Unit 2b: EXCRETION OF DRUGS

By

Ms.M.Gayathri Mpharm (PhD)

Department of Pharmaceutics

Krishna Teja Pharmacy college

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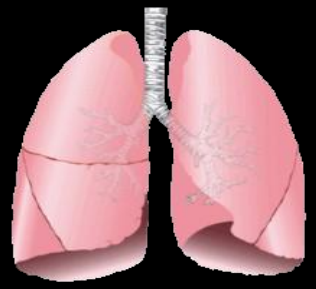
Excretion, along with metabolism and tissue redistribution, is important in determining both the duration of drug action and the rate of drug elimination.



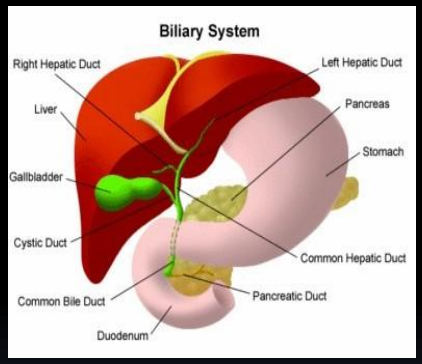
The irreversible loss of drug from the body

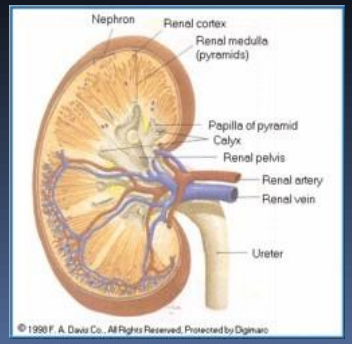
- primarily via kidney and bile (feces, sweat, saliva, tears, expired air & breast milk to lesser degrees)

NOTE: **Excretion ≠ Elimination**

Excretion:	irreversible loss of drug from body
Elimination:	irreversible loss of parent drug by metabolism and/or excretion

∴ Elimination = Metabolism &/or Excretion





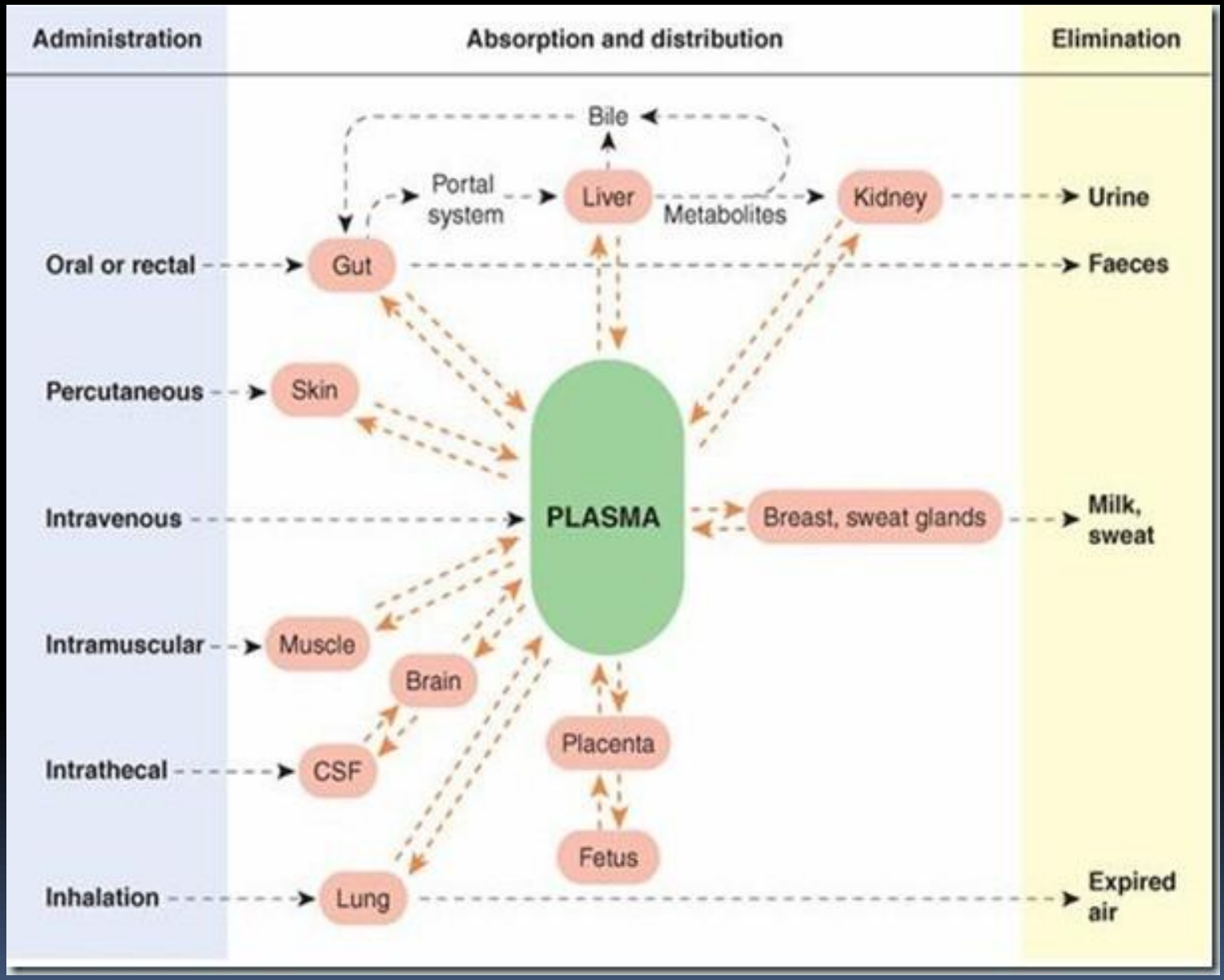
Routes of Excretion

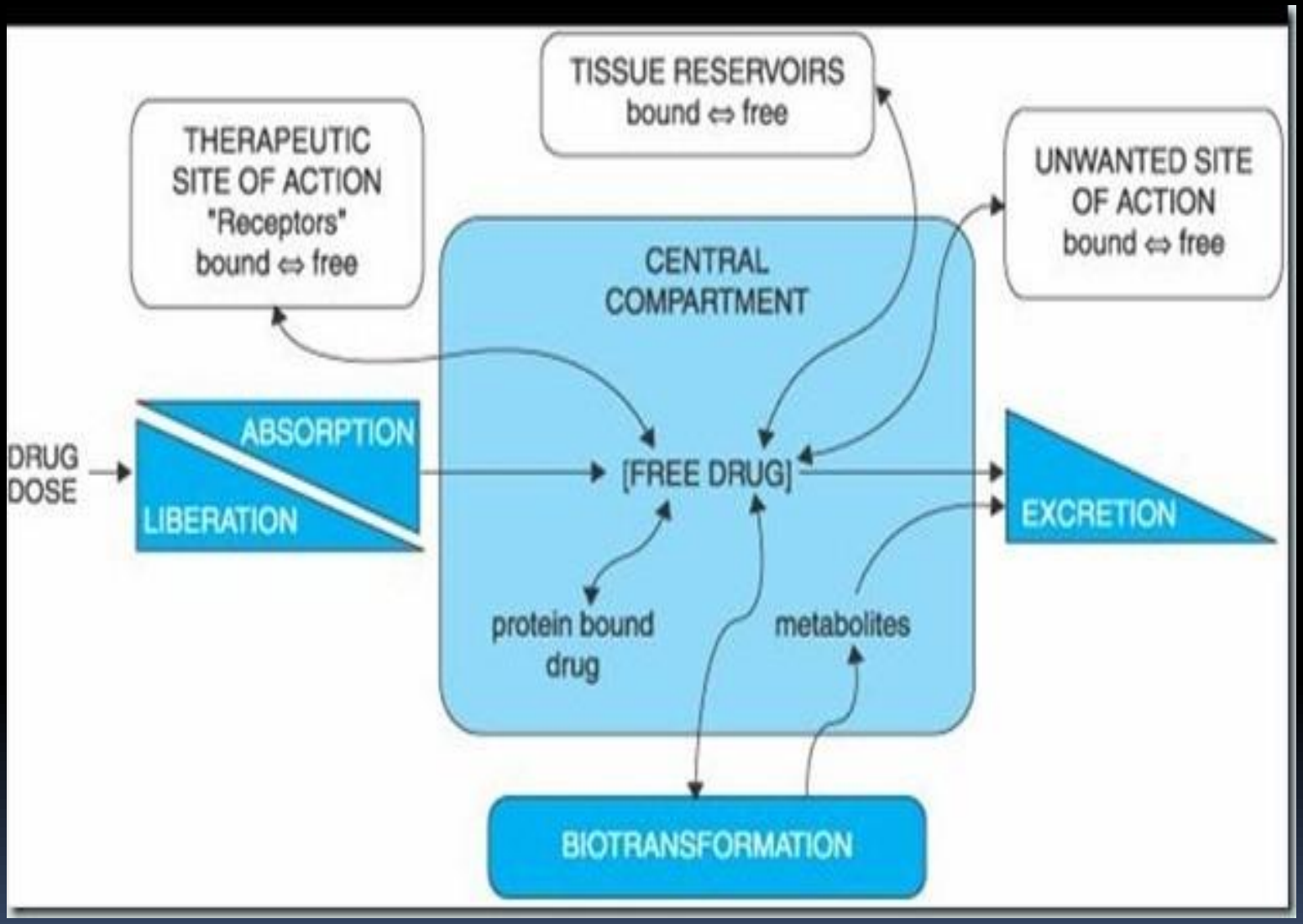
Main Routes of Excretion

- Renal Excretion
- Biliary Excretion

Minor Routes of Excretion

- Exhaled air (Exhalation)
- Salivary
- Sweat
- Milk
- Tears


Administration
Absorption and distribution
Elimination
Bile
Portal system
Liver
Metabolites
Kidney
Urine
Oral or rectal
Gut
Faeces
Percutaneous
Skin
PLASMA
Intravenous
Breast, sweat glands
Milk, sweat
Intramuscular
Muscle
Brain
Placenta
Intrathecal
CSF
Fetus
Inhalation
Lung
Expired air


TISSUE RESERVOIRS
bound ⇔ free
THERAPEUTIC
SITE OF ACTION
"Receptors"
bound ⇔ free
UNWANTED SITE
OF ACTION
bound ⇔ free
CENTRAL
COMPARTMENT
DRUG
DOSE
ABSORPTION
LIBERATION
[FREE DRUG]
EXCRETION
protein bound
drug
metabolites
BIOTRANSFORMATION

RENAL EXCRETION

- Kidney is the primary organ of removal for most drugs especially for those that are water soluble and not volatile.

The three principal processes that determine the urinary excretion of a drug are

1. Glomerular filtration
2. Tubular secretion and
3. Tubular reabsorption (mostly passive back-diffusion)

- The ultrastructure of the glomerular capillary wall is such that it permits a high degree of fluid filtration while restricting the passage of compounds having relatively large molecular weights.

- This selective filtration is important in that it prevents the filtration of plasma proteins (e.g., albumin) that are important for maintaining an osmotic gradient in the vasculature and thus plasma volume.
- Several factors, including molecular size, charge, and shape, influence the glomerular filtration of large molecules.
- As the ultrafiltrate is formed, any drug that is free in the plasma water, that is, not bound to plasma proteins or the formed elements in the blood (e.g., red blood cells), will be filtered as a result of the driving force provided by cardiac pumping.

- All unbound drugs will be filtered as long as their molecular size, charge, and shape are not excessively large.

▪ The greater restriction to filtration of charged molecules, particularly anions, is probably due to an electrostatic interaction between the filtered molecule and the fixed negative charges within the glomerular capillary wall.

Factors that affect the glomerular filtration rate

(GFR) also can influence the rate of drug clearance.

- For instance, inflammation of the glomerular capillaries may increase GFR and hence drug filtration.

- Most drugs are at least partially bound to plasma proteins, and therefore their actual filtration rates are less than the theoretical GFR.

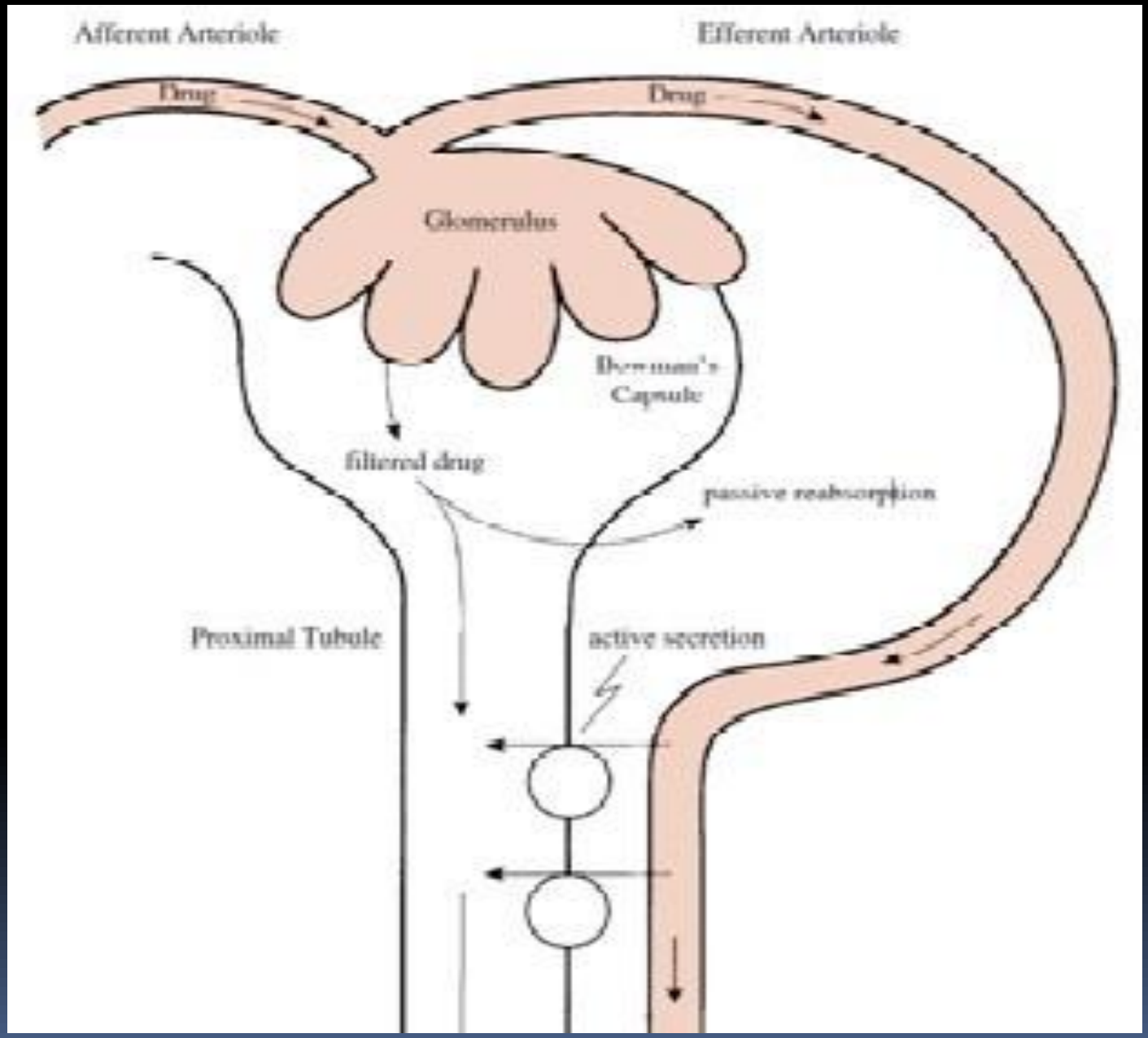
- Anything that alters drug–protein binding, however, will change the drug filtration rate.

- The usual range of half-lives seen for most drugs that are cleared solely by glomerular filtration is 1 to 4 hours.

- However, considerably longer half-lives will be seen if extensive protein binding occurs.

- Also, since water constitutes a larger percentage of the total body weight of the newborn than of individuals in other age groups, the apparent Vd of water-soluble drugs is greater in neonates.
- This results in a lower concentration of drug in the blood coming to the kidneys per unit of time and hence a decreased rate of drug clearance.

- The lower renal plasma flow in the newborn also may decrease the glomerular filtration of drugs.


Afferent Arteriole
Efferent Arteriole
Drug
Drug
Glomerulus
Bowman's Capsule
filtered drug
passive reabsorption
Proximal Tubule
active secretion

Passive Diffusion

- Urinary excretion of drugs (i.e., weak electrolytes) is the extent to which substances diffuse back across the tubular membranes and reenter the circulation.
- In general, the movement of drugs is favored from the tubular lumen to blood, partly because of the reabsorption of water that occurs throughout most portions of the nephron, which results in an increased concentration of drug in the luminal fluid.
- The pH of the urine (usually between 4.5 and 8) can markedly affect the rate of passive back-diffusion.
- The back-diffusion occurs primarily in the distal tubules and collecting ducts, (most of the urine acidification takes place)
- Acidification increases reabsorption (or decreases elimination) of weak acids, such as salicylates, and decreases reabsorption (or promotes elimination) of weak bases, such as amphetamines.

- Effects of pH on urinary drug elimination may have important applications, especially in cases of overdose.

  Eg: enhance the elimination of a barbiturate (a weak acid) by administering bicarbonate to the patient.

- This procedure alkalinizes the urine and thus promotes the excretion of more completely ionized drug.

  Excretion of bases can be increased by making the urine more acidic through the use of an acidifying salt, such as ammonium chloride.

Active Tubular Secretion

- A number of drugs can serve as substrates for the two active secretory systems in the PCT
- Actively transfer drugs from blood to luminal fluid, are independent of each other; one secretes organic anions, and the other secretes organic cations.
- The secretory capacity of both the organic anion and organic cation secretory systems can be saturated at high drug concentrations.
- Each drug will have its own characteristic maximum rate of secretion (transport **maximum,Tm)**.
- Some drugs that are not candidates for active tubular secretion.
- Eg: Metabolites that are formed as a result of conjugative reactions.

Organic Anion Transport

Acetazolamide	Acetylcholine
Bile salts	Atropine
Hydrochlorothiazide	Cimetidine
Furosemide	Dopamine
Indomethacin	Epinephrine
Penicillin G	Morphine
Prostaglandins	Neostigmine
Salicylate	Quinine

Active Tubular Reabsorption

- Some substances filtered at the glomerulus are reabsorbed by active transport systems found primarily in the proximal tubules.
- Active reabsorption is particularly important for endogenous substances, such as ions, glucose, and amino acids, although a small number of drugs also may be actively reabsorbed.
- The probable location of the active transport system is on the luminal side of the proximal cell membrane.
- *Bidirectional active transport across the proximal* tubule also occurs for some compounds; that is, a drug may be both actively reabsorbed and secreted.

  The major portion of *filtered* urate is probably reabsorbed, whereas that eventually found in the urine is mostly derived from active tubular secretion.

Clinical Implications of Renal Excretion

- The rate of urinary drug excretion will depend on the drug's volume of distribution, its degree of protein binding, and the following renal factors:

a. Glomerular filtration rate
b. Tubular fluid pH
c. Extent of back-diffusion of the unionized form
d. Extent of active tubular secretion of the compound
e. Possibly, extent of active tubular reabsorption

Biliary Excretion

Bile flow and composition depend on the secretory activity of the hepatic cells that line the biliary canaliculi.

In the gallbladder, composition of the bile is modified further through reabsorptive processes.

The passage of most foreign compounds from the blood into the liver normally is not restricted because the endothelium of the hepatic blood sinusoids behaves as a porous membrane.

The subsequent passage of substances into the bile, however, is much more selective.

At least three groups of compounds enter the bile.

Group A - concentration in bile and plasma are almost identical (bile–plasma ratio of 1).

Ex. Glucose, and ions such as Na, K, and Cl.

Group B - ratio of bile to blood is much greater than 1, usually 10 to 1,000.

Ex. bile salts, bilirubin glucuronide, sulfobromophthalein, procainamide

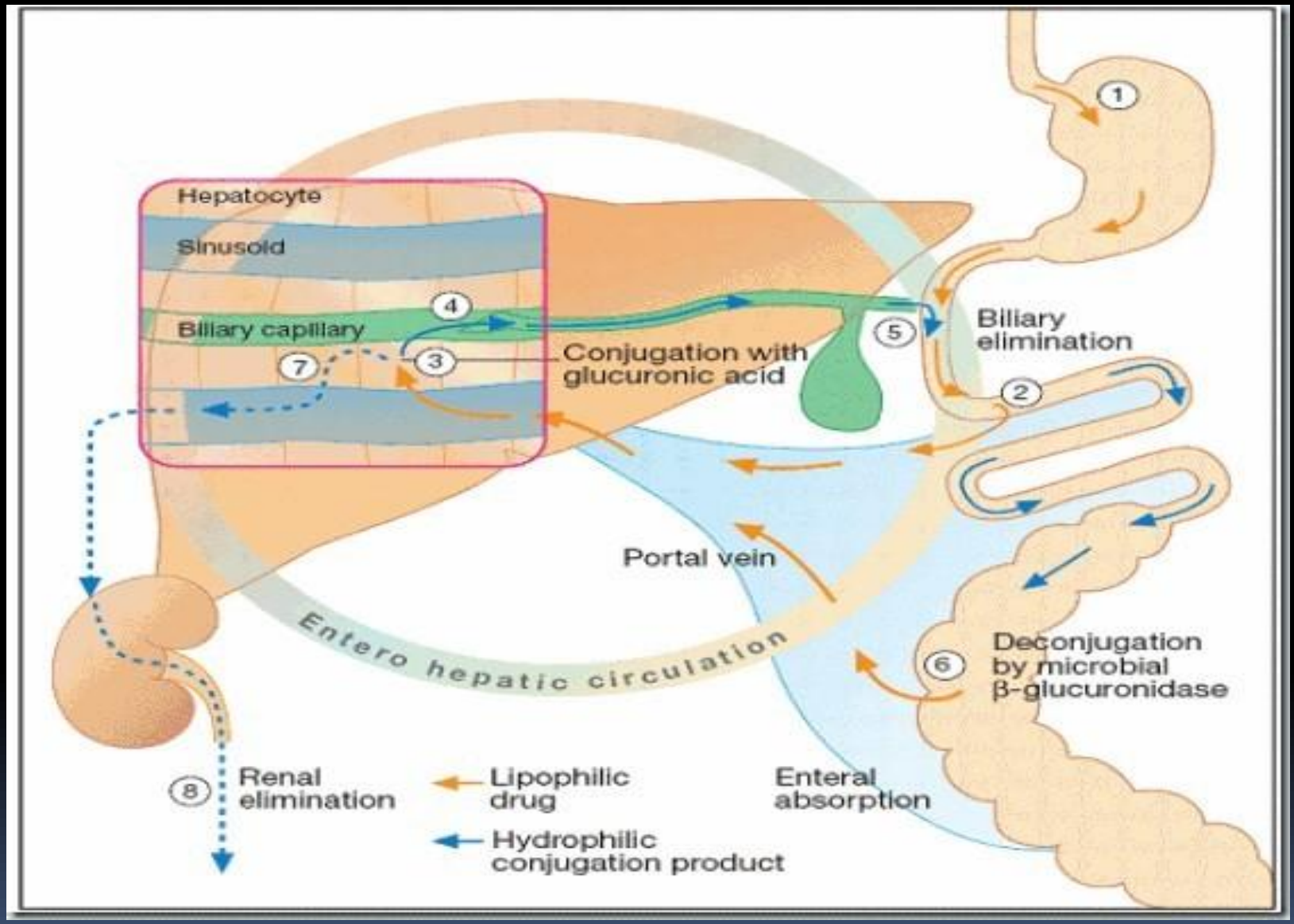
Group C - ratio of bile to blood is less than 1, for

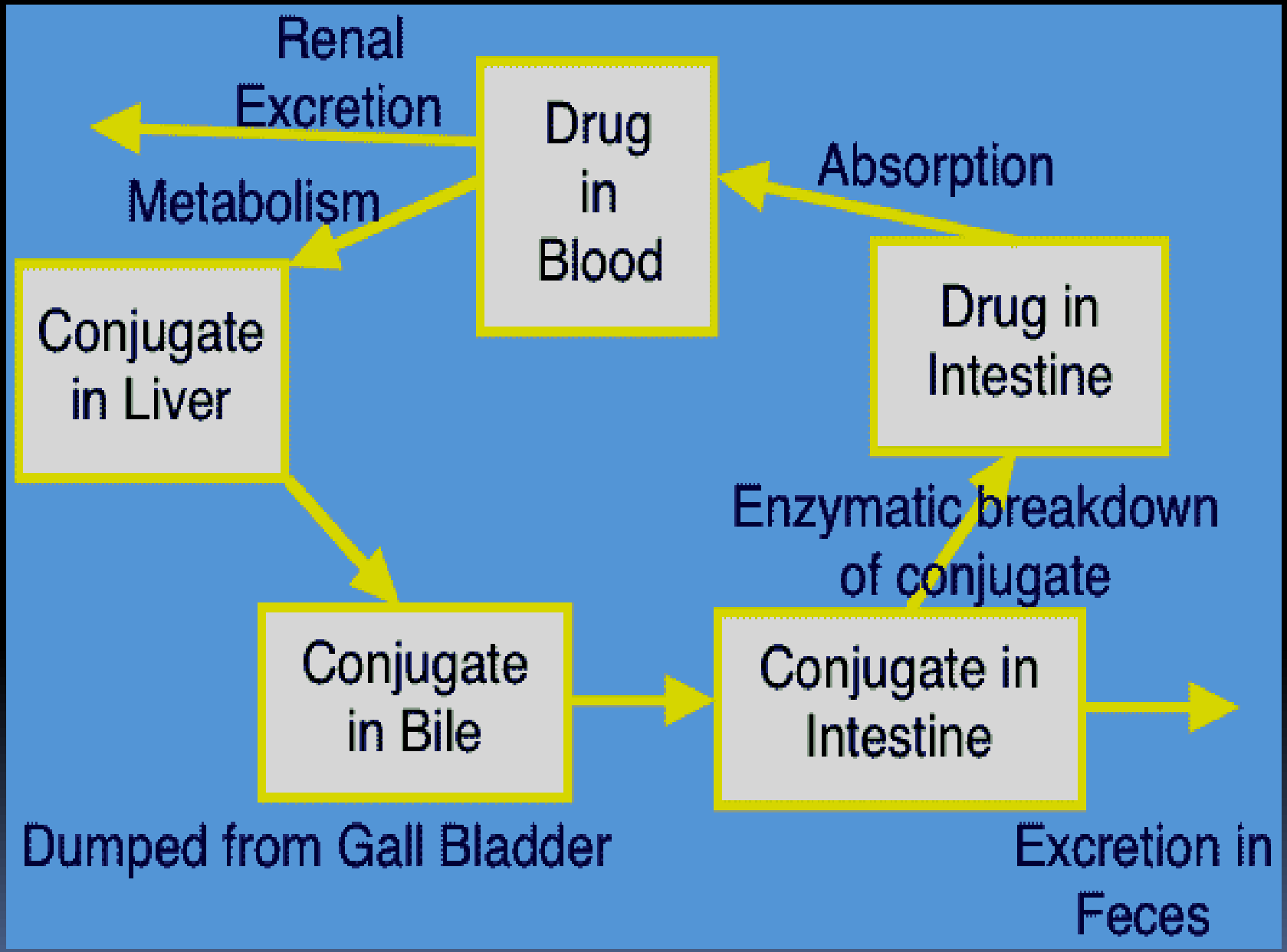
Ex. insulin, sucrose, and proteins.

- On the other hand, most drugs that are secreted by the liver into the bile and then into the small intestine are not eliminated through the feces.

ENTEROHEPATIC CIRCULATION

- The physicochemical properties of most drugs are sufficiently favorable for passive intestinal absorption that the compound will reenter the blood that perfuses the intestine and again be carried to the liver.
- Such recycling may continue (*enterohepatic cycle or circulation) until the drug either undergoes* metabolic changes in the liver, is excreted by the kidneys, or both.
- This process permits the conservation of such important endogenous substances as the bile acids, vitamins D3 and B12, folic acid, and estrogens


Hepatocyte
Sinusoid
Biliary capillary
4
3
7
Conjugation with glucuronic acid
5
Biliary elimination
1
2
Portal vein
Entero hepatic circulation
6
Deconjugation by microbial β-glucuronidase
8
Renal elimination
Lipophilic drug
Hydrophilic conjugation product
Enteral absorption


Renal Excretion
Drug in Blood
Absorption
Metabolism
Conjugate in Liver
Drug in Intestine
Enzymatic breakdown of conjugate
Conjugate in Bile
Conjugate in Intestine
Dumped from Gall Bladder
Excretion in Feces

Drugs that Undergo Enterohepatic Recirculation

Adriamycin	Methadone
Amphetamine	Metronidazole
Chlordecone	Morphine
1,25-Dihydroxyvitamin D3	Phenytoin
Estradiol	Polar Glucuronic Acid Conjugates
Indomethacin	Polar Sulfate Conjugates
Mestranol	Sulindac

PULMONARY EXCRETION

- Any volatile material, irrespective of its route of administration, has the potential for pulmonary excretion.
- Certainly, gases and other volatile substances that enter the body primarily through the respiratory tract can be expected to be excreted by this route.
- *No* specialized transport systems are involved in the loss of substances in expired air; simple diffusion across cell membranes is predominant.
- The rate of loss of gases is not constant; it depends on the rate of respiration and pulmonary blood flow.
- Gases such as nitrous oxide, which are not very soluble in blood, will be excreted rapidly, that is, almost at the rate at which the blood delivers the drug to the lungs.

- *Increasing cardiac output has the greatest effect on the removal of poorly soluble gases; for example, doubling the cardiac output nearly* doubles the rates of loss.

- Agents with high blood and tissue solubility, on the other hand, are only slowly transferred from pulmonary capillary blood to the alveoli.

- Ethanol, which has a relatively high blood gas solubility, is excreted very slowly by the lungs.

EXCRETION IN OTHER BODY FLUIDS

Sweat and Saliva

- Minor importance for most drugs.
- Mainly depends on the diffusion of the un-ionized lipid-soluble form of the drug across the epithelial cells of the glands.
- Thus, the **p*Ka of the drug and* the pH of the individual secretion formed in the glands** are important determinants of the total quantity of drug
- Lipid-insoluble compounds, **urea and glycerol, enter saliva and sweat at rates proportional to their molecular weight,** because of filtration through the aqueous channels in the secretory cell membrane.
- Substances excreted into saliva are swallowed, and their fate is the same as that of orally administered drugs

MilK

The physicochemical properties that govern the excretion of drugs into saliva and sweat also apply to the passage of drugs into milk.

Since milk is more acidic (pH 6.5) than plasma, basic compounds (e.g., alkaloids, such as morphine and codeine) may be somewhat more concentrated in this fluid.

In contrast, **the levels of weak organic acids will probably be lower than those in plasma**.

In general, a **high maternal plasma protein binding of drug will be associated with a low milk** concentration.

A highly lipid-soluble drug should accumulate in milk fat.

- Low-molecular weight un-ionized water-soluble drugs will diffuse passively across the mammary epithelium and transfer into milk.

- There they may reside in association with one or more milk components, for example, bound to protein such as lactalbumin, dissolved within fat globules, or free in the aqueous compartment.

- Substances that are not electrolytes, such as ethanol, urea, and antipyrine, readily enter milk and reach approximately the same concentration as in plasma.

- Finally, antibiotics such as the tetracyclines, which can function as chelating agents and bind calcium, have a higher milk than plasma concentration.

THANK YOU