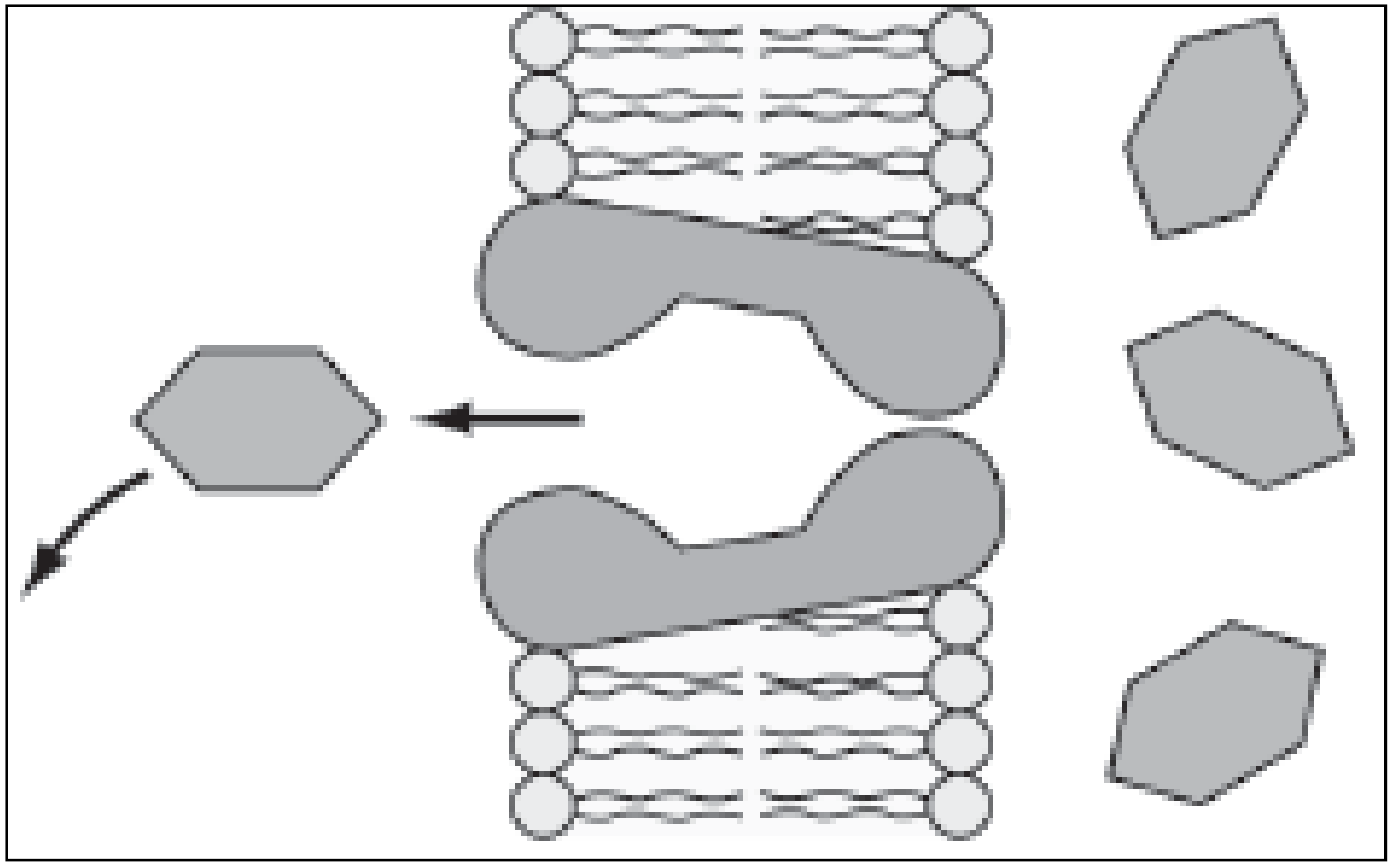
Step Two



Modes in which a toxicant can cross a cell membrane:

(c) facilitated diffusion

Step Three



Active transport

* These type of chemicals are transported against a concentration gradient.

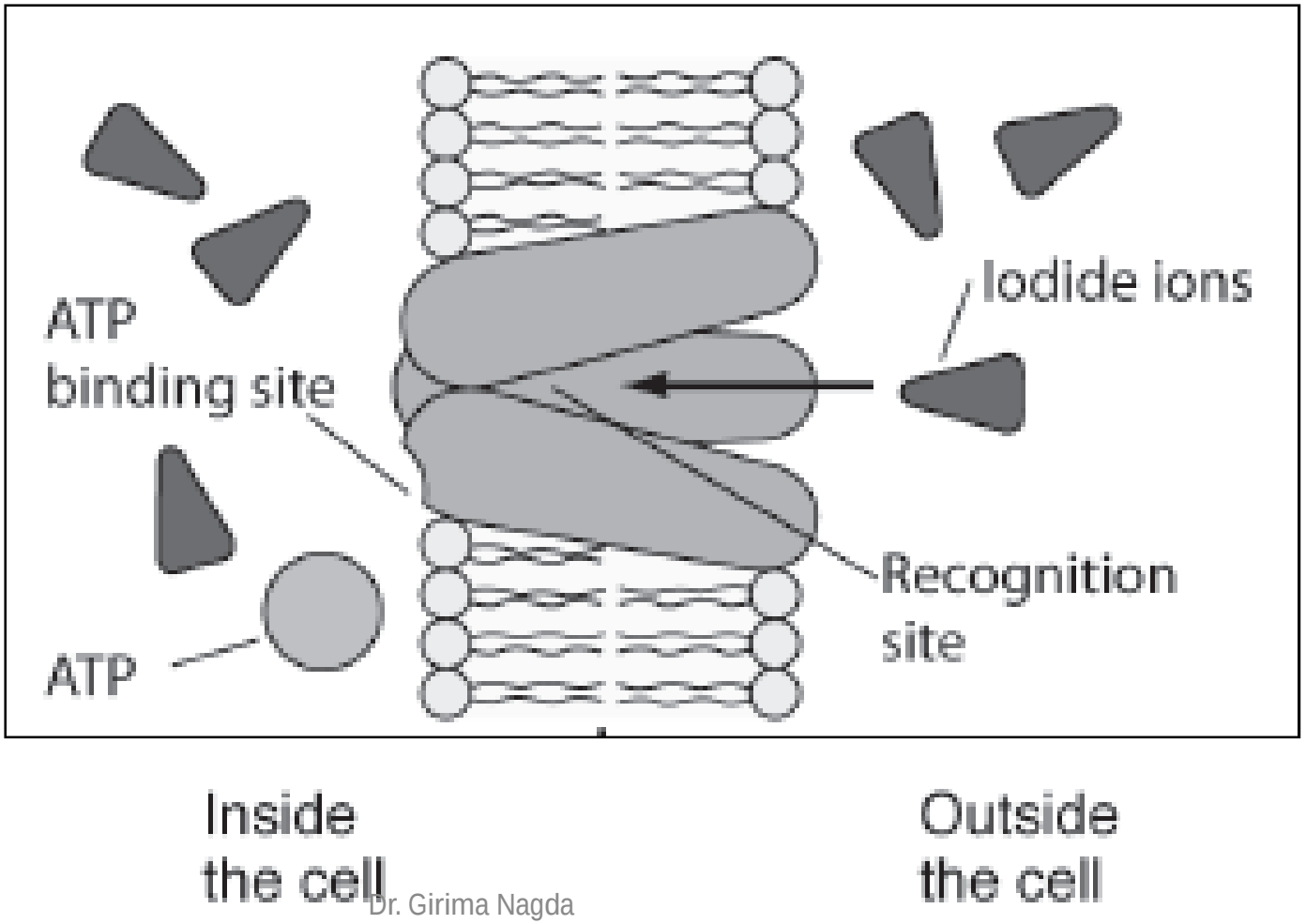
* Specific membrane *carrier proteins* are used.

* This process is energy dependent(ATP)

Modes in which a toxicant can cross a cell membrane:

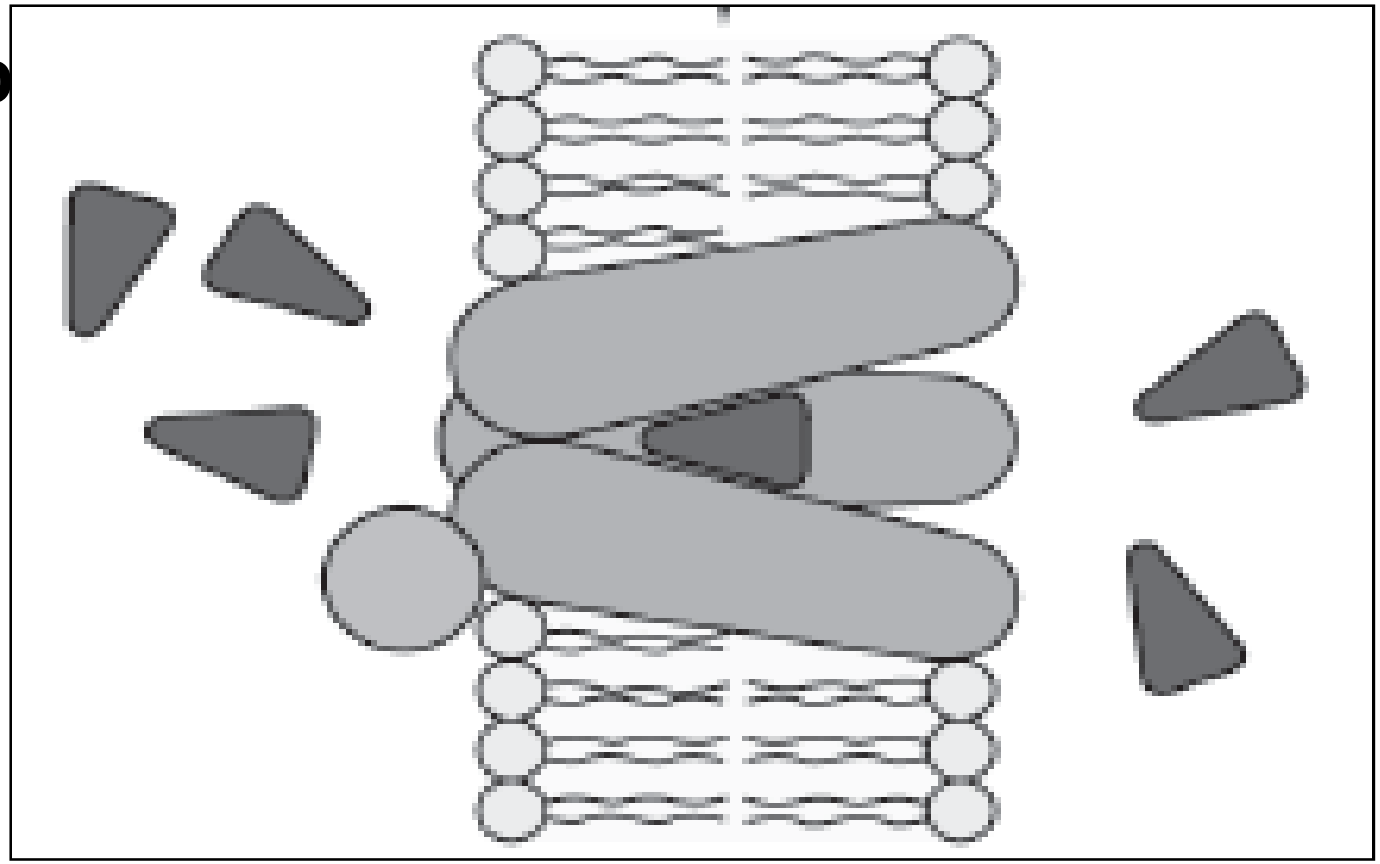
(d) active transport

Step One



Modes in which a toxicant can cross a cell membrane:
(d) active transport

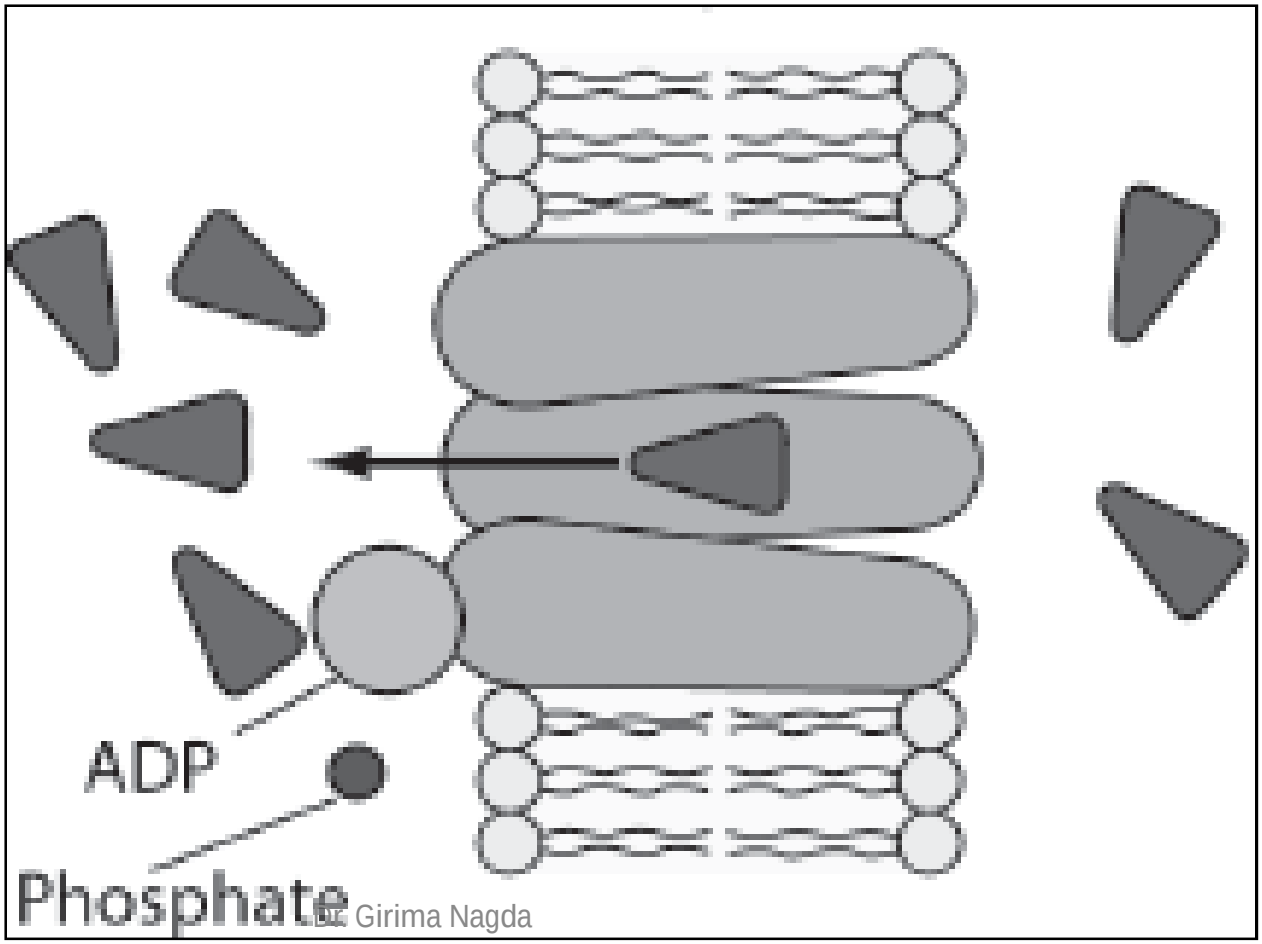
Step Two



Modes in which a toxicant can cross a cell membrane:

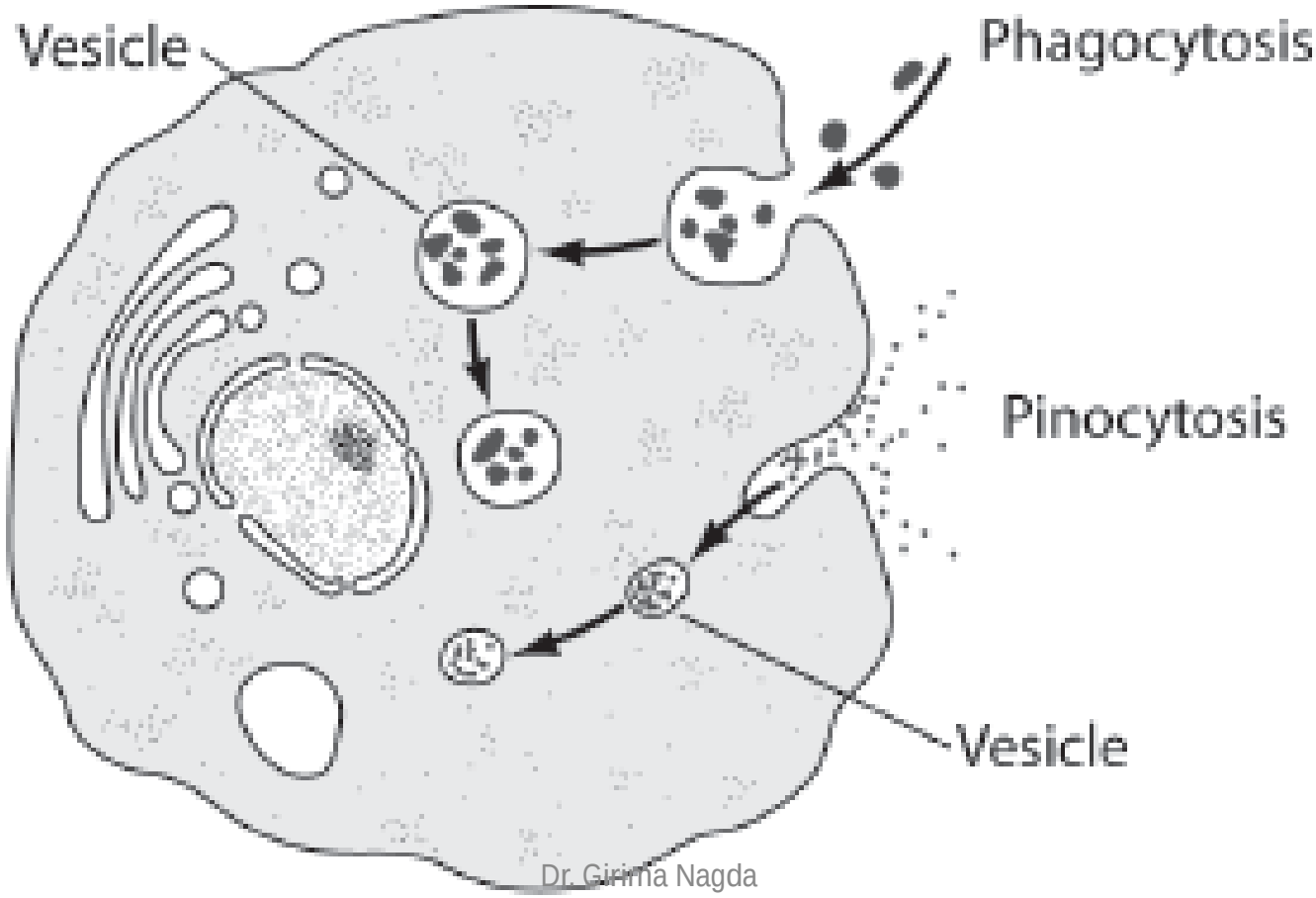
(d) active transport

Step Three



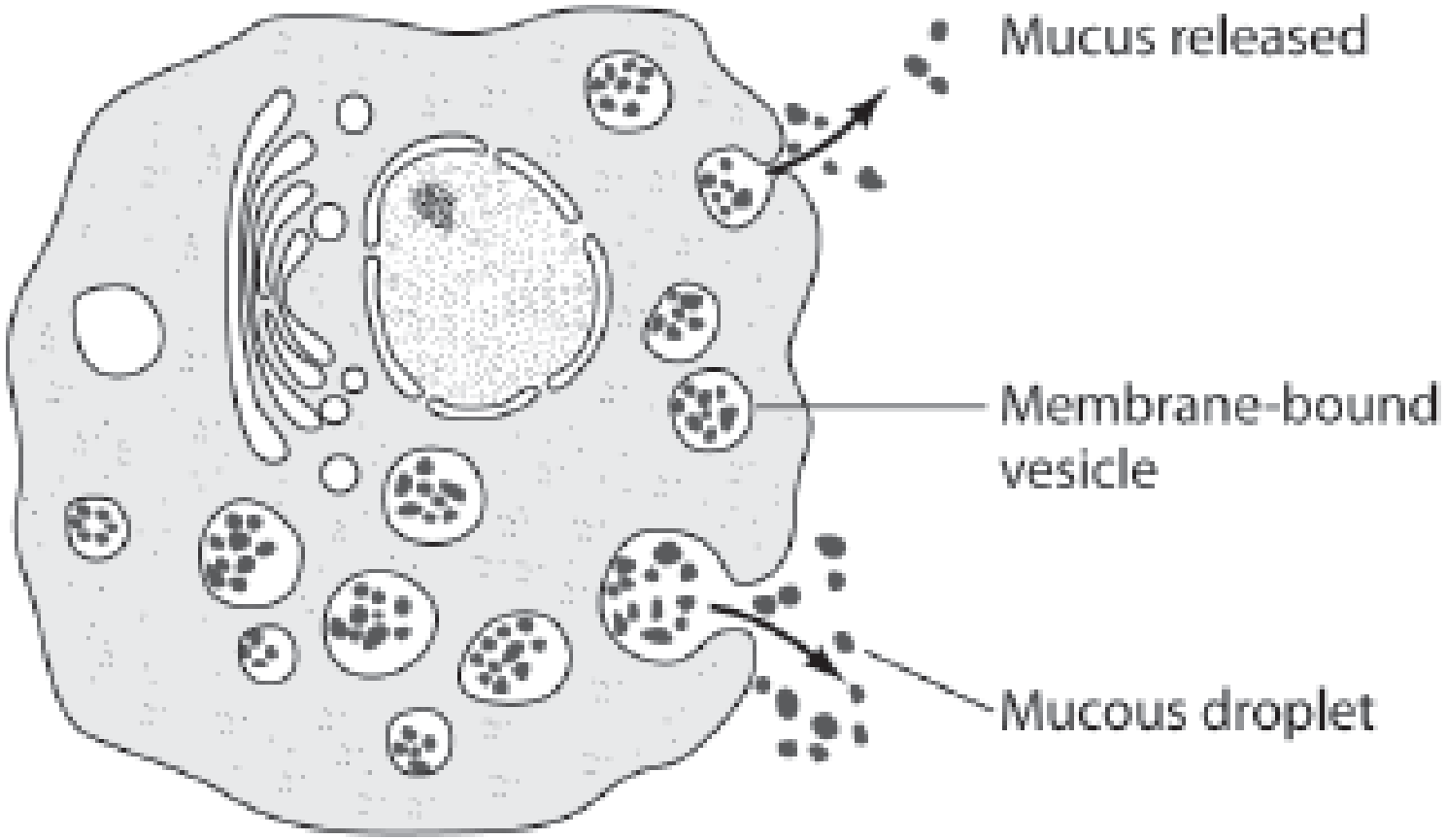
Modes in which a toxicant can cross a cell membrane:

(e) Endocytosis



Modes in which a toxicant can cross a cell membrane:

(f) Exocytosis



2. Factors related with site of exposure

a. Blood flow rate at site of exposure

High perfusion results high rate absorption rate

b. Surface area and permeability

There is a linear relationship between exposed surface area and absorption.

Passive Diffusion is Dependent on 3 Factors

1. Concentration gradient across membrane
2. Lipid solubility of compound
3. Ionization state

Concentration gradient controls rate of diffusion which is governed by Fick's Law

$$\text{Rate of diffusion} = \frac{k\ A\ (c_1 - c_2)}{d}$$

where $(c_1 - c_2)$ = concentration gradient

A = area of membrane

d = thickness of membrane

k = diffusion constant of chemical

3. Dermal (Skin)

√ Human skin comes into contact with many toxic agents such as pesticides and other *environmental and occupational chemicals*.

√ A multilayered barrier not very permeable.

√ The rate-determining barrier is the stratum corneum, the upper layer of epidermis.

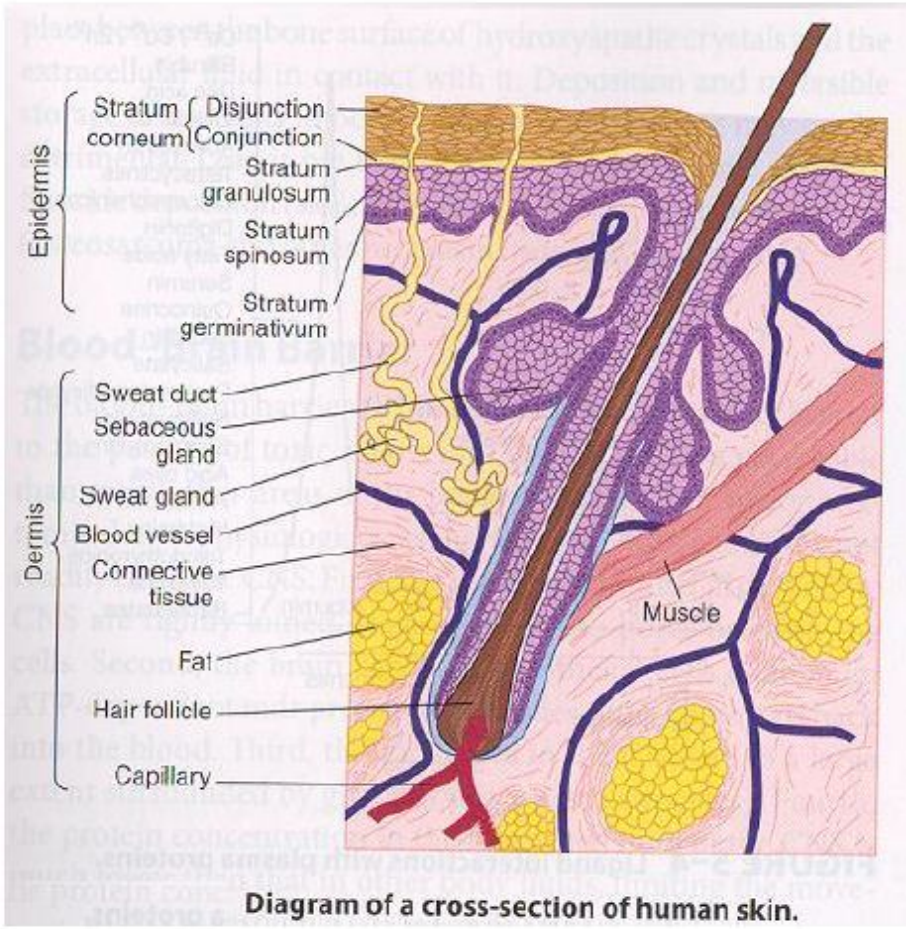


Diagram of a cross-section of human skin.

Factors important here are:

lipid solubility

hydration of skin

site (e.g. sole of feet

The Skin Has Important Roles:

- Barrier against entry of toxicants and microorganisms
- Protects against harmful effects of UV radiation
- Assists in the biotransformation of toxicants
- Eliminates toxicants via sweat or cellular secretion
- Regulates body temperature
- Houses sensory receptors for temperature, pain and pressure

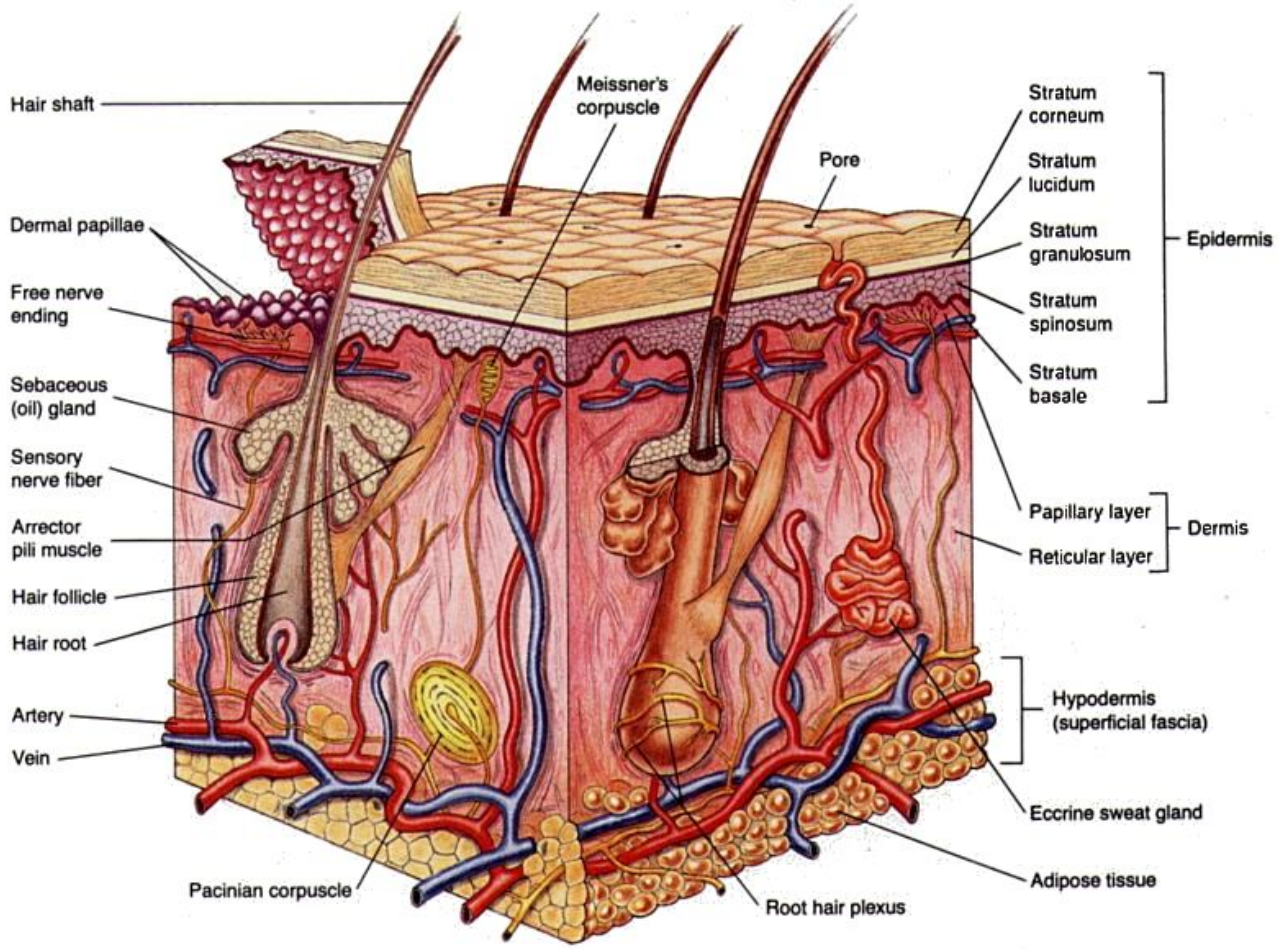
Factors Affecting Absorption through the Skin

How quickly a toxicant diffuses through the epidermis is affected by:

- Dose
- Length of exposure
- Lipid solubility
- Skin location

**Toxicants that are small, non-polar, and lipid-soluble will diffuse most rapidly.

Routes of Exposures: Dermal (skin)

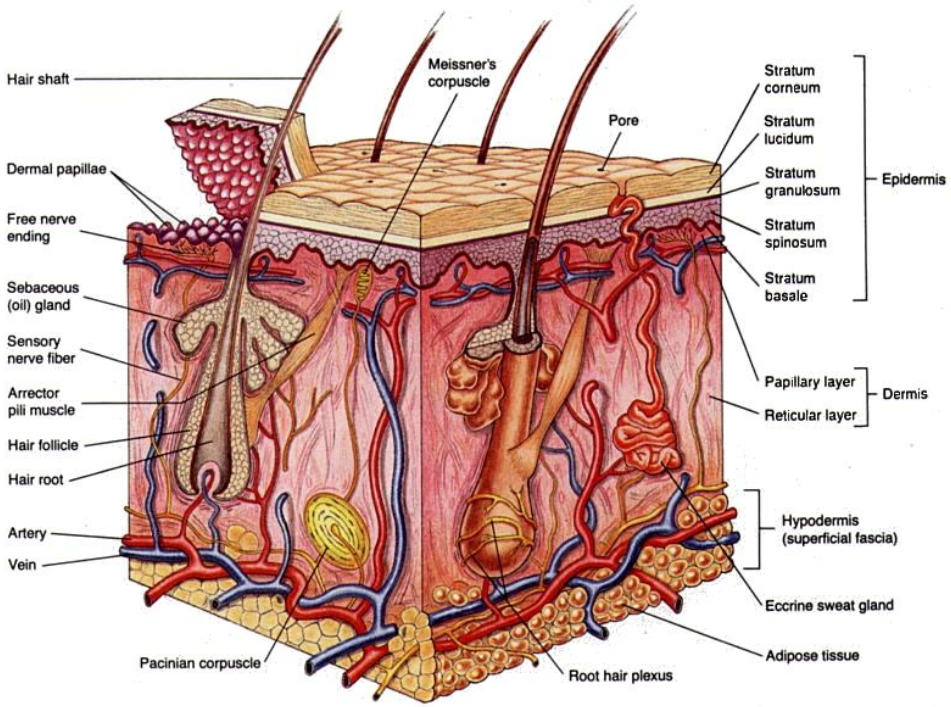


Human skin comes into contact with many toxic agents. Fortunately, the skin is not very permeable and is a good barrier for separating organisms from their environment.

Factors for Dermal Absorption

•To be absorbed through the skin, a toxicant must pass through the epidermis or the appendages (sweat and sebaceous glands and hair follicles).

•Once absorbed through the skin, toxicants must pass through several tissue layers before entering the small blood and lymph capillaries in the dermis.



•The rate-determining barrier in the dermal absorption of chemicals is the epidermis—especially the *stratum corneum* (horny layer), the upper most layer of the epidermis.

•The cell walls are chemically resistant, two-times thicker than for other cells and dry, and in a keratinous semisolid state with much lower permeability for toxicants by diffusion—the *stratum corneum* cells have lost their nuclei and are biologically inactive (dead).

•Once a toxicant is absorbed through the *stratum corneum*, absorption through the other epidermal layers is rapid.

All toxicants move across the *stratum corneum* by passive diffusion

•Polar substances diffuse through the outer surface of protein filaments of the hydrated *stratum corneum*.

•Non-polar molecules dissolve and diffuse through the lipid matrix between protein filaments.

•The rate of diffusion is proportional to lipid solubility and inversely proportional to molecular weight.

Once absorbed, the toxicant enters the systemic circulation by-passing first-pass metabolism.

Factors that Affect *Stratum Corneum* Absorption of Toxicants

1. Hydration of the *stratum corneum*

- The *stratum corneum* is normally 7% hydrated which greatly increases permeability of toxicants. (10-fold better than completely dry skin)
- On additional contact with water, toxicant absorption can increase by 2- to 3-fold.

2. Damage to the *stratum corneum*

- Acids, alkalis and mustard gases injure the epidermis and increase absorption of toxicants.
- Burns and skin diseases can increase permeability to toxicants.

3. Solvent Administration

- Carrier solvents and creams can aid in increased absorption of toxicants and drugs (e.g. dimethylsulfoxide (DMSO)).

Main exposure routes

1. Oral (GI tract)

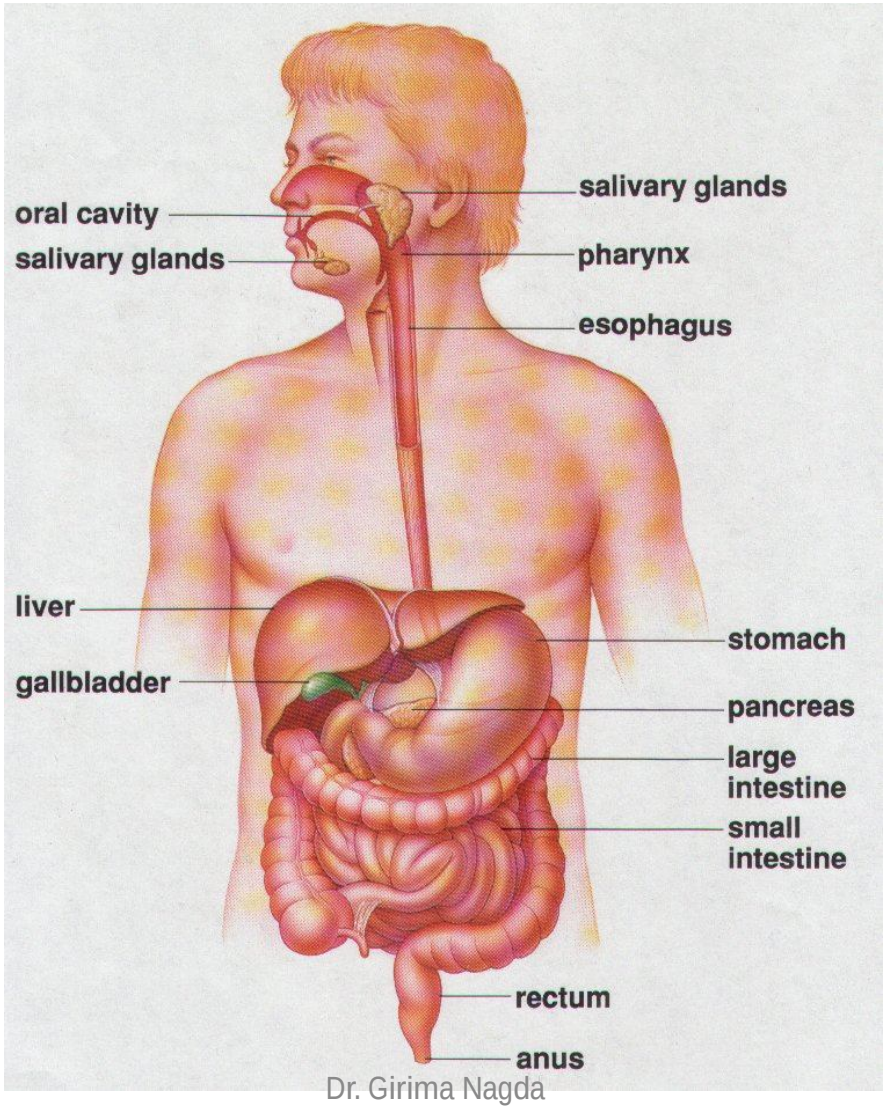
* One of the most important absorption site.

* Important for food/water contaminants and drugs.

* Absorption of xenobiotics can take place along entire GI tract.

* To enter the body via the GIT, chemicals must pass through the GIT lining and capillary membranes before entering the blood.

Digestive System



Digestive System

1. mouth
2. oral cavity
3. esophagus
4. stomach
5. small intestine
6. large intestine
7. rectum
8. Anus

accessory organs, such as pancreas & liver

Absorption Through the Digestive System

1. Takes place anywhere along the digestive system.

2. Mouth and esophagus are not a major site of absorption.

3. Stomach, where food may remain for about 2 hours, is the site where mechanical digestion occurs and where food is chemically broken down.

4. Most absorption occurs in the small intestine.
    - ** Villi structure is important.

5. Large intestine removes liquid from chyme and forms feces. This region lacks villi and it is not considered a major site for absorption of toxicants.

Mouth and oesophagus: Little absorption occurs in here.

Stomach (pH: 1-3):Weak organic acids are absorbed here due to asidic media. (Surface area:<5m^2)

Small intestine(pH:7-8): The greatest absorption of xenobiotics takes place in here (Surface area: 200m^2) particularly alkaline ones and food. The rate of absorption increases with the residency time. The residency time of a xenobiotic in here depends on intestinal motility.

Colon and rectum: Absorption is negligible in here.
(Surface area : <m^2).

Gastrointestinal Absorption

- Chemicals entering the gastrointestinal tract must first cross the mucosa somewhere along the tract before gaining entry into the blood. Only by absorption from the gastrointestinal tract can a chemical exert a toxic effect that could be considered as systemic.
- The degree of absorption is dependent on:
  - Site
  - pH
  - time
  - the physicochemical properties of the chemical

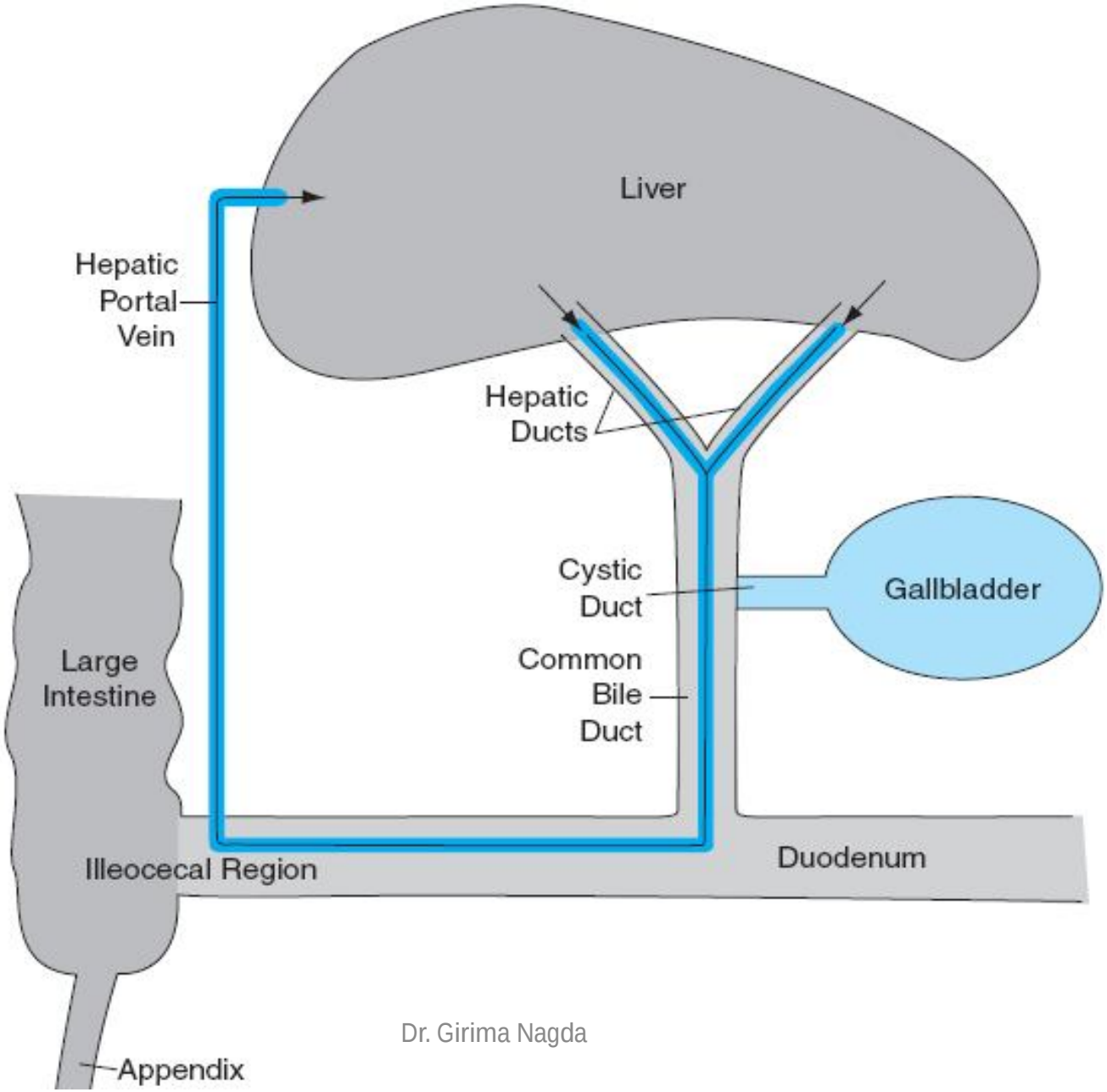
Gastrointestinal Absorption

- Toxicant absorption in the oral cavity and the esophagus is generally poor for many chemicals because of the relatively short residence compared to the slower transport through the stomach and the gastrointestinal tract.
- The absorption of chemicals from the stomach and intestinal tract first pass through the liver circulation before entering into the general circulation of the body, and therefore they cannot escape hepatic metabolism.

Gastrointestinal Absorption

- It is in the liver where a significant amount of toxicant is removed from the venous blood and excreted into the bile, metabolically converted (first-pass metabolism), or stored.
- Unchanged toxicant or its metabolite can be excreted into the bile and back into the small intestine where they may be absorbed (in the case of the first-pass metabolite) or reabsorbed (in the case of the unmetabolized toxicant).
- This process may continue once again and would tend to reduce the rate of elimination of toxicant from the body.
- This is referred to as ***enterohepatic circulation***.

Enterohepatic circulation



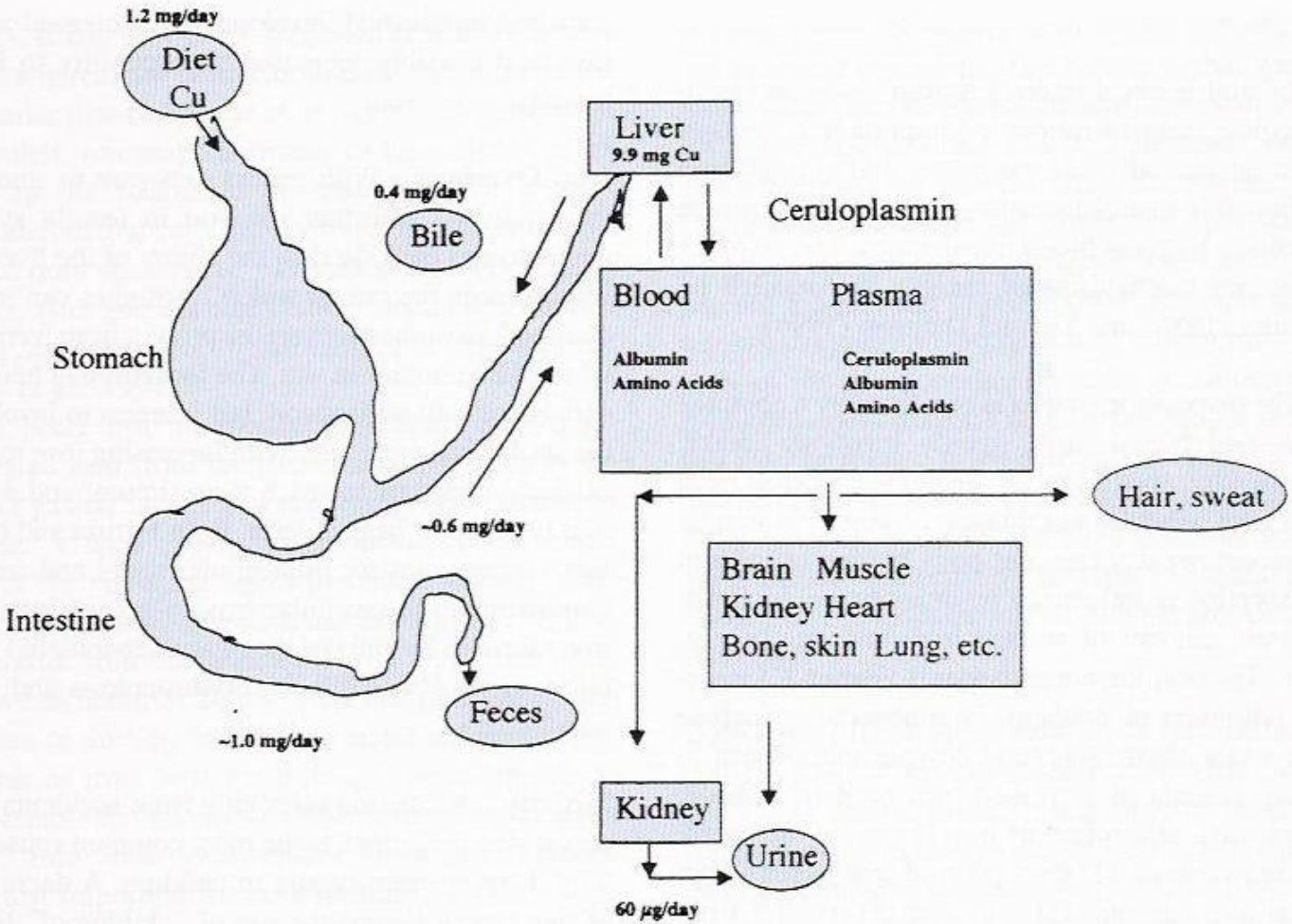
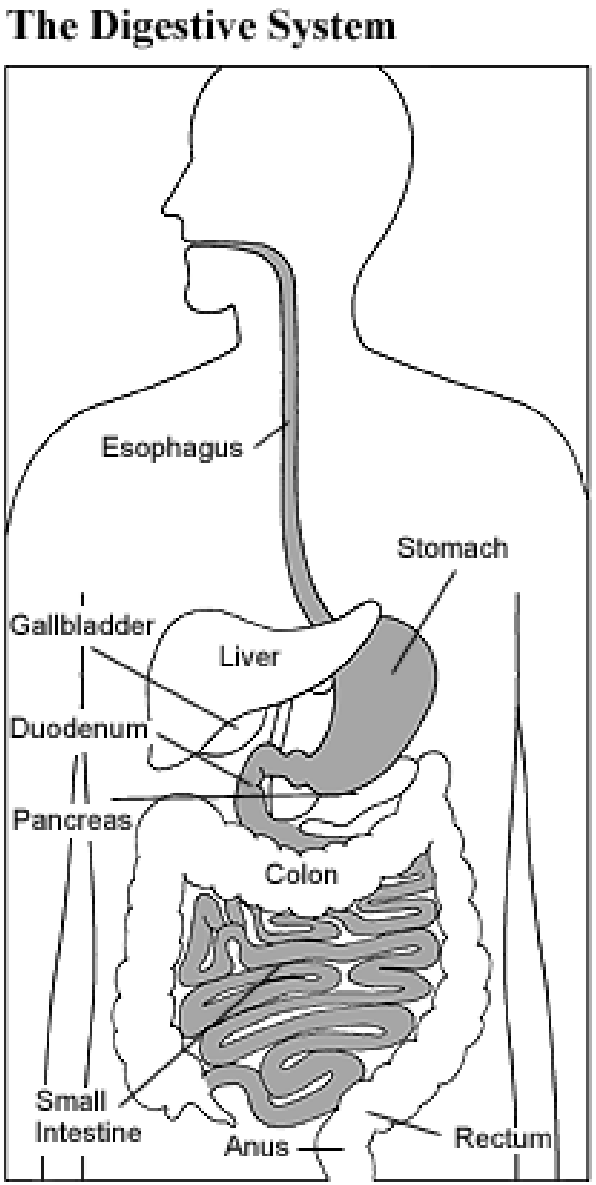


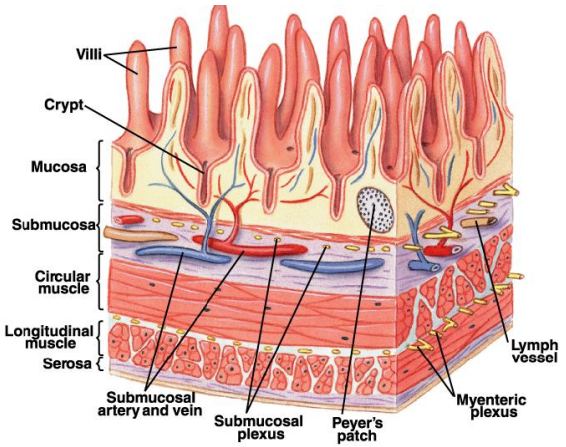
Figure 23-8. Overview of copper absorption, transport, and excretion.

The liver receives copper from the intestine via the portal circulation and redistributes the copper to the tissue via ceruloplasmin, albumin, and amino acids. Approximately half the copper consumed is not absorbed and passes into the feces. Another two-thirds of the daily intake is returned to the liver and released into the bile. Consequently fecal excretion accounts quantitatively for nearly all of the copper consumed as the systems endeavor to stay in balance. A small amount, 60 μg/day, is excreted by the kidney via the urine, and still lesser amounts appear in hair and sweat. This interplay among the various systems maintains homeostasis and balance throughout the organism. The values in the figure are based on a dietary input of 1.2 mg/day. [Adapted from Harris (1997).]

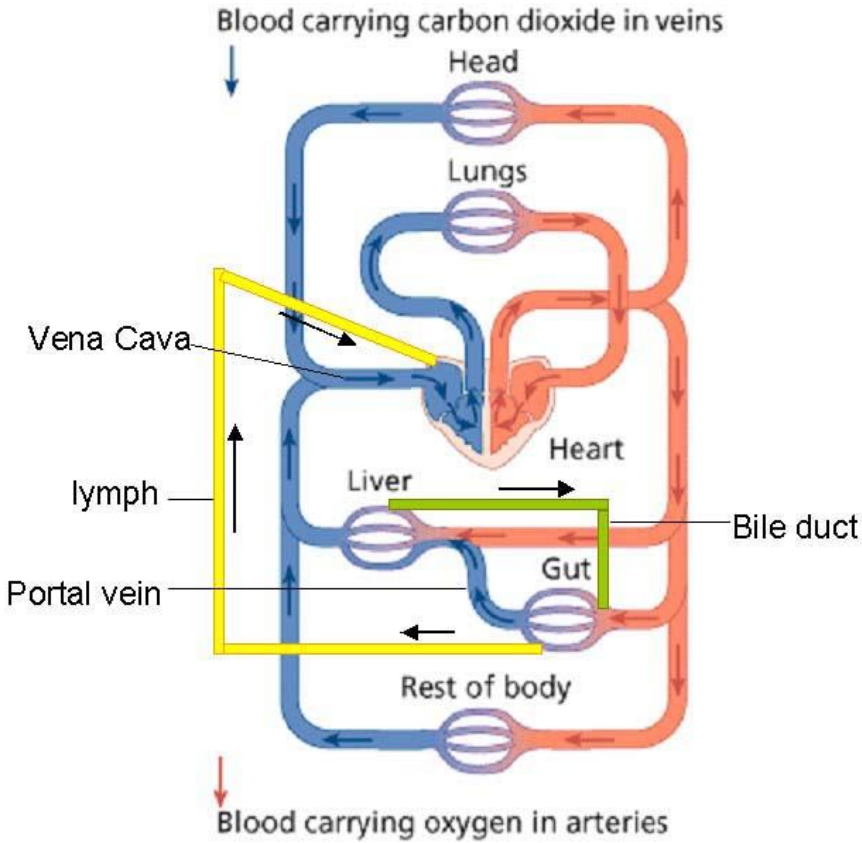
Routes of Exposure: Oral (GI tract)



- GI tract can be viewed as a tube traversing the body.
- Although the GI tract is in the body, its contents can be considered exterior to most of the body's metabolism.
- Unless the toxicant is an irritant or has caustic properties, poisons in the GI tract do not produce systemic injury <u>until absorbed.</u>
- Absorption can occur anywhere in the GI tract including the mouth and rectum.
- Initial metabolism can occur in gastric cells.

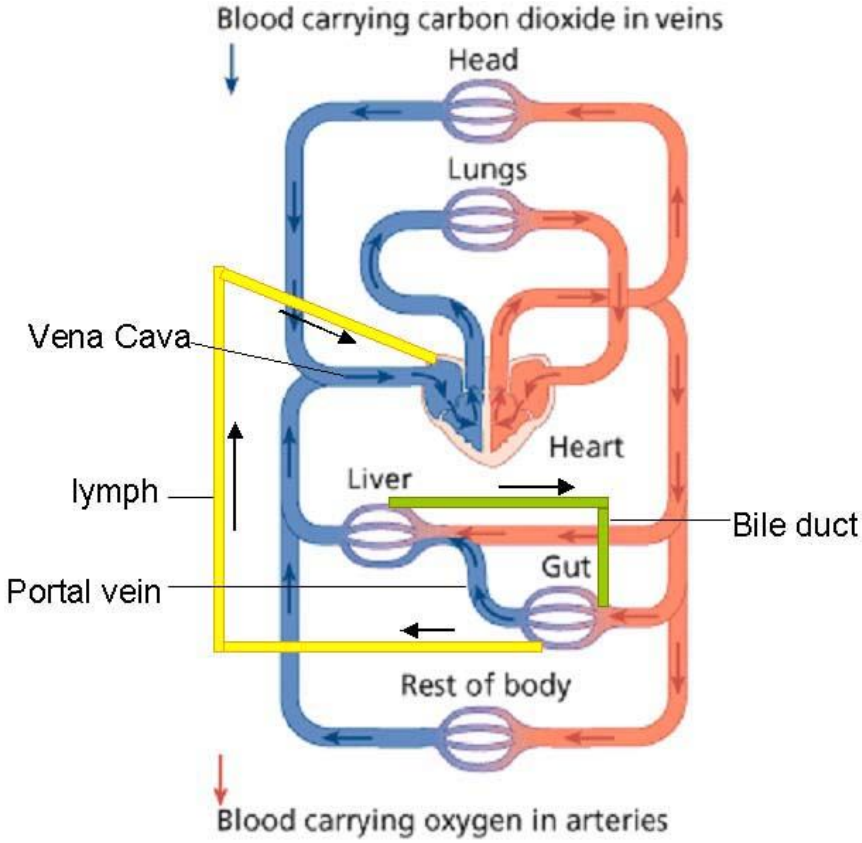


GI Tract Absorption



- **<u>Weak acids and bases</u>** will be absorbed by simple diffusion to a greater extent in the part of the GI tract in which they exist in the most lipid-soluble (non-ionized) form—hydrophilic substances will be transported to the liver by the portal vein
- **<u>Highly hydrophilic substances</u>** may be absorbed through transporters (xenobiotics with similar structures to endogenous substrates).
- **<u>Highly hydrophobic compounds</u>** may be absorbed into the lymphatic system via chylomicrons and drained into venous circulation near the heart.
- **The greatest level of absorption** for most ingested substances occurs in the small intestine.

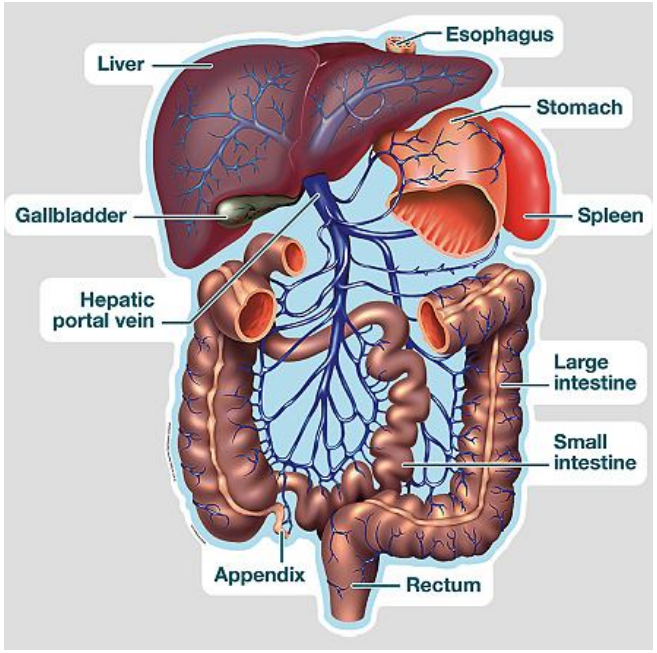
Polar versus Nonpolar GI Absorption



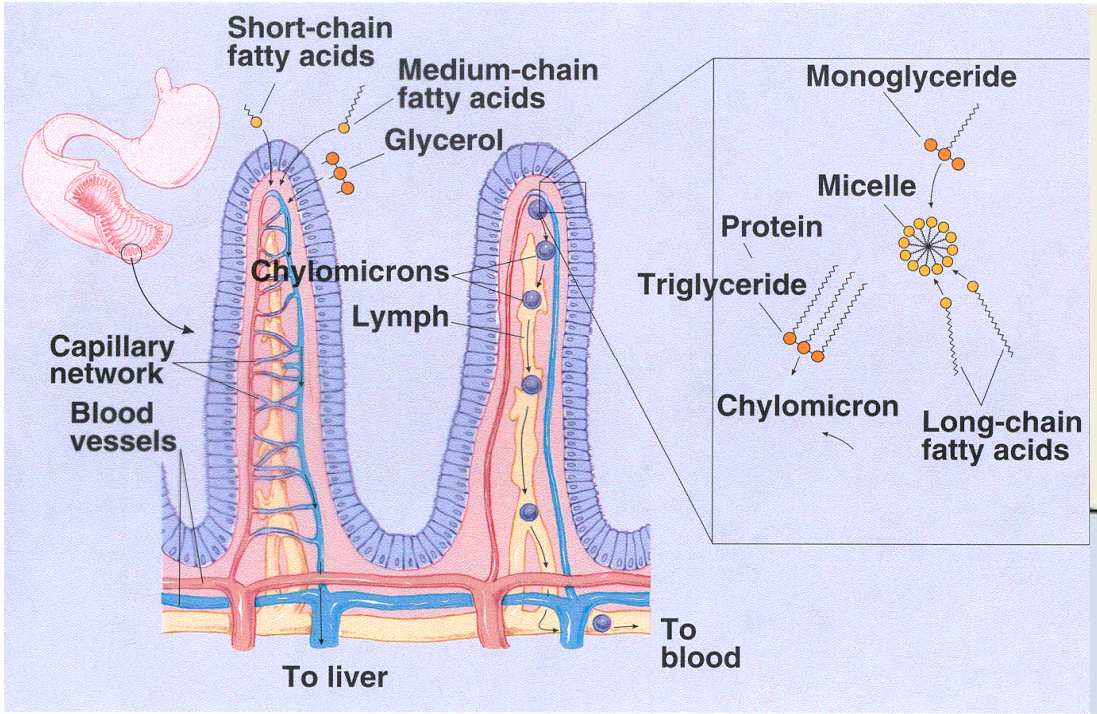
<u>Polar substances</u> that are absorbed:

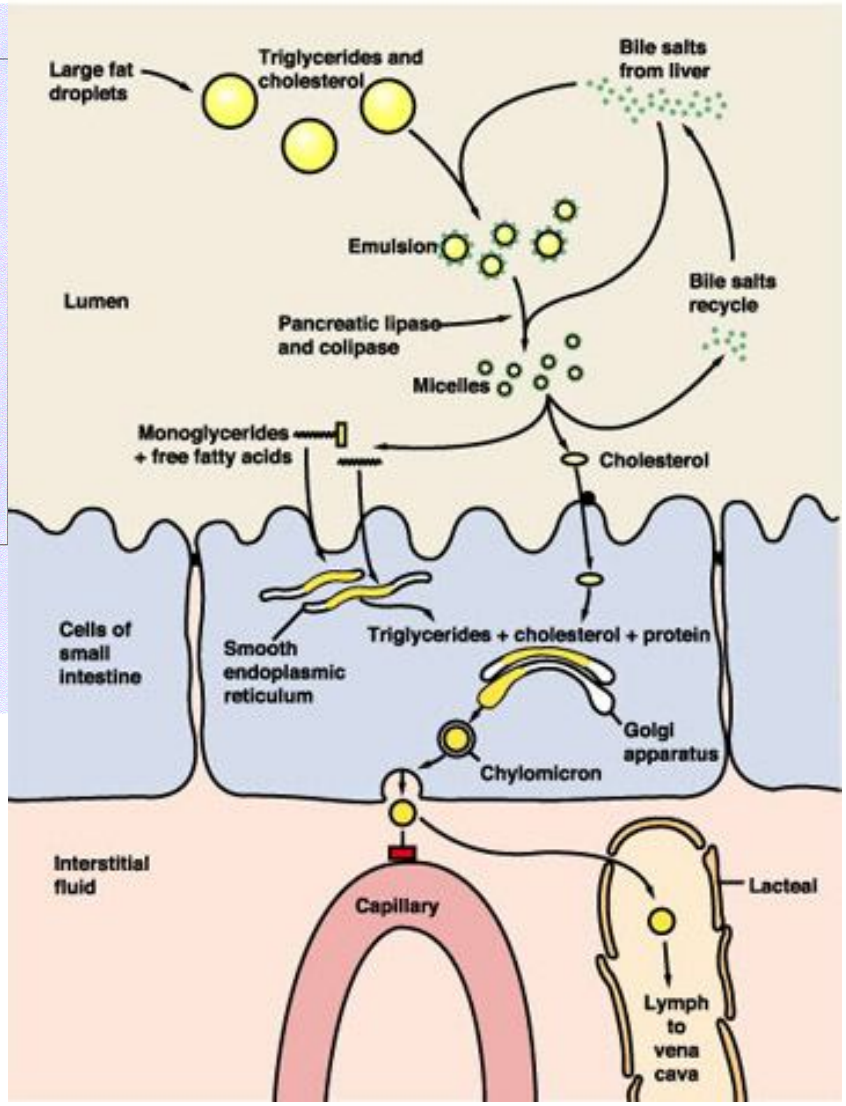
1. go to the liver via the **<u>portal vein.</u>**
2. may undergo **<u>first-pass metabolism</u>** or **<u>presystemic elimination</u>** in gastric and/or liver cells where xenobiotics may be biotransformed.
3. can be excreted into the bile without entrance into the systemic circulation or enter the systemic circulation.

The liver and first-pass metabolism serve as a defense against most xenobiotics. The liver is the organ with the highest metabolic capacity for xenobiotics.



Polar versus Non-Polar GI Absorption





<u>Lipophilic, non-polar substances (e.g. polycyclic aromatic hydrocarbons)</u>

1. Ride on the "coat-tails" of lipids via micelles and follow lipid absorption to the lymphatic system (via chylomicrons) to the lungs.

2. Non-polar substances may by-pass first-pass metabolism. e.g. PAH have selective toxicity in the lung, where they may be metabolically activated.

- The presence of microvilli in the intestine is an increase of 600 - fold in **SURFACE AREA** compared to a hollow tube of comparable length.
- There is no absorption, except for water, in the large intestine.
- Most of the absorption is by **PASSIVE DIFFUSION**, except for nutrients; glucose, amino acids, and drugs that look like these substances are taken up by active transport.
- Lipophilic toxicants are presented as emulsions, and brought into solution through the action of detergent - like bile acids. The product of this mixing is large surface area micelles (hydrophobic interior) that deliver the lipids to the brush border of the intestine for diffusion across the membrane.
- Very strong bases and strong acids are not readily absorbed in the GIT.
- The smaller the **PARTICLE SIZE** of the toxicant, the greater the absorption

GIT MOTILITY has a significant effect on absorption. For example, excessively rapid movement of gut contents can reduce absorption by reducing residence time in the GIT, while the presence of food in the stomach can delay the progress of drugs from the stomach to the small intestine where most of the absorption will occur.

Increased **BLOOD FLOW** after a meal can result in absorption of several drugs but in hypovolemic states, absorption can be reduced.

Biotransformation in the GIT prior to absorption can have a signifi cant impact on bioavailability of a toxicant.

B. Respiratory System

The respiratory system is composed of three anatomical regions:

1. **Head airways region:**
   - Nose
   - Mouth
   - Larynx
   - Pharynx
2. **Tracheobronchial region**
   - Trachea
   - Bronchi
   - Bronchioles
3. **Alveolar (gas exchange) region**
   - Terminal bronchioles
   - Alveoli

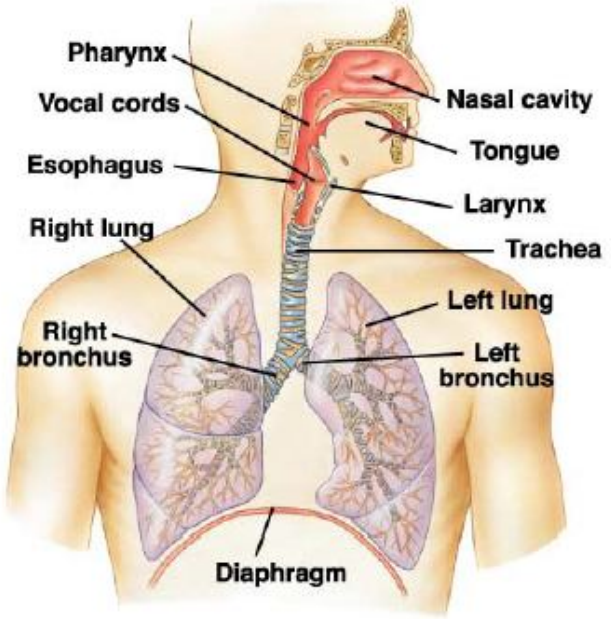
Routes of Exposure: Inhalation (Lung)

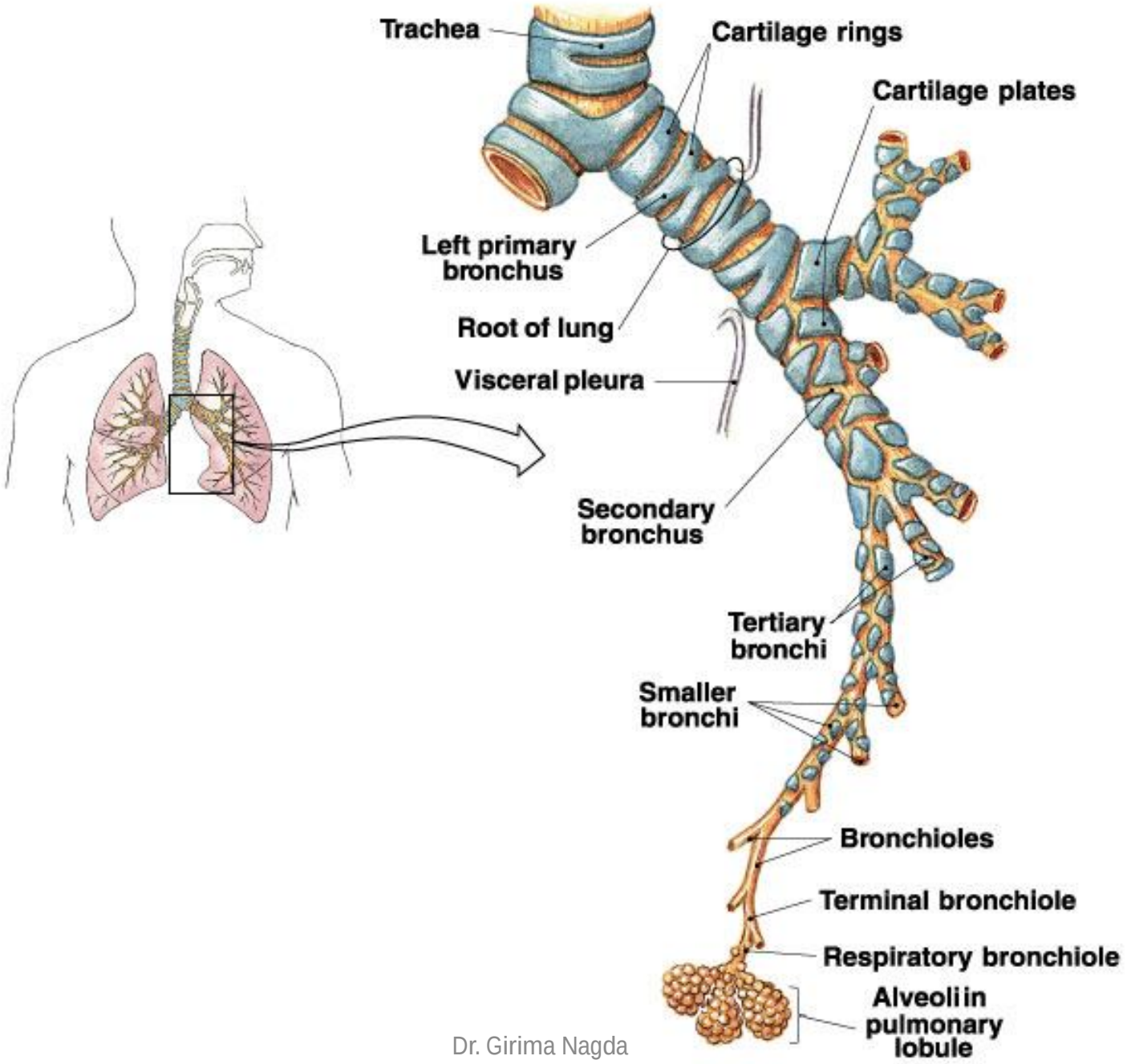
Toxicants absorbed by the lung are:

1. Gases (e.g. carbon monoxide, nitrogen dioxide, sulfur dioxide, phosgene)
2. Vapors or volatile liquids (e.g. benzene and carbon tetrachloride)
3. Aerosols

The respiratory system

The respiratory system consists of the upper respiratory system (mouth, nasal cavity, pharynx, larynx) and the lower respiratory system (trachea, bronchi, lungs). The lower respiratory system is enclosed in the thorax, bounded by the ribs, spine, and diaphragm.

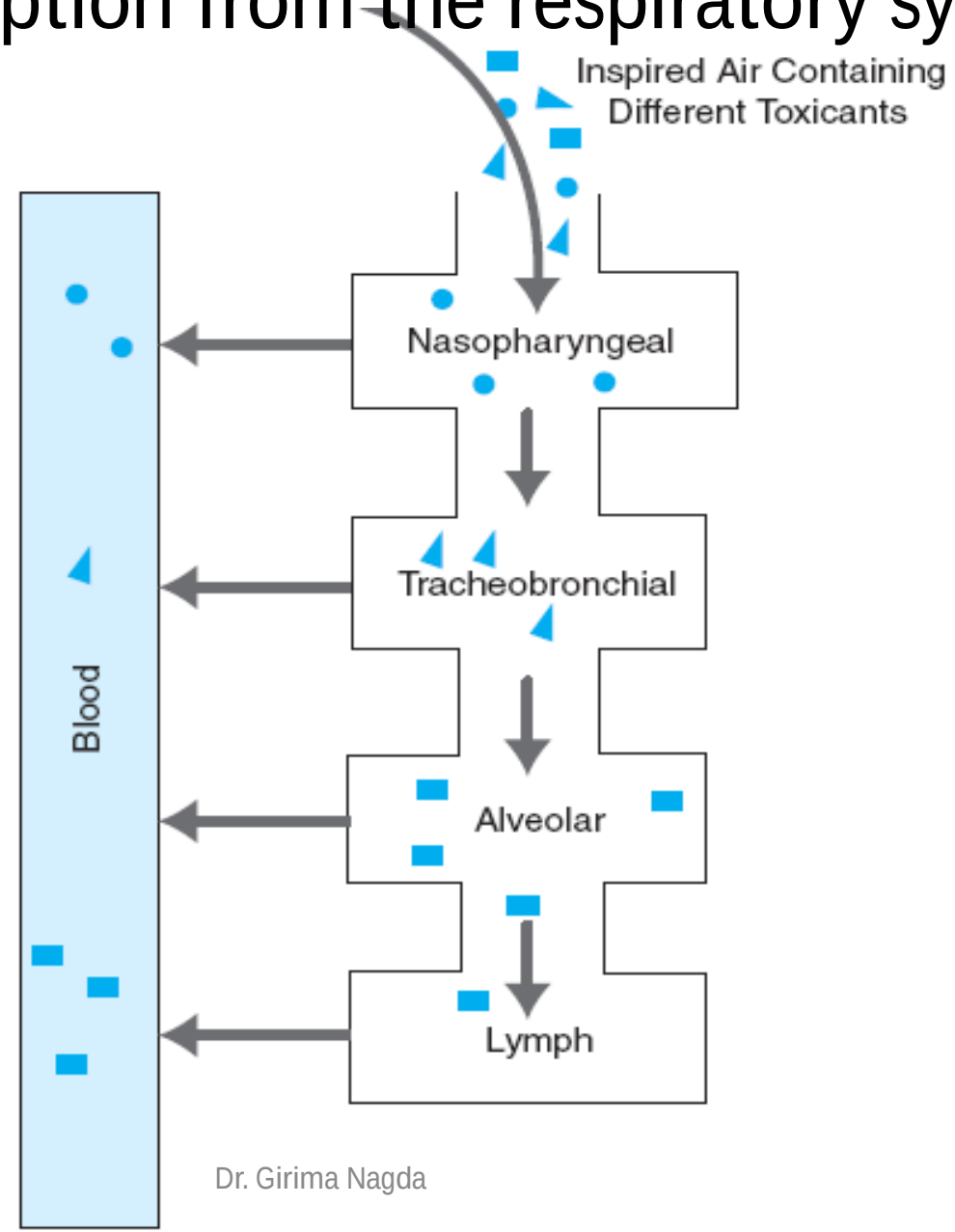



Trachea
Cartilage rings
Cartilage plates
Left primary bronchus
Root of lung
Visceral pleura
Secondary bronchus
Tertiary bronchi
Smaller bronchi
Bronchioles
Terminal bronchiole
Respiratory bronchiole
Alveoli in pulmonary lobule

Respiratory Absorption

- The respiratory system constitutes a very important route of exposure for airborne contaminants (e.g., toxic gases, particulates, aerosols, volatile organic solvents).
- Toxicants that are contained within our breathing zone may be absorbed in the nasopharyngeal, tracheobronchial, or pulmonary exchange surfaces of the lungs, depending on the physical and chemical properties of the toxicant.

Toxicant absorption from the respiratory system



Respiratory Absorption

- A rapidly absorbed toxicant is quickly distributed throughout the body.
  - Consider the rapidity of poisonings that can occur from respiratory exposure to nitrous oxide (laughing gas), hydrocyanic acid (HCN), ether, or chloroform.
- Lipophilic and low-molecular-weight gases are quickly absorbed.
  - The greater the degree of lipophilicity, the greater the potential rate of absorption.
  - For hydrophilic chemicals the rate of absorption decreases with increasing molecular size.

Respiratory Absorption

- For volatile chemicals one can experimentally measure the retention of the chemical in the body by measuring the difference in the concentration between inspired and expired air.
- Particles are also taken into the respiratory system during breathing; depending on the characteristics of the particulates and their interaction with the cells in the lungs, this determines the extent of their retention, absorption, and potential to produce local or systemic toxicity.

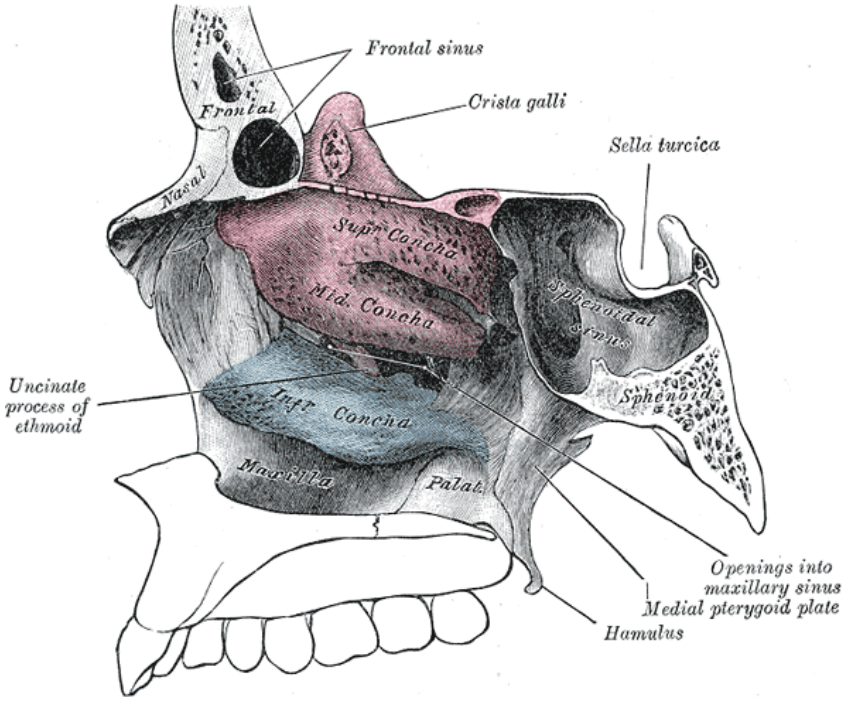
Respiratory Absorption

- In the lungs pulmonary macrophages can engulf particulates, some of which may be cleared into the lymphatic system, or may remain within the lungs for an indefinite period of time, as is the case for asbestos and coal dust.
- Material that remains within the respiratory system may produce local toxicity in which they take the form of:
  - lung cancer, chronic bronchitis, lung fibrosis, and emphysema

Gases and Vapors

The absorption of inhaled gases and vapors starts in the nasal cavity which has:

1. Turbinates, which increase the surface area for increased absorption (bony projections in the breathing passage of the nose improving smell).
2. Mucosa covered by a film of fluid.



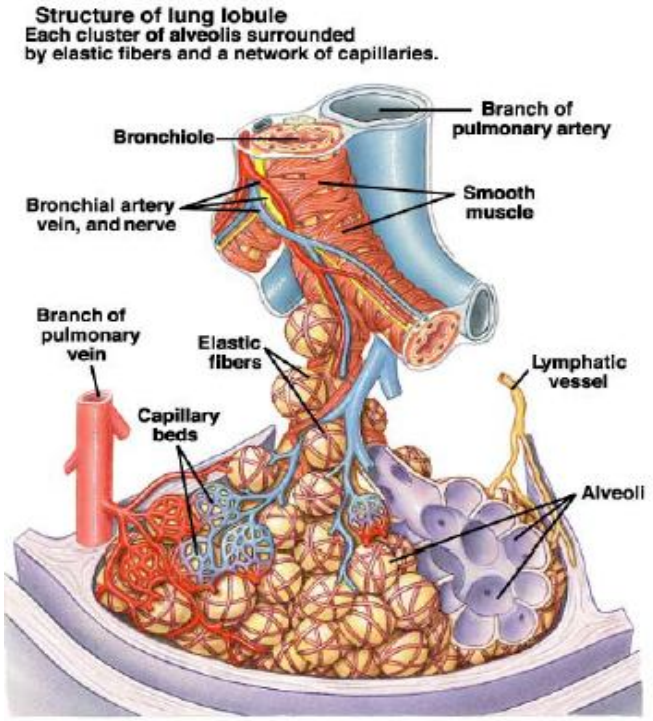
3. The nose can act as a “scrubber” for water-soluble gases and highly reactive gases, partially protecting the lungs from potentially injurious insults (e.g. formaldehyde, SO_2).
   -Rats develop tumors in the nasal turbinates when exposed to formaldehyde.

Absorption of Gases

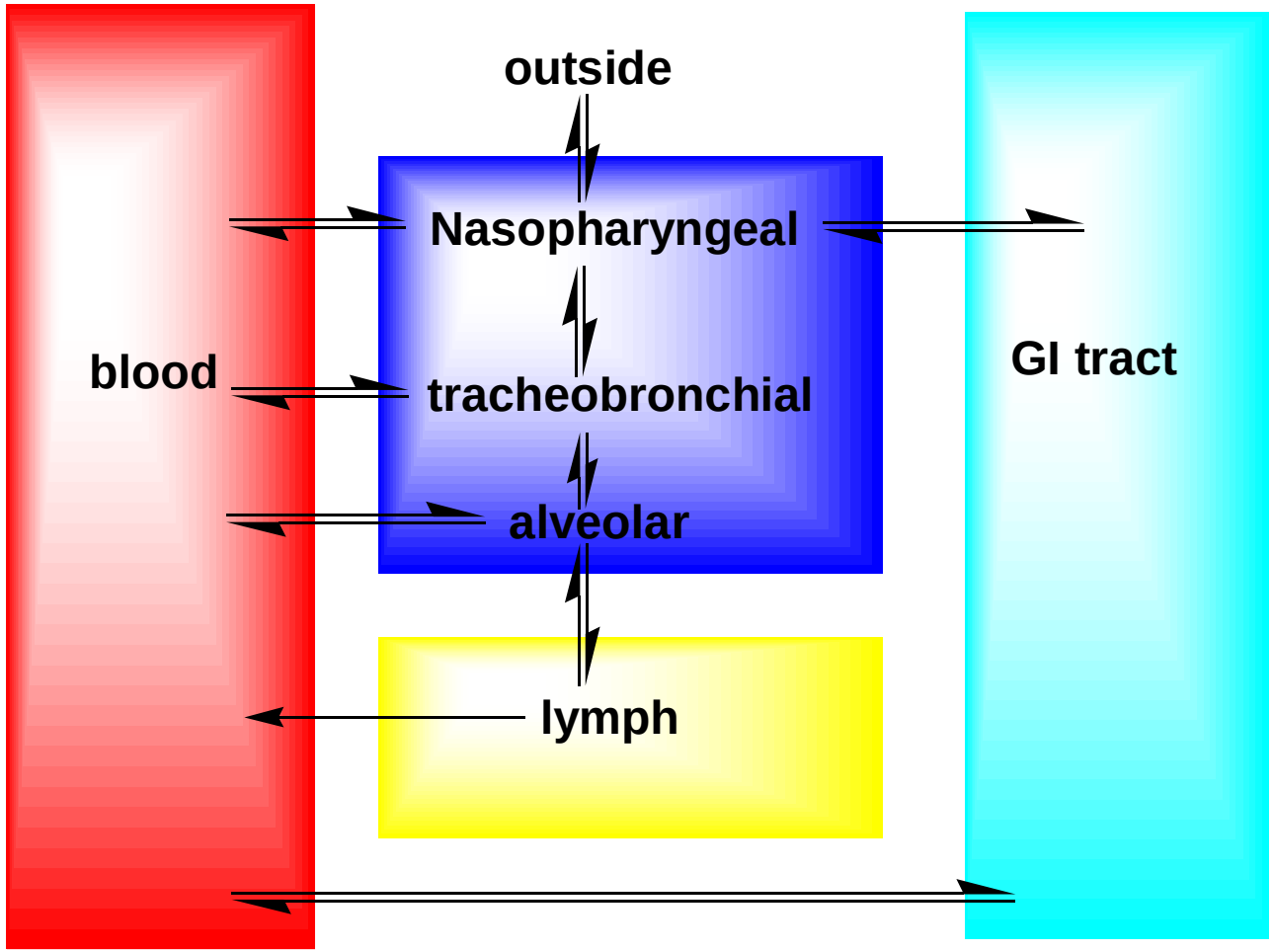
Absorption of gases differs from intestinal and percutaneous absorption of compounds because:

1. Ionized molecules are of very low volatility, so their ambient air concentration is insignificant.

2. Epithelial cells lining the alveoli (type I pneumocytes) are very thin and the capillaries are in close contact with the pneumocytes, so the diffusion distance is very short.



3. Chemicals absorbed by the lungs are rapidly removed by the blood (3-4 seconds for blood to go through lung capillary network).



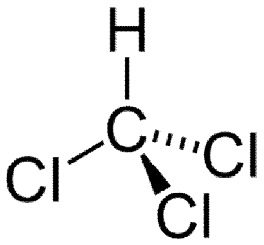
• When a gas is inhaled into the lungs, gas molecules diffuse from the alveolar space into the blood and then dissolve.

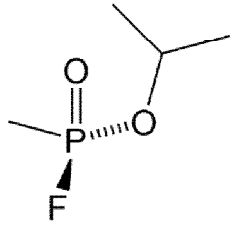
• The gas molecules partition between the air and blood during the absorptive phase, and between blood and other tissues during the distributive phase.

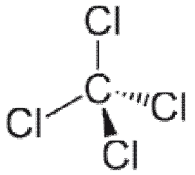
•Note that **<u>inhalation bypasses first-pass metabolism.</u>**

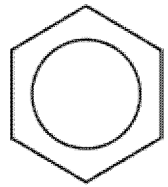
Examples of Toxicant Gases or Volatile Liquids

1. **Carbon monoxide**—binds hemoglobin (with >200x affinity compared to O2) and displaces oxygen leading to impaired oxygenation of tissues, energy impairment, and death
2. **Chloroform**—anesthetic that depresses the nervous system, but can also be metabolized to phosgene, a reactive metabolite that modifies proteins and causes toxicity in lung, kidney, and liver.
3. **Sarin gas—**chemical warfare agent (recently used in Syria) that causes excessive neuronal excitation, convulsions, seizures, tearing, salivation, suffocation, and death through inhibition of acetylcholinesterase
4. **Carbon tetrachloride—**volatile liquid used widely as a cleaning agent and refrigerant, currently banned—greenhouse gas and carbon tetrachloride can be bioactivated in the liver to produce a potent hepatotoxin
5. **Benzene—**largely found in crude oil, but also found in tobacco smoke and used to be found in glues, paints, and detergents—benzene metabolism leads to bioactivated carcinogens that cause leukemia









Aerosols and Particles

Size Location of Absorption

>5 µm Deposited in nasopharyngeal region (or mouth).

1. Removed by nose wiping, blowing or sneezing.
2. The mucous blanket of the ciliated nasal surface can propel insoluble particles by movement of cilia and be swallowed.
3. Soluble particles can dissolve in mucus and be carried to the pharynx or nasal epithelia and into blood. (asbestos-lung cancer)

2-5 µm Deposited in tracheobronchiolar regions of the lungs.

1. Cleared by retrograde movement of mucus layer in ciliated portion of respiratory tract.
2. Coughing can increase expulsion rate.
3. Particles can be swallowed and absorbed from the GI tract. (asbestosis—lung fibrosis, wheezing)

<1 µm Penetrates to alveolar sacs of lungs and is absorbed into blood or cleared through lymphatic system after being scavenged by alveolar macrophages. (asbestos and silica dust can cause silicosis—cough, shortness of breath, inflammation, immunodeficiency through damaging pulmonary macrophages)

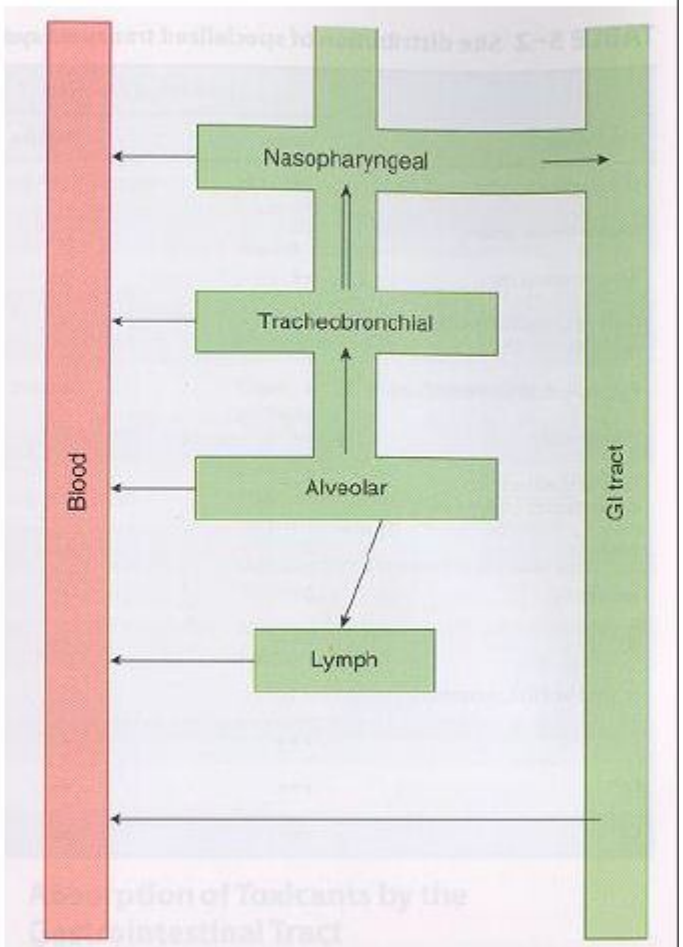
Inhalation (lung:respiratory tract)

√ Xenobiotics such as gases, vapors of volatile liquids and aerosols are absorbed by this route.

√ The absorption of gas depends on its solubility in blood.

√ The physical form and particle size of the xenobiotic determines penetration.

√ *Particular very small particles (<1 µm in diameter)* are able to reach alveoles and can enter bloodstream.



Schematic diagram of the absorption and translocation of chemicals by lungs.

Special Routes of Exposure

Toxicants usually enter the bloodstream after absorption through the skin, lungs or GI tract. Special routes include:

1. Subcutaneous injection (SC) (under the skin)

   -by-passes the epidermal barrier, slow absorption but directly into systemic circulation; affected by blood flow

2. Intramuscular injection (IM) (into muscle)

   -slower absorption than IP but steady and directly into systemic circulation; affected by blood flow

3. Intraperitoneal injection (IP) (into the peritoneal cavity)

   -quick absorption due to high vascularization and large surface area

   -absorbed primarily into the portal circulation (to liver—first-pass metabolism) as well as directly into the systemic circulation.

4. Intravenous injection (IV) (into blood stream) -directly into systemic circulation

Other Exposure Routes

- Intravenous and intraarterial routes provide direct entry of chemicals into the blood vascular system.
  - This is important clinically when rapid action must be taken to stabilize a patient.
  - This exposure pathway results in 100% of the dose being absorbed.
- Injection of a chemical into the skin is a method to facilitate its systemic absorption.
  - Both intradermal and subcutaneous injections are common clinical routes for the delivery of chemicals.
  - Systemic absorption via intradermal injection is generally much slower than by subcutaneous injection because the tissue here is very well vascularized, thus facilitating rapid absorption into the systemic circulation.

Other Exposure Routes, cont.

- Injection directly into the muscle is referred to as intramuscular and is a common route for the delivery of many pharmaceuticals and vaccines.
  - Skeletal muscle is well vascularized, and absorption via this route of administration is comparable with the subcutaneous route.
- The direct injection of chemicals into the body by any route is referred to as a parenteral route of delivery.
  - In laboratory studies, animals are often injected with chemicals directly into either the abdominal cavity or into the chest cavity, and these methods are referred to as intraperitoneal and intrapleural injections, respectively.
  - These exposure routes, rarely used clinically, generally result in a relatively slow absorption of chemicals into the blood.

Absorptive surface area in GIT

REGION	ABSORPTIVE SURFACE AREA (%)
• Mouth	0.02
• Stomach	0.10-0.20
• Small Intestine	100
• Large intestine	0.50-1.0
• Rectum	0.04-0.07

Transport mechanism of toxicant

Mechanism	Nature of substance
• Diffusion through lipid membrane	Hydrophobic
• Diffusion through pores	Small hydrophilic
• Filtration	Small hydrophilic
• Facilitated diffusion	substances that can bind to carriers
• Active Transport	substances that can bind to carriers
• Phagocytosis & Pinocytosis	Macromolecules

Summary on Absorption

- Route of exposure and physicochemical properties of xenobiotic determine how a chemical is absorbed and whether it goes through first-pass metabolism or is subjected to systemic circulation.
- Rate of absorption depends on :
  - Nature of chemical
  - Site of administration (Absorption through skin very slow, lungs very rapid through GIT complex)
  - degree of ionization (Highly polar are absorbed slowly but eliminated rapidly)
  - lipid solubility of chemicals (Lipophilic: absorbed rapidly, eliminated slowly)
  - For exposure to aerosols and particles, the size and water solubility are important.
  - For dermal absorption, polarity, molecular weight and carrier solvent of the toxicant and hydration of the epidermis are important.
  - Extent of absorption depends on the bioavailability of the substance (fraction of dose absorbed into the circulation from the site of exposure)

- In general, absorption follows either:
  - **First order process**: at low doses, rate of reaction is directly proportional to amount of toxicant present
  - **Zero order reaction**: as the concentration of substances increases, a point may be reached at which there no further increase in rate of absorption