Pharmacokinetics

Patients may recover in spite of drugs or because of them.'

J H Gaddum 1959

- *'But know also, man has an inborn craving for medicine ... The desire to take medicine is one feature which distinguishes man the animal, from his fellow creatures.*
- *It is really one of the most serious difficulties with which we have to contend* ***doctor's visit is not thought to be complete without a prescription.'***

Drugs are used in three principal ways

- **to cure disease**
- **to suppress disease**
- **to prevent disease: (prophylaxis) primary and secondary**

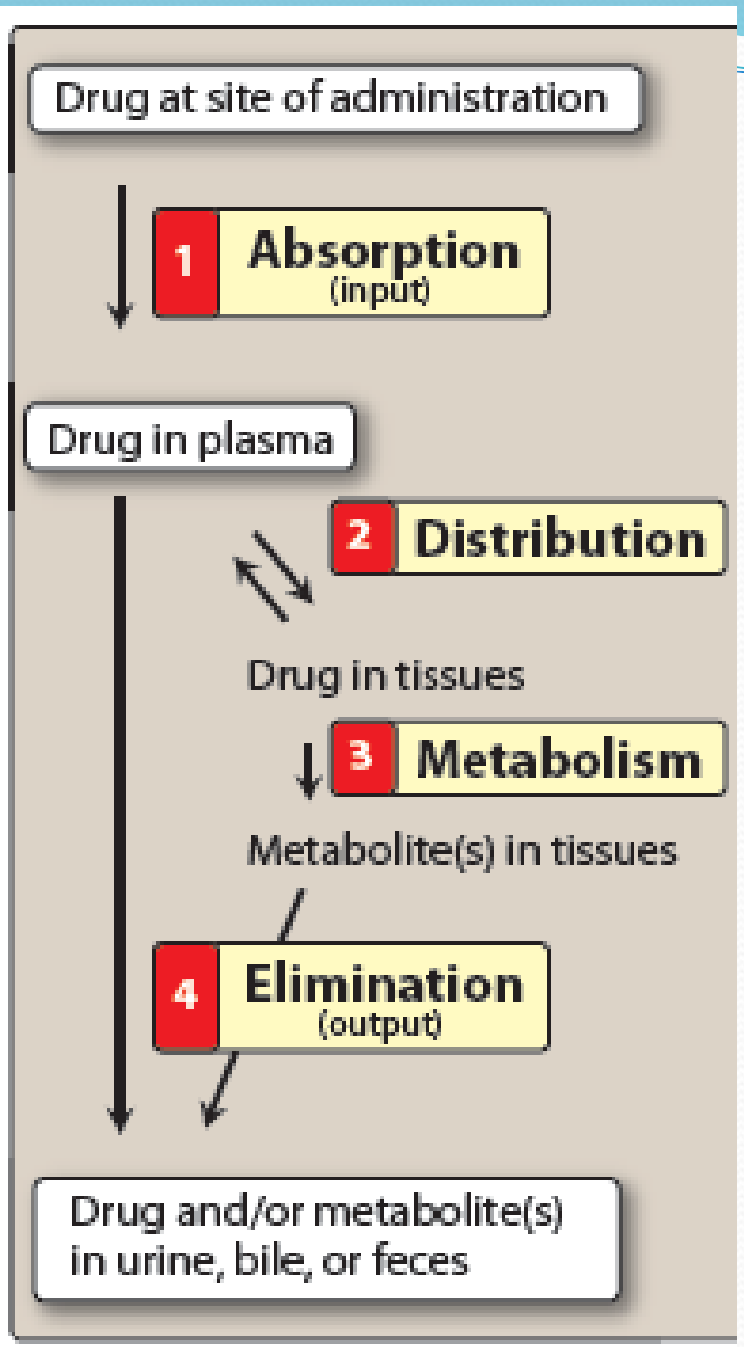
THE FOUR MAJOR PROCESSESS

1. **Absorption: First, drug absorption from the site of administration** permits entry of the therapeutic agent (either directly or indirectly) into plasma.

2. **Distribution: Second, the drug may then reversibly leave the** bloodstream and distribute into the interstitial and intra cellular fluids.
3. **Metabolism: Third, the drug may be biotransformed by metabolism** by the liver, or other tissues.
4. **Elimination: Finally, the drug and its metabolites are eliminated** from the body in urine, bile, or feces

WHY IMPORTANT?

- Pharmacokinetic parameters allow the clinician to design **treatment** regimens
- decisions regarding route of administration for a specific drug
- The amount and frequency of each dose
- Duration of treatment.



Schematic representation of drug absorption, distribution, metabolism, and elimination.

Lippincott's illustrated reviews,5th edition,2012

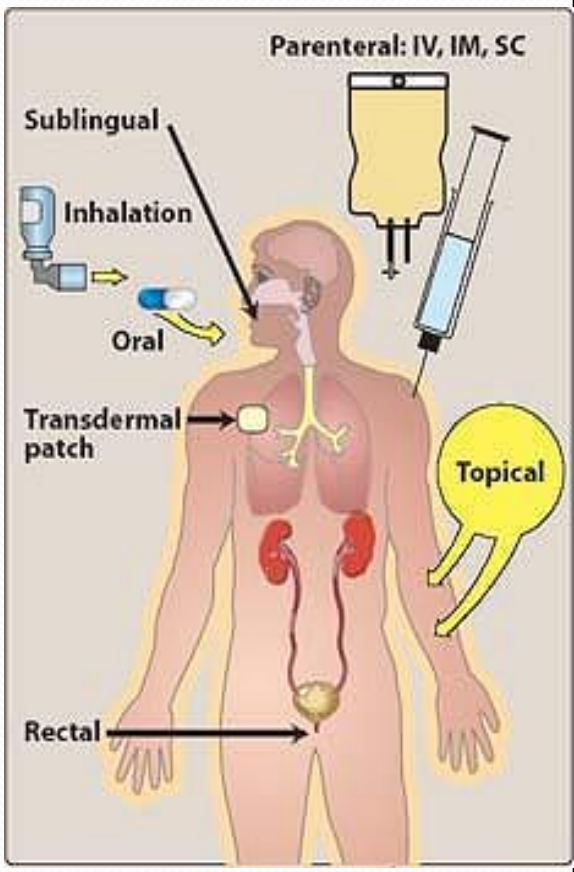
Factors guiding route of administration

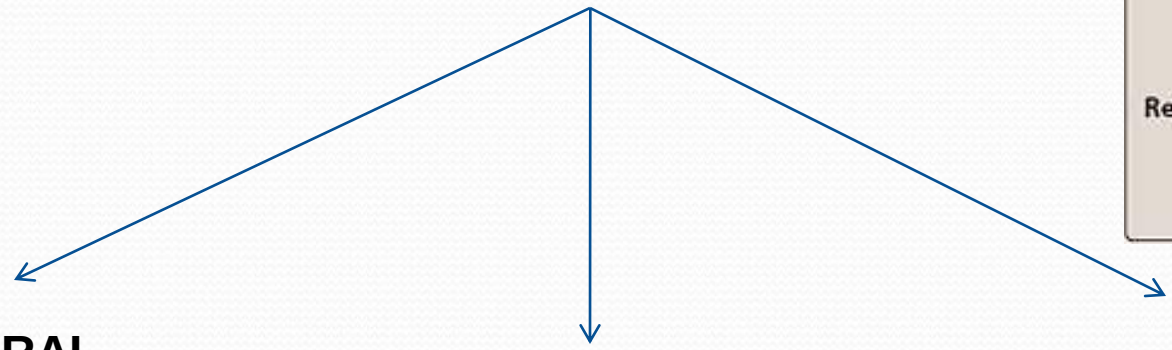
- **Properties of the drug**
- **Therapeutic objectives**

Desirability of a rapid onset of action,

Need for long-term treatment

Restriction of delivery to a local site





ENTERAL

PARENTERAL

TOPICAL

Enteral

- administering a drug by mouth
- safest
- most common
- convenient,
- economical method of drug administration.
- When the drug is given in the mouth, it may be swallowed, allowing oral delivery, or it may be placed under the tongue **(sublingual),** facilitating direct absorption into the bloodstream.

DISADVANTAGES??

Parenteral

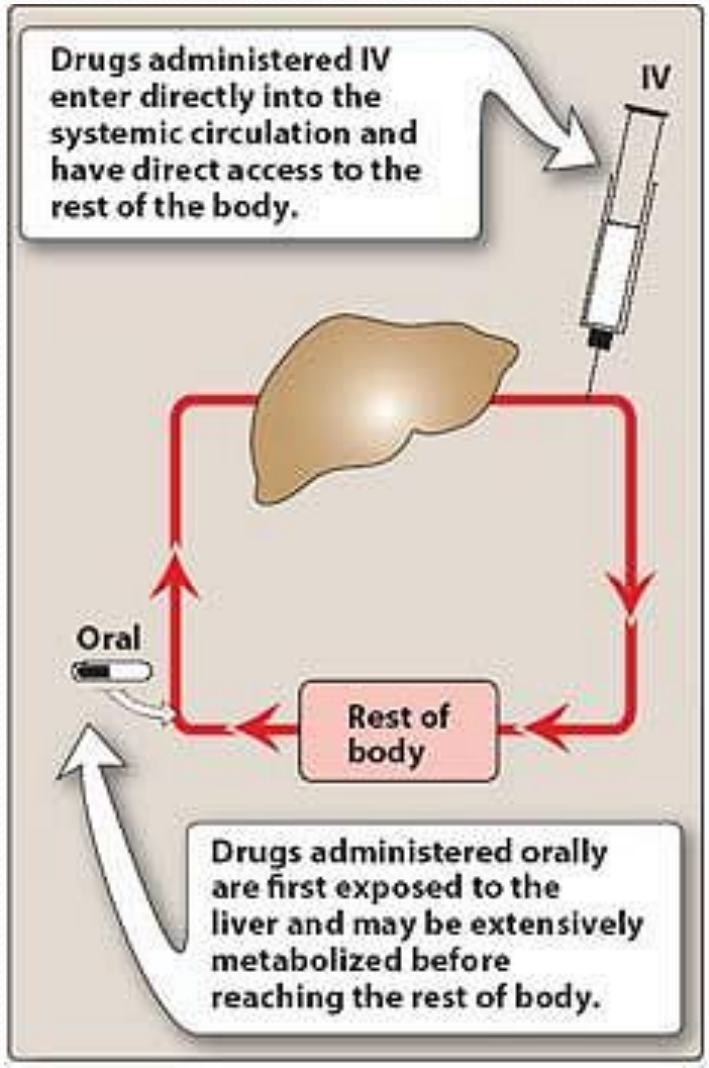
- introduces drugs directly across into the systemic circulation or other vascular tissue

Used for drugs

- poorly absorbed from the GIT
- unstable in the GI tract (for example, insulin).
- treatment of unconscious patients
- circumstances that require a rapid onset of action.
- highest bioavailability
- not subject to harsh GI environments.
- provides most control over the actual dose of drug delivered to the body.
- routes are irreversible

Three major parenteral routes

- ✓ **Intravascular**
  - *intravenous*
  - *intra-arterial*
- ✓ **Intramuscular**
- ✓ **Subcutaneous**



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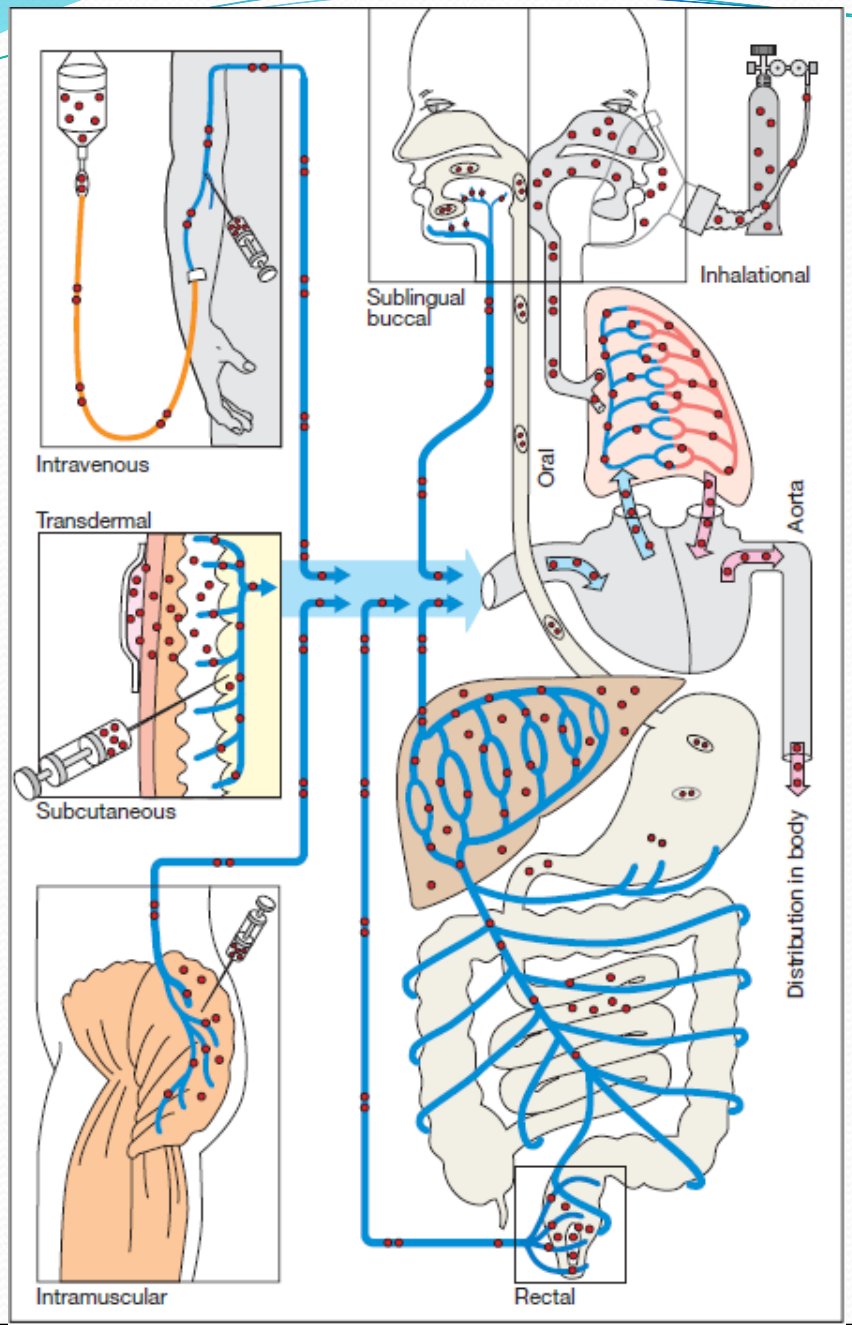
From application to distribution



Color Atlas of Pharmacology,3rd edition 2005,Thieme

Which route of administration is most likely to subject a drug to a first-pass effect?

a. Intravenous
b. Inhalational
c. Oral
d. Sublingual (SL)
e. Intramuscular

Drug absorption

Drug Absorption

Absorption is the process by which a drug enters the bloodstream without being chemically altered

PHARMACOKINETICS : WHAT THE BODY DOES TO THE DRUG??

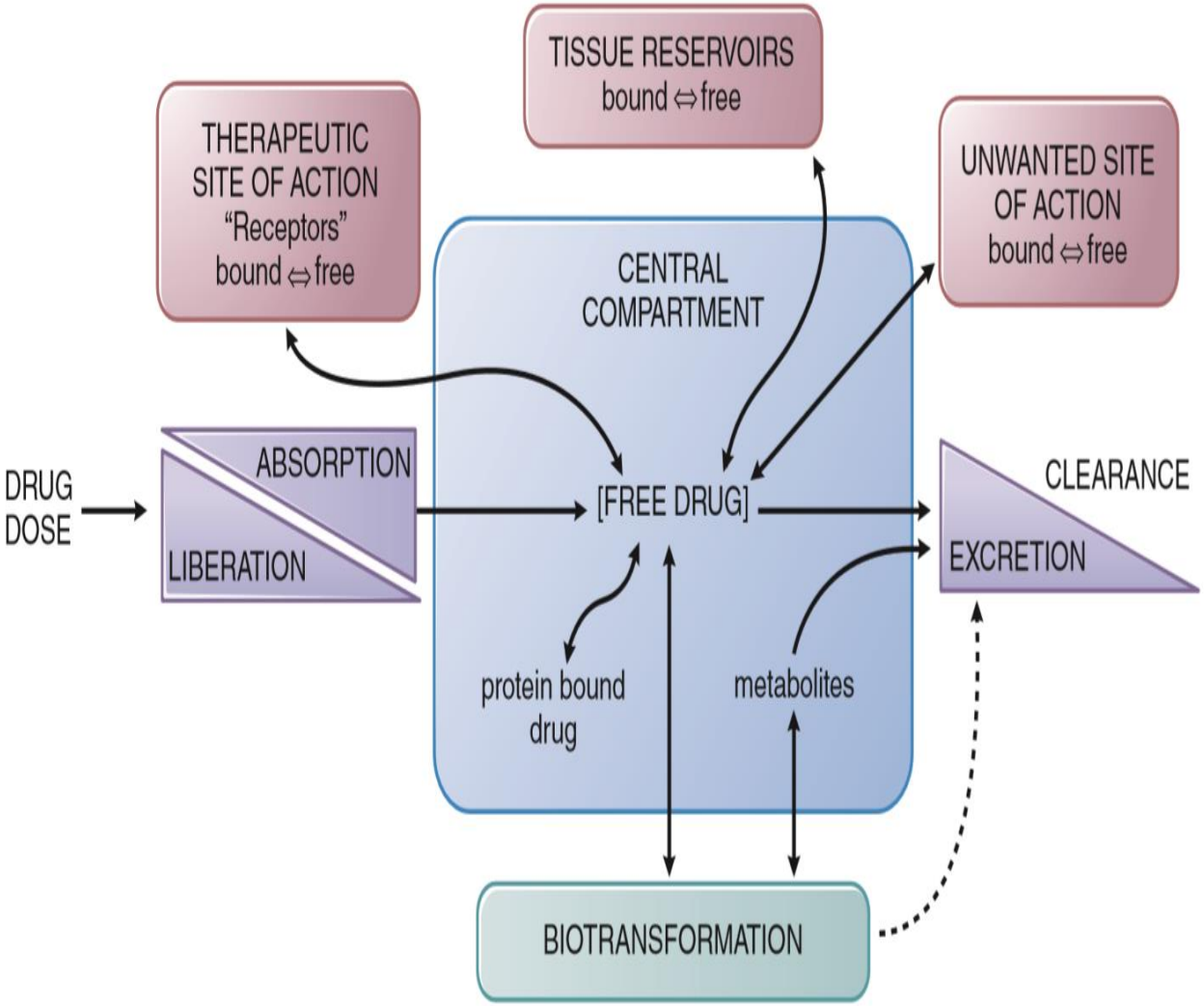
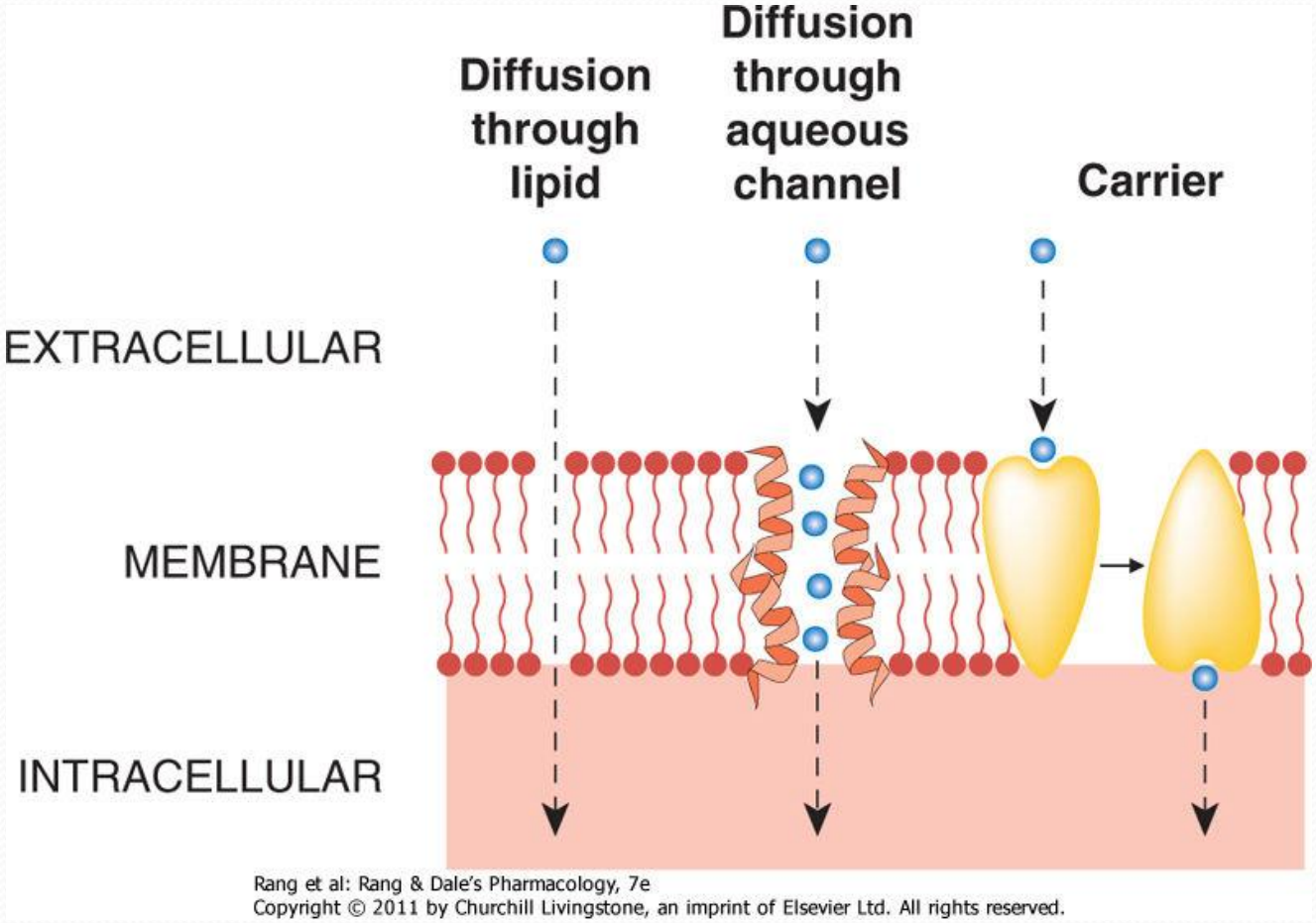


Figure 2–1 *The interrelationship of the absorption, distribution, binding, metabolism, and excretion of a drug and its concentration at its sites of action.* Possible distribution and binding of metabolites in relation to their potential actions at receptors are not depicted.

There are **four** main ways by which small molecules cross cell membranes

1) by diffusing directly through the lipid
2) by diffusing through aqueous pores formed by special proteins (*aquaporins*) that traverse the lipid
3) by combination with a *solute carrier* (SLC) or other membrane transporter
4) by *pinocytosis*.

Routes by which drugs can traverse cell membranes



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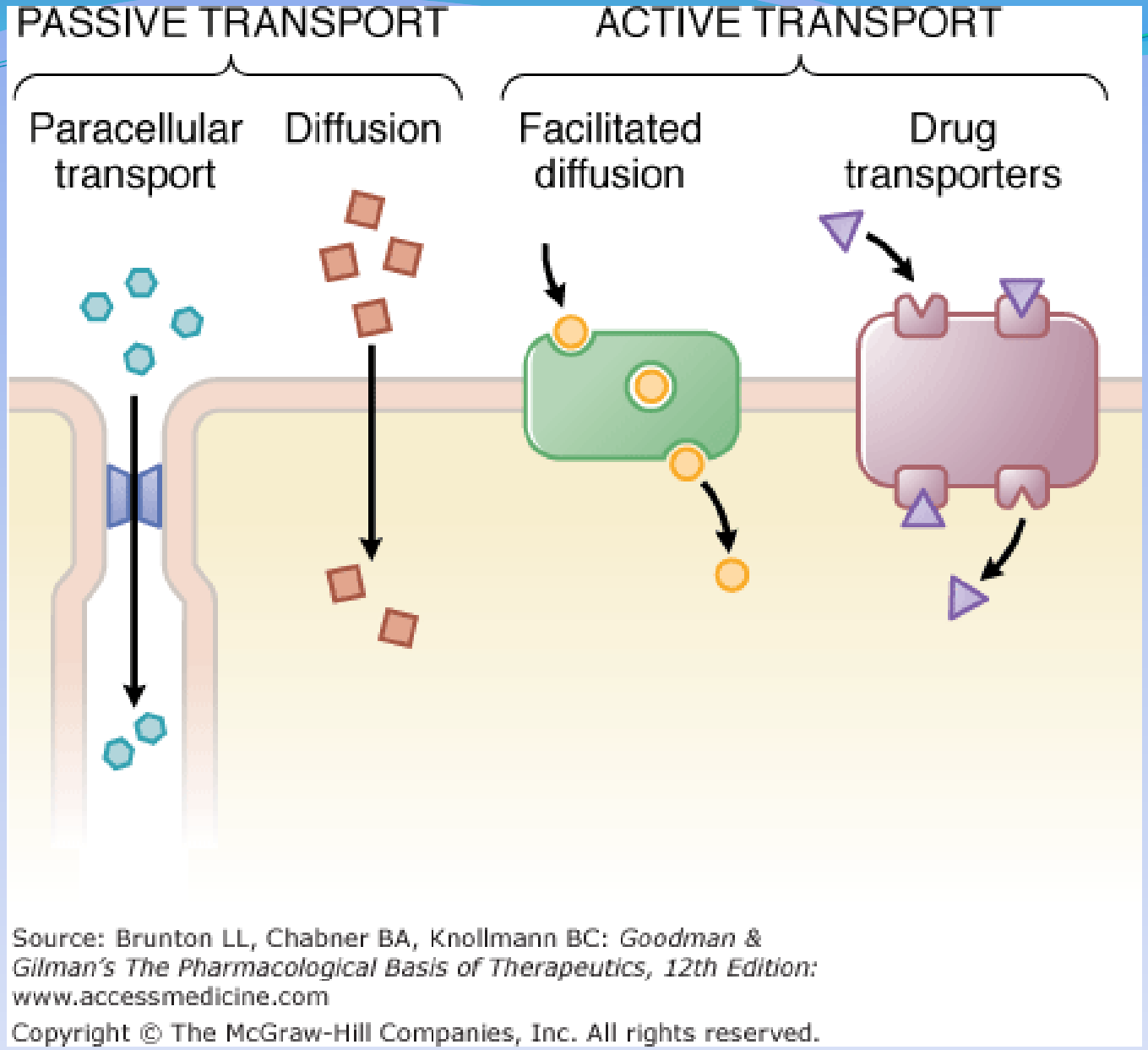

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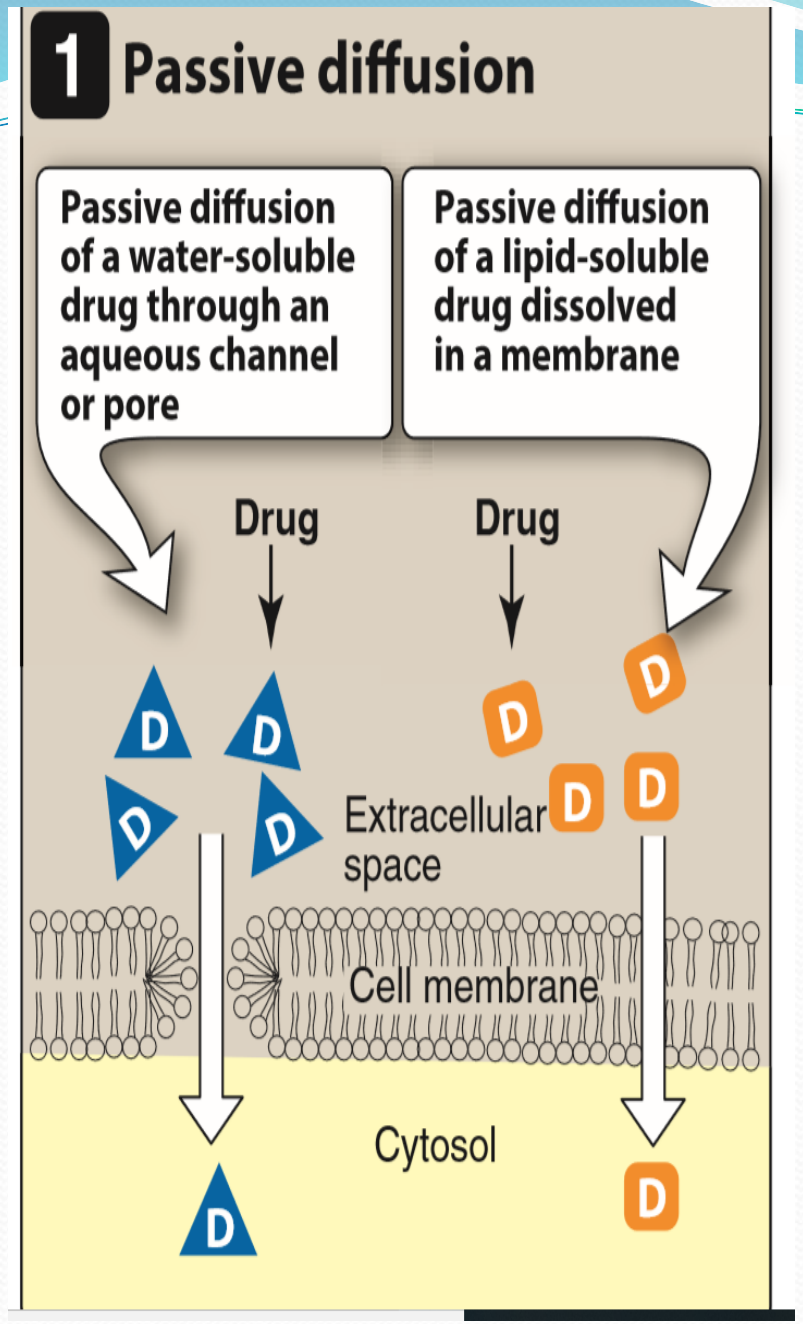
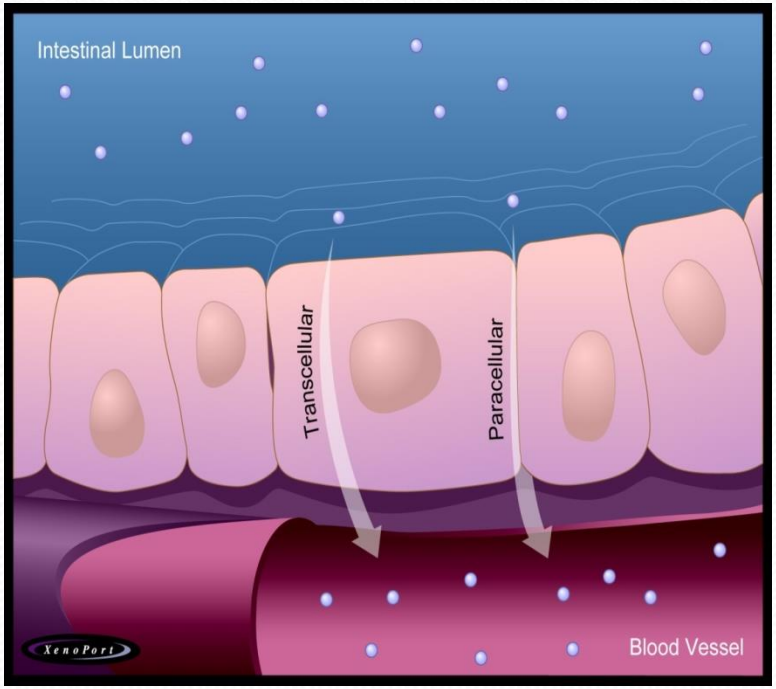


- Such transfer is directly proportional…
  - To the magnitude of the concentration gradient across the membrane
  - To the lipid: water partition coefficient of the drug
  - To the membrane surface area exposed to the drug

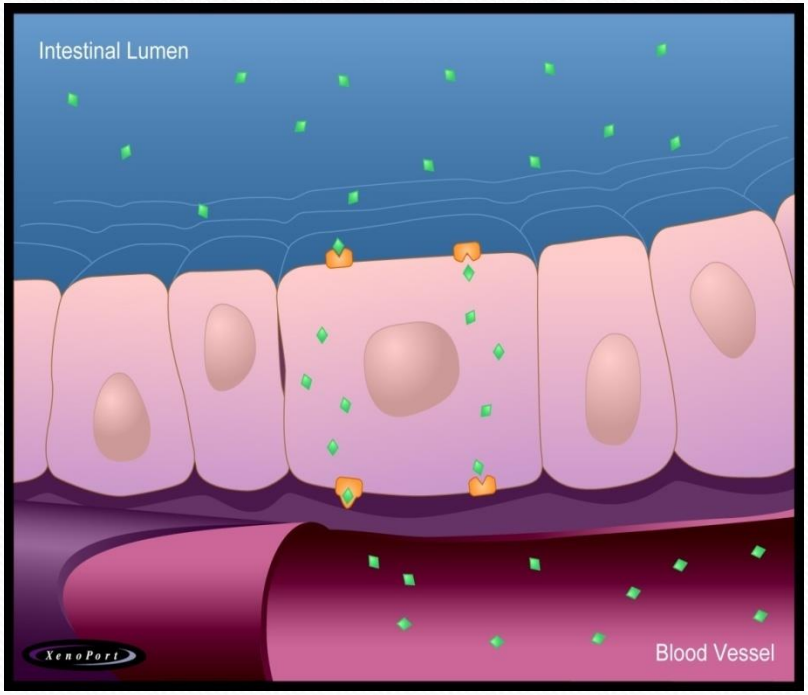
Intestinal Absorption of Oral Drugs

Passive Diffusion

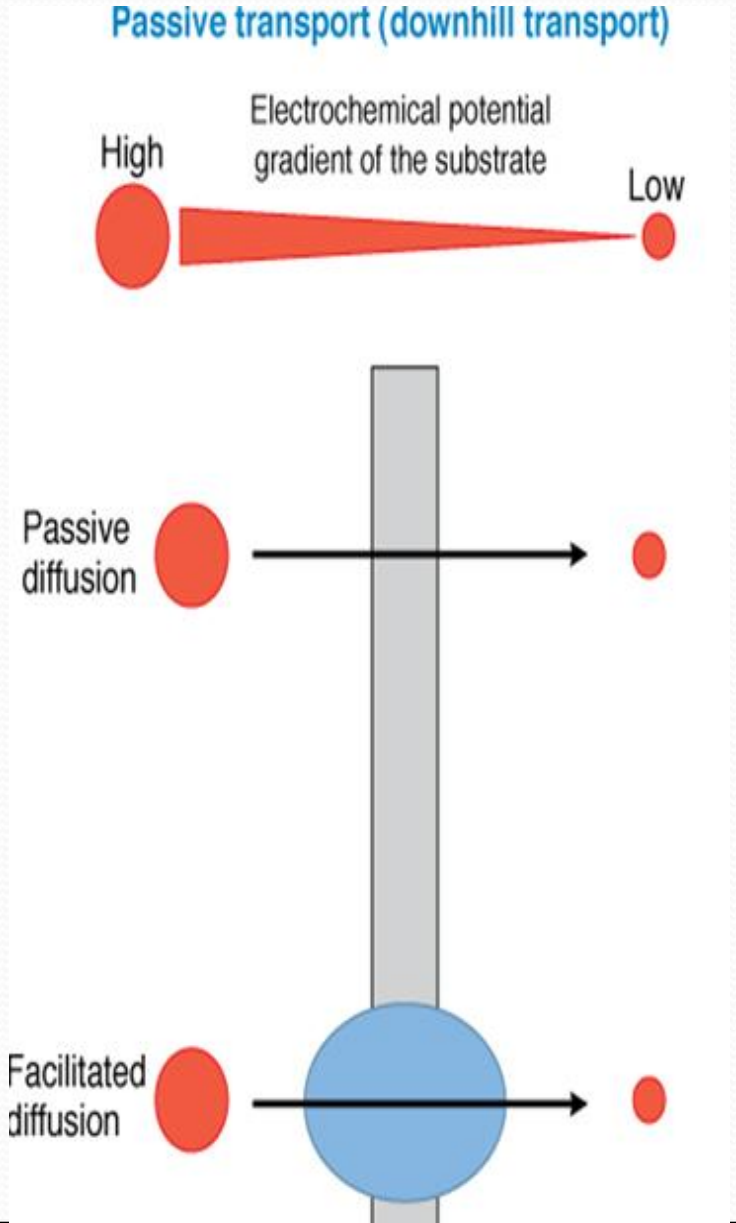


Most approved oral drugs

Active Transport



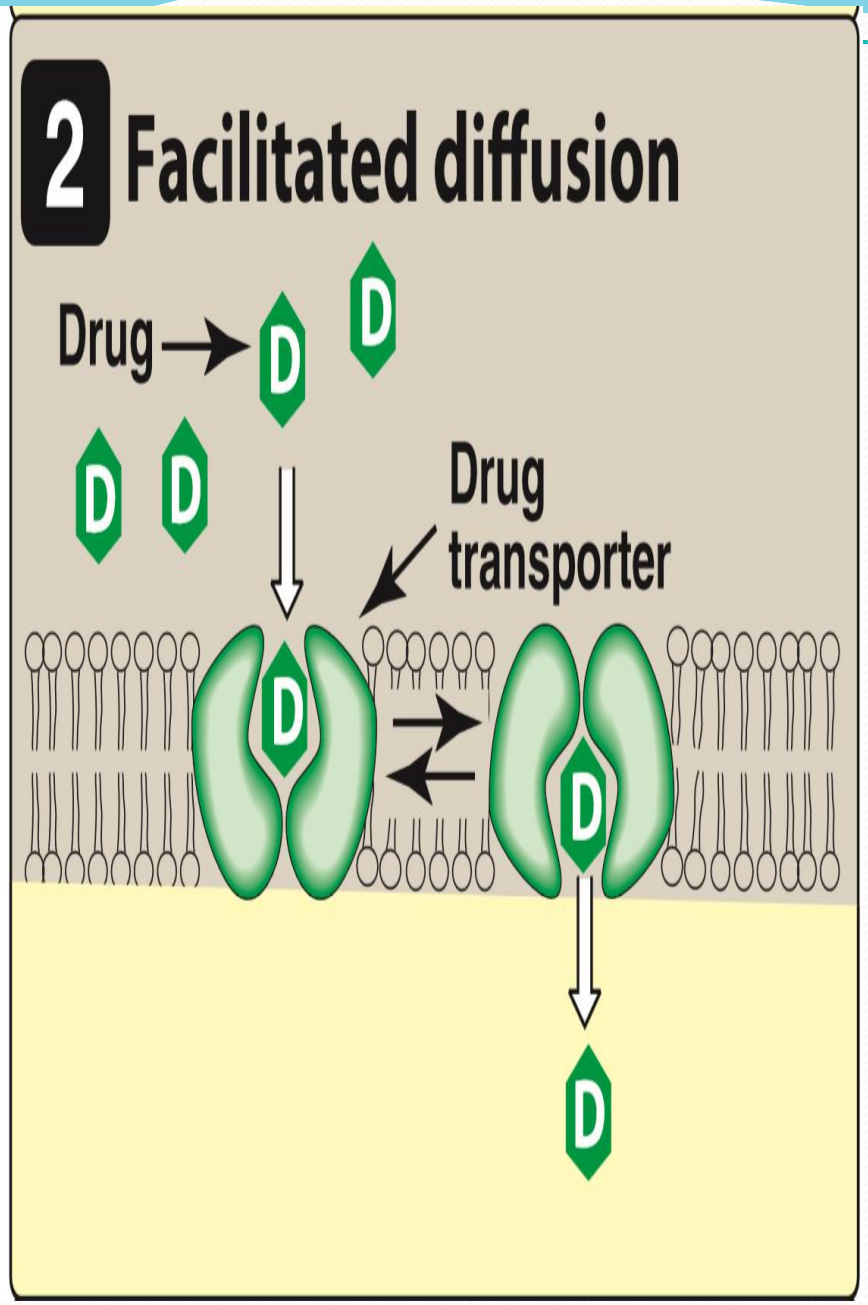
- Nutrients (small peptides, amino acids, vitamins, fatty acids, etc.)
- Selected drugs: valacyclovir, ACE inhibitors cephalosporins, pravastatin, etc.


Passive transport (downhill transport)
Electrochemical potential
gradient of the substrate
High
Low
Passive
diffusion
Facilitated
diffusion

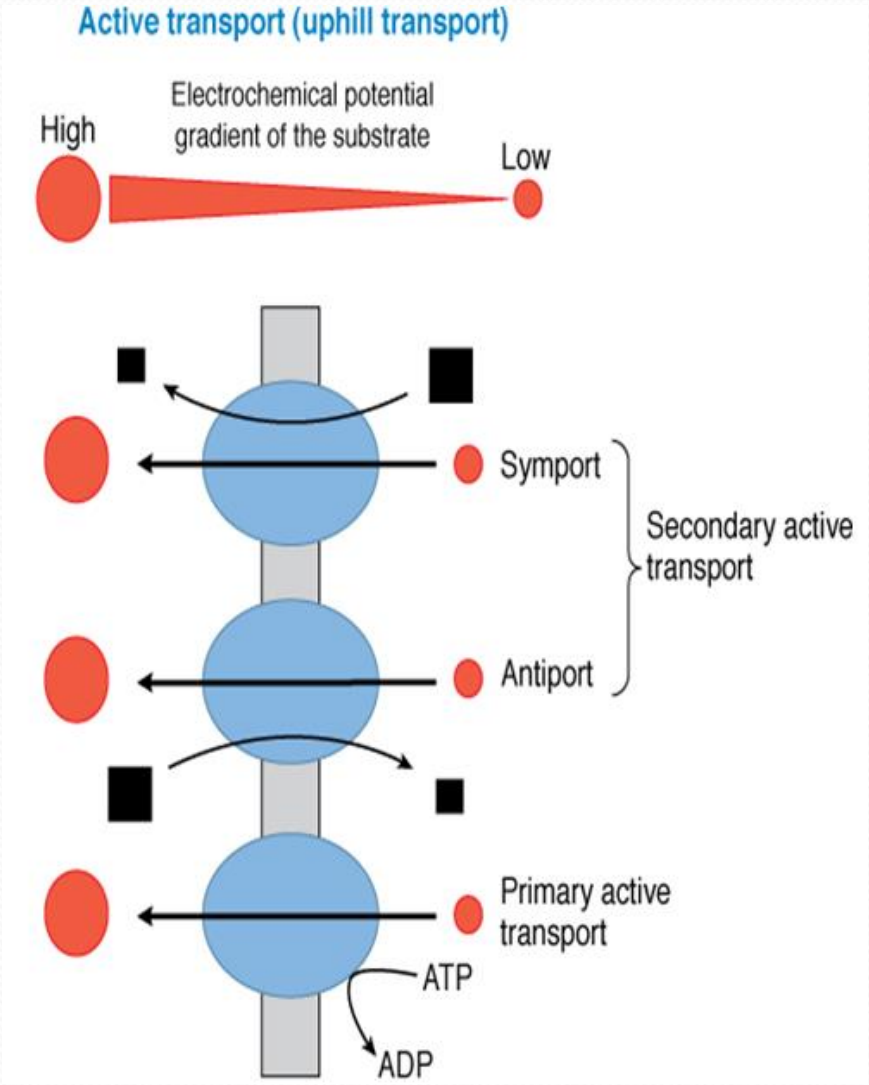
Facilitated Diffusion

- ✓ does not require energy input.
- ✓ Just as in passive diffusion, the transport occurs down their electrochemical potential gradient.
- ✓ The transporter belongs to the superfamily of solute carrier (SLC)
- ✓ Facilitates permeation of poorly diffusible substrate

  entry of glucose into muscles by GLUT4



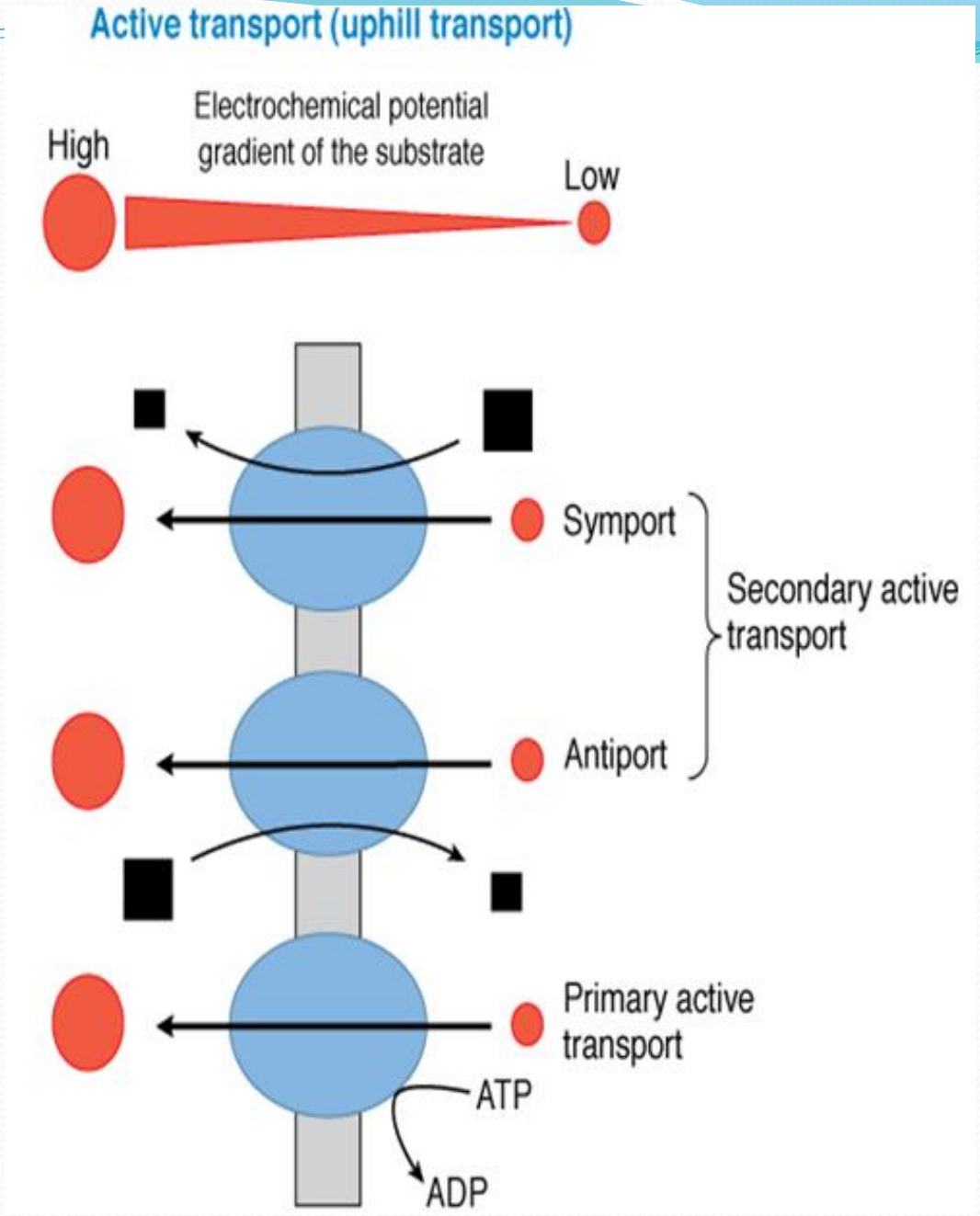
- Carrier mediated transport.
- The driving force is electrochemical gradient of the transported solute.
- Facilitates solute movement either in or out of cells, depending on the direction of the electrochemical gradient.
- Doesn’t require energy.
- Can be saturated, and may be inhibited by compounds that compete for the carrier.


Active transport (uphill transport)
Electrochemical potential gradient of the substrate
High
Low
Symport
Antiport
Secondary active transport
Primary active transport
ATP
ADP

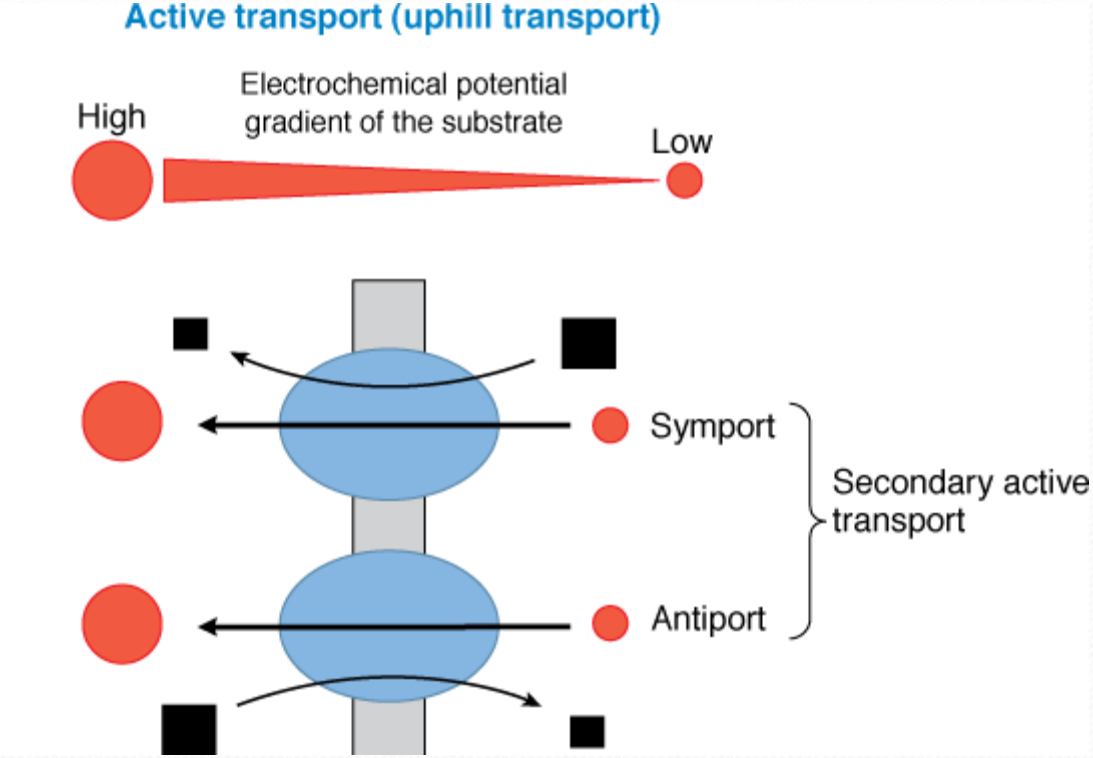
Active Transport

Primary Active Transport

- Membrane transport that directly couples with ATP hydrolysis is called *primary active transport*.
- ABC(ATP binding cassettes) transporters are examples of primary active transporters.
- Mediate efflux of the solute from the cytoplasm.
- ABC transporters mediate the **unidirectional efflux** of solutes across biological membranes.
- **P-gp**


Active transport (uphill transport)
Electrochemical potential gradient of the substrate
High
Low
Symport
Secondary active transport
Antiport
Primary active transport
ATP
ADP

Secondary Active Transport



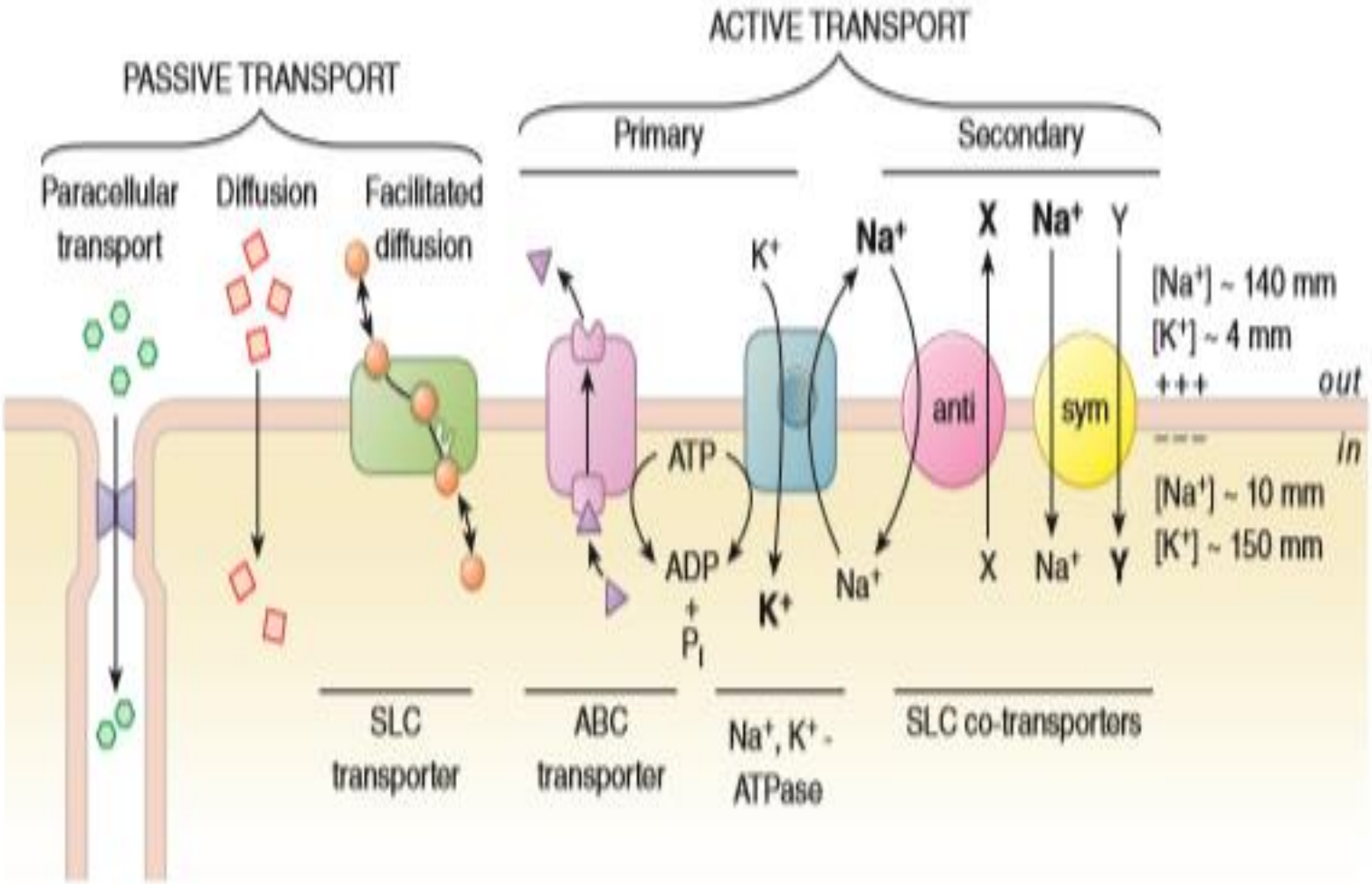
- Symporters also called cotransporters

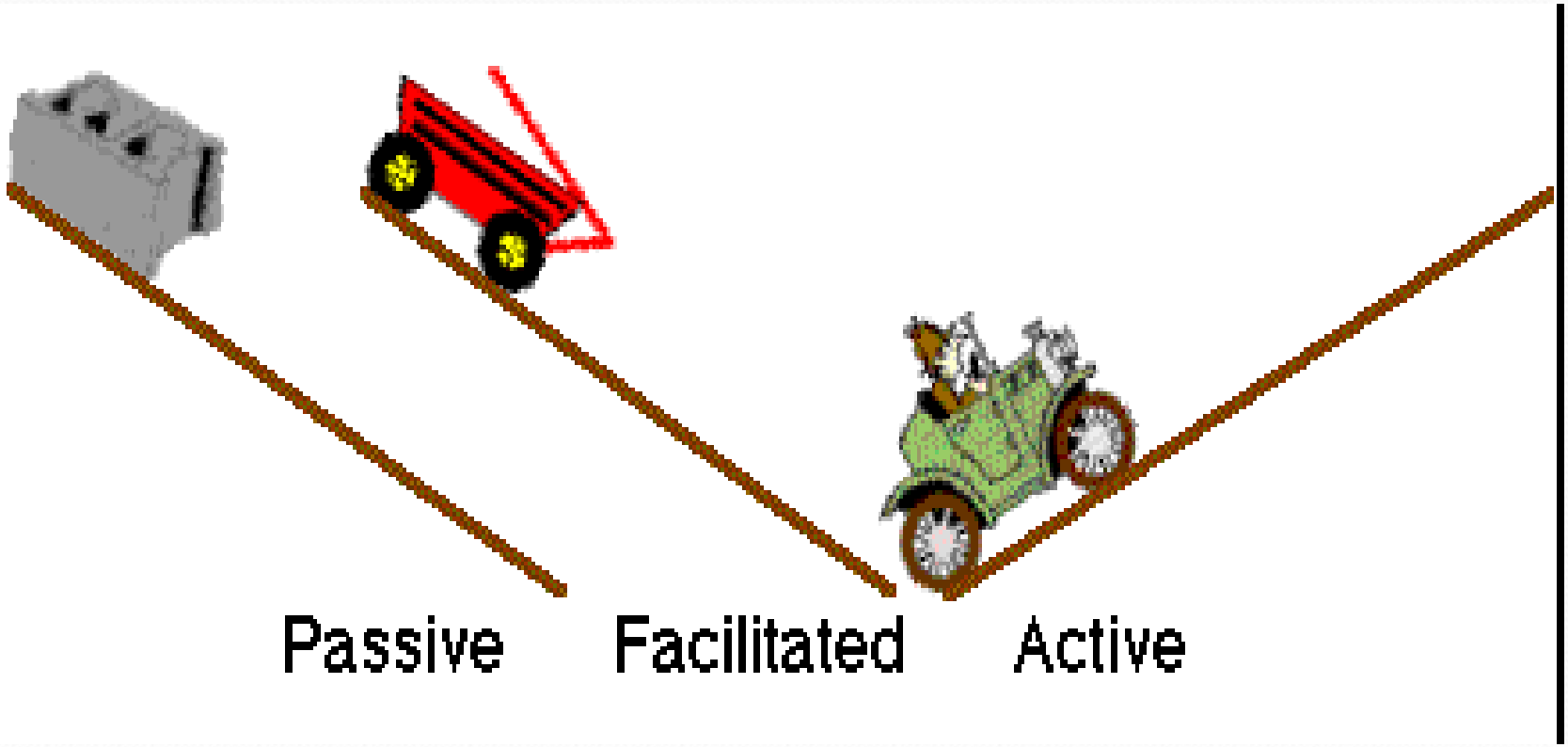
NaI symporter

Na-Cl symporter

- Antiporters ,also called exchangers move their substrates in opposite direction

Sodium calcium exchanger


ACTIVE TRANSPORT
PASSIVE TRANSPORT
Primary
Secondary
Paracellular transport
Diffusion
Facilitated diffusion
K+
Na+
X
Na+
Y
[Na+] ~ 140 mm
[K+] ~ 4 mm
+++
out
anti
sym
---
in
ATP
[Na+] ~ 10 mm
[K+] ~ 150 mm
ADP + PI
K+
Na+
X
Na+
Y
SLC transporter
ABC transporter
Na+, K+ - ATPase
SLC co-transporters


Passive
Facilitated
Active

Of the following characteristics, which is unlikely to be associated with the process of facilitated diffusion of drugs?

a. The transport mechanism becomes saturated at high drug concentrations
b. The process is selective for certain ionic or structural configurations of the drug
c. If two compounds are transported by the same mechanism, one will competitively inhibit the transport of the other
d. The drug crosses the membrane against a concentration gradient and the process requires cellular energy
e. The transport process can be inhibited noncompetitively by substances that interfere with cellular metabolism

Drug Absorption

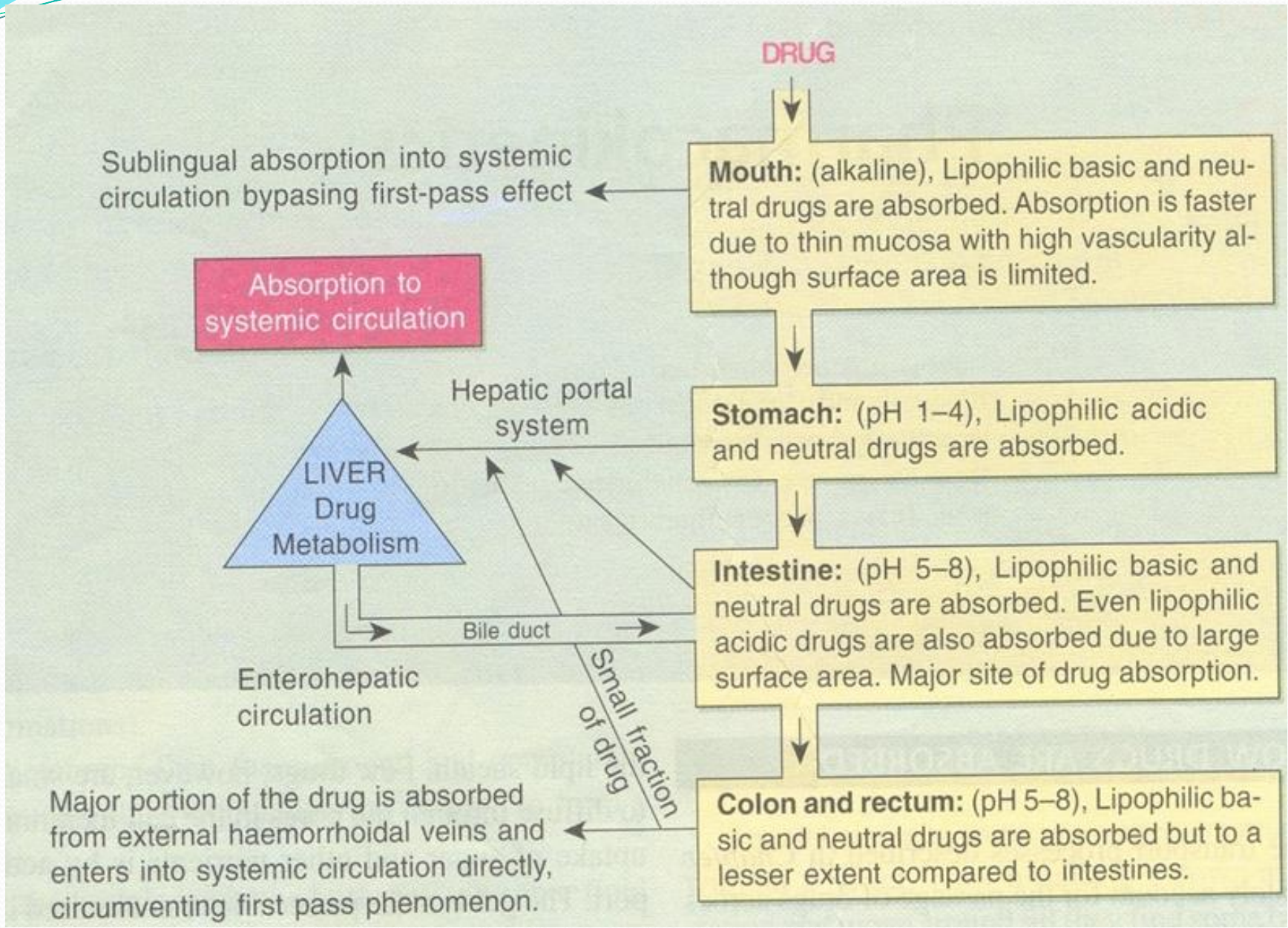
- The drug is absorbed from the GI tract and passes via the portal vein into the liver where it is metabolized
- As a result of first pass metabolism only a proportion of the drug reaches the circulation
- First pass metabolism can occur in the gut and liver

Drug Absorption

Factors which influence the rate of absorption

- Formulation of the drug
- the physicochemical properties of the drug
- routes of administration
- dosage forms
- circulation at the site of absorption
- concentration of the drug

Processes of absorption through GIT



Factors affecting drug absorption:

1) Lipid-water partition co-efficient:

More lipid soluble and less water soluble has high lipid-water partition co-efficient, it will absorbed rapidly

pH and ionization

Many drugs are weak acids or bases that are present in solution as both the non-ionized and ionized species.

✓We need to Determine how much drug will be found on either side of a membrane.

- The relationship of pKa and the ratio of acid-base concentrations to pH is expressed by the **Henderson-Hasselbalch equation.**

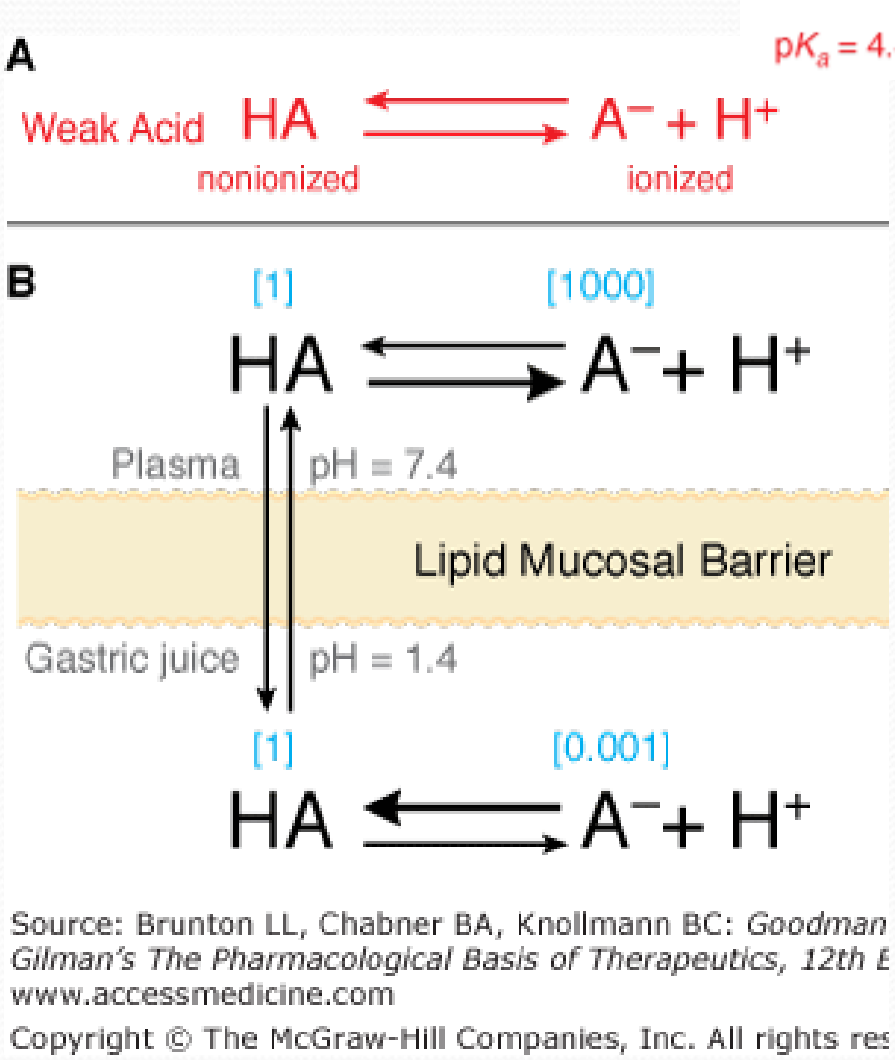
For weak acids,

$$pH = pKa + \log \frac{[A^-]\text{(ionized species)}}{[HA]\text{(unionized species)}}$$

pKa : *negative logarithm of acidic dissociation constant of the weak electrolyte .*

pH=pka

Influence of pH on the distribution of a weak acid between plasma and gastric juice



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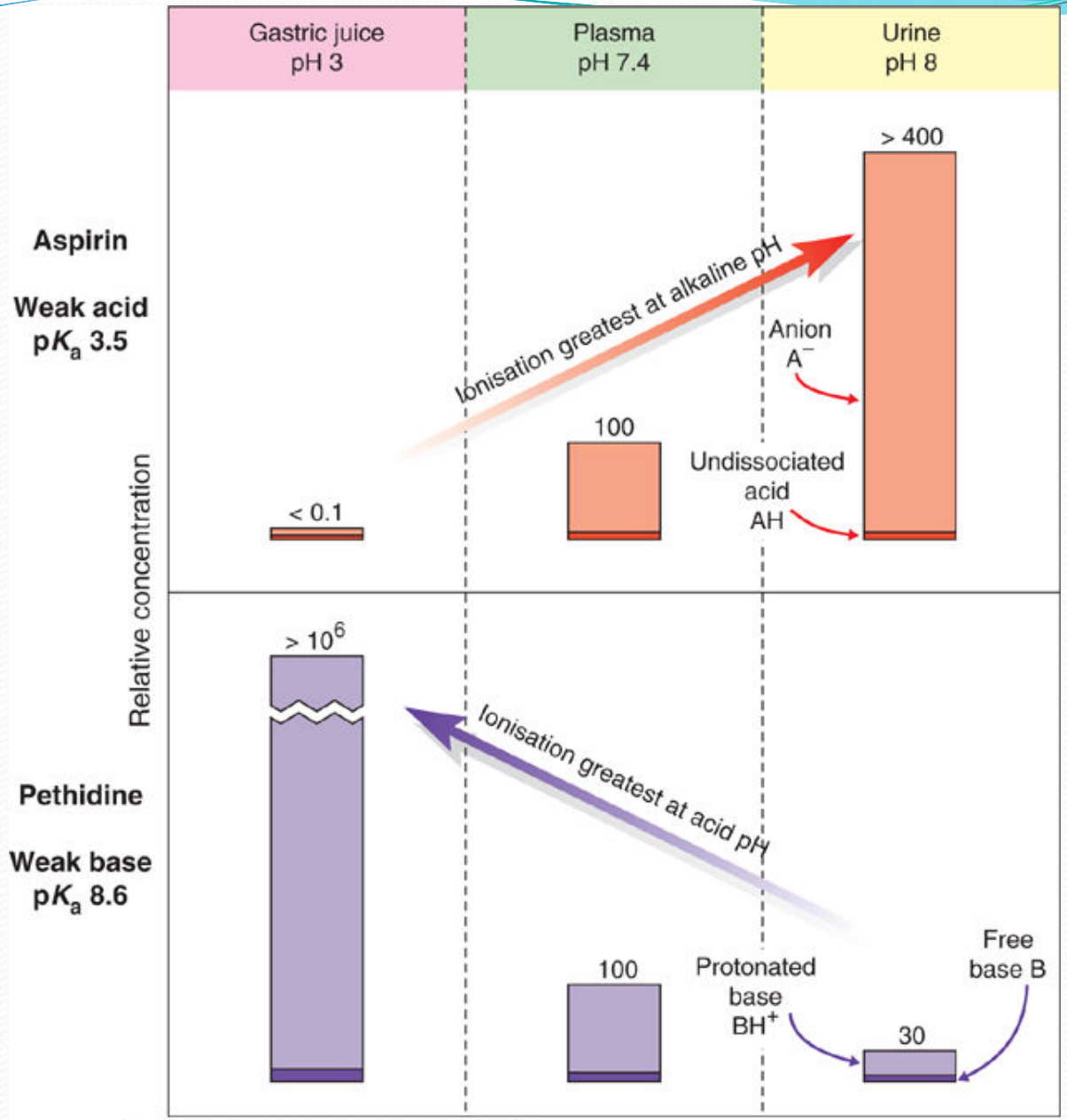
Drug	Acidic	BASIC
Ionized	At basic pH	At acidic pH
Non-Ionized	At acidic pH	At basic pH
Absorption	Better in acidic medium	Better in alkaline medium
Overdose	Urine is made alkaline by $NaHCO_3$ / Acetazolamide to enhance its excretion	Urine made acidic by NH_4Cl / Ascorbic acid to enhance its excretion
Binds to	Albumin	α 1 glycoprotein
Examples	• Aspirin • Ampicillin • Warfarin • Phenobarbitone	• Amphetamine • Morphine • Beta blockers • Pethidine



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- It is convenient to remember that when the pH of the environment is the same as the pKa of a drug within it, then the ratio of un-ionised to ionised molecules is 1:1.
- But for every unit by which pH is changed, the ratio of un-ionised to ionised molecules changes 10-fold.
- Thus when the pH is 2 units less than the pKa, molecules of an acid become 100 times more *unionised* and when the pH is 2 units more than the pKa, molecules of an acid become 100 more *ionised*.
- Such pH change profoundly affects drug kinetics.

2 **Drug solubility**: drugs given in aqueous solutions are more rapidly soluble than when given in oily solution, suspension or solid form.

3 **Dosage form**: Tablets and capsules, rate of **disintegration** and **dissolution** is limiting factor in their absorption. After dissolution, smaller the particle size, more efficient will be absorption

4-<u>Circulation at the site</u>: Increased blood flow increase absorption

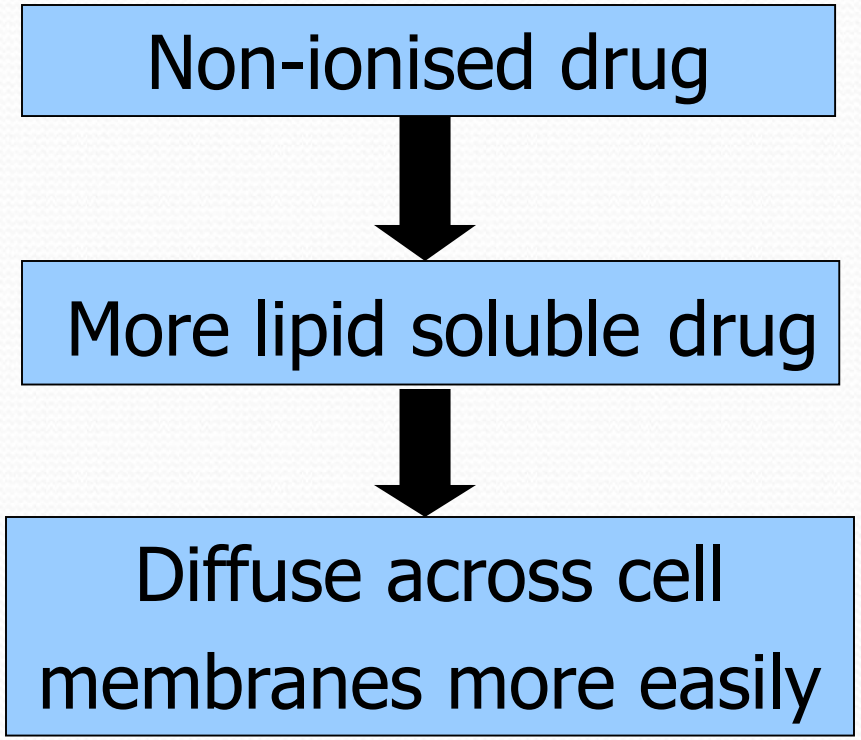
- How blood flow increase?
- How blood flow decrease?

5- <u>Total surface area available for absorption:</u> intestine has a surface rich in microvilli- more efficient absorption

6- <u>Effect of pH</u>: Most drugs are either weak acids or weak bases..

- Weak acids become less ionized(charged) in an acidic medium and weak bases become less ionized in an alkaline medium
- Unionized drug is lipid soluble and diffusible

Absorption & Ionization



7)Intestinal motility (Transit Time)

Diarrhea reduces absorption

8)Drug-Drug interactions

9)Food-drug interaction

- **slows gastric emptying**
- **generally slows absorption**
- **Tetracycline, penicillin V**

Absorption Via Parenteral Sites

IM/SC site:

- passive diffusion
- Lipid soluble, large lipid insoluble molecules, ions → absorbed at capillaries
- Very large molecules are absorbed through lymphatics.

- **Inj. IV** → completely absorbed

Absorption Via Lungs:

- Lipid soluble drugs

  simple diffusion

- Absorption is rapid because of large surface area and high vascularity.

Topical Sites:

(skin, mucous membranes, cornea)

- **Primarily depend on lipid solubility of drugs.**

- **Only few drugs significantly penetrate intact skin.**

  ---Transdermal application

  --- application of some drugs on mucous membranes(e.g. oxytocin and vasopressin as nasal spray)

- **enhance systemic absorption due to thin and highly vascular surface.**

Alkalinization of urine hastens the excretion of :

A-Weakly basic drugs

B-Weakly acidic drugs

C-Strong electrolytes

D-Nonpolar drugs

Diffusion of drugs across cell membrane :

A-Is dependent upon metabolic activity of the cell

B-Is competitively inhibited by chemically related drugs

C-Is affected by extent of ionization of drug molecules

D-Exhibits saturation kinetics

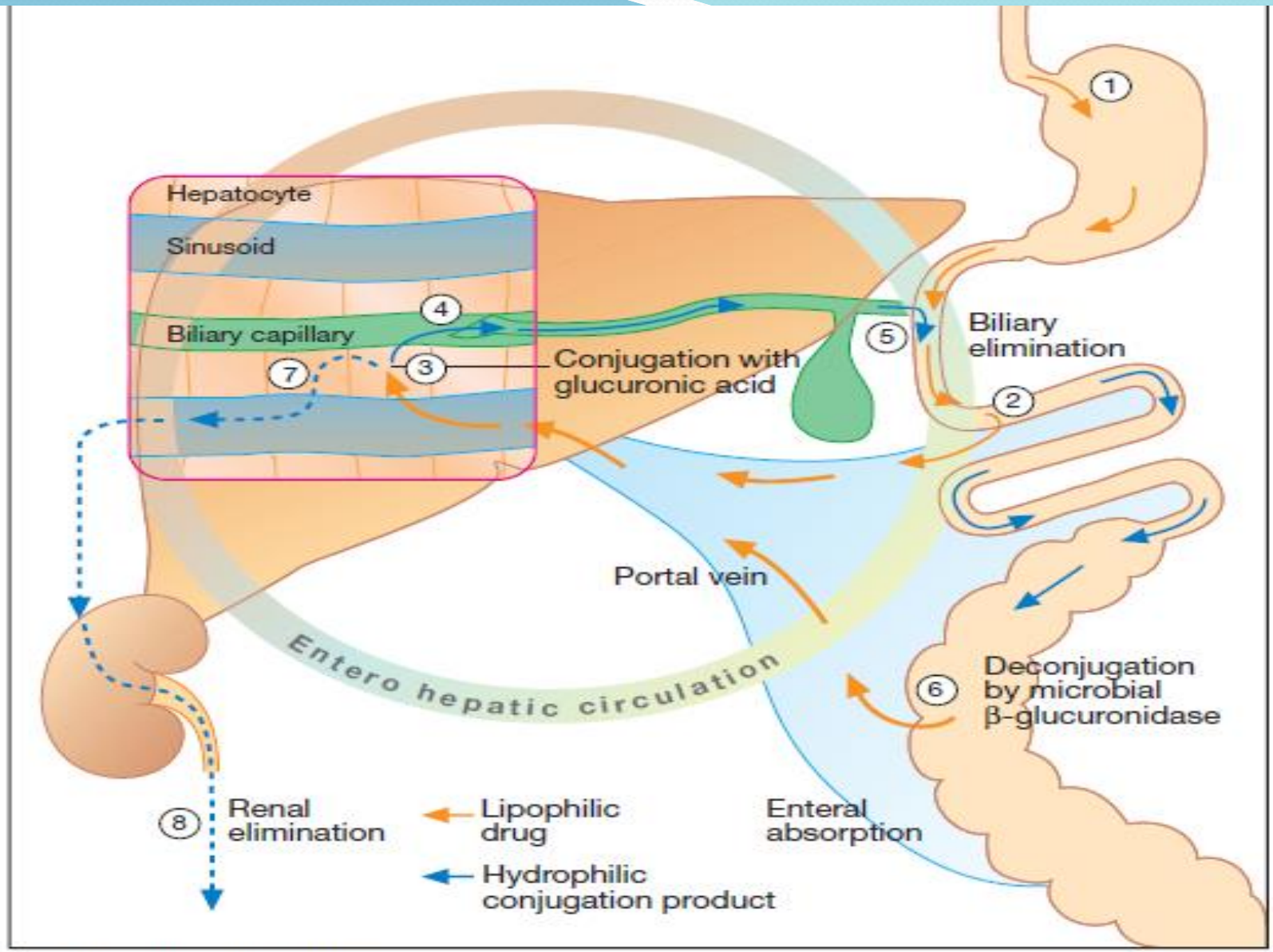
What kind of substances can’t permeate membranes by passive diffusion?

A- Lipid-soluble

B- Non-ionized substances

C- Hydrophobic substances

D- Hydrophilic substances



A. Enterohepatic cycle

BIOAVAILABILITY (F)

- Bioavailability is defined as the fraction of unchanged drug reaching its site of action or systemic circulation following administration by any route.

- For example;
  - 100 mg of a drug is administered orally
  - 70 mg is absorbed unchanged
  - The bioavailability is 0.7 or 70%
- Determining bioavailability is important for calculating drug dosages for non intravenous routes of administration.

History :

- Unusual incidence of phenytoin toxicity in epileptic patients year 1968 in Australia
- Pharmaceutical firm marketing “Dilantin Sodium Capsules” was using calcium sulphate as inert excipient.
- Since stocks of calcium sulphate got exhausted, they substituted it with lactose thinking that this minor change in inert excipient should be immaterial.
- this “reformulated product” the plasma concentration reached **30 ug/ml** leading to phenytoin toxicity.
- The reason was that lactose gets more easily wetted.
- **This resulted in faster dissolution** with implied quicker absorption and consequently higher plasma concentration, leading to toxicity.

Bioavailability

Definition: the fraction of the administered dose reaching the systemic circulation in its unchanged form from its site of administration

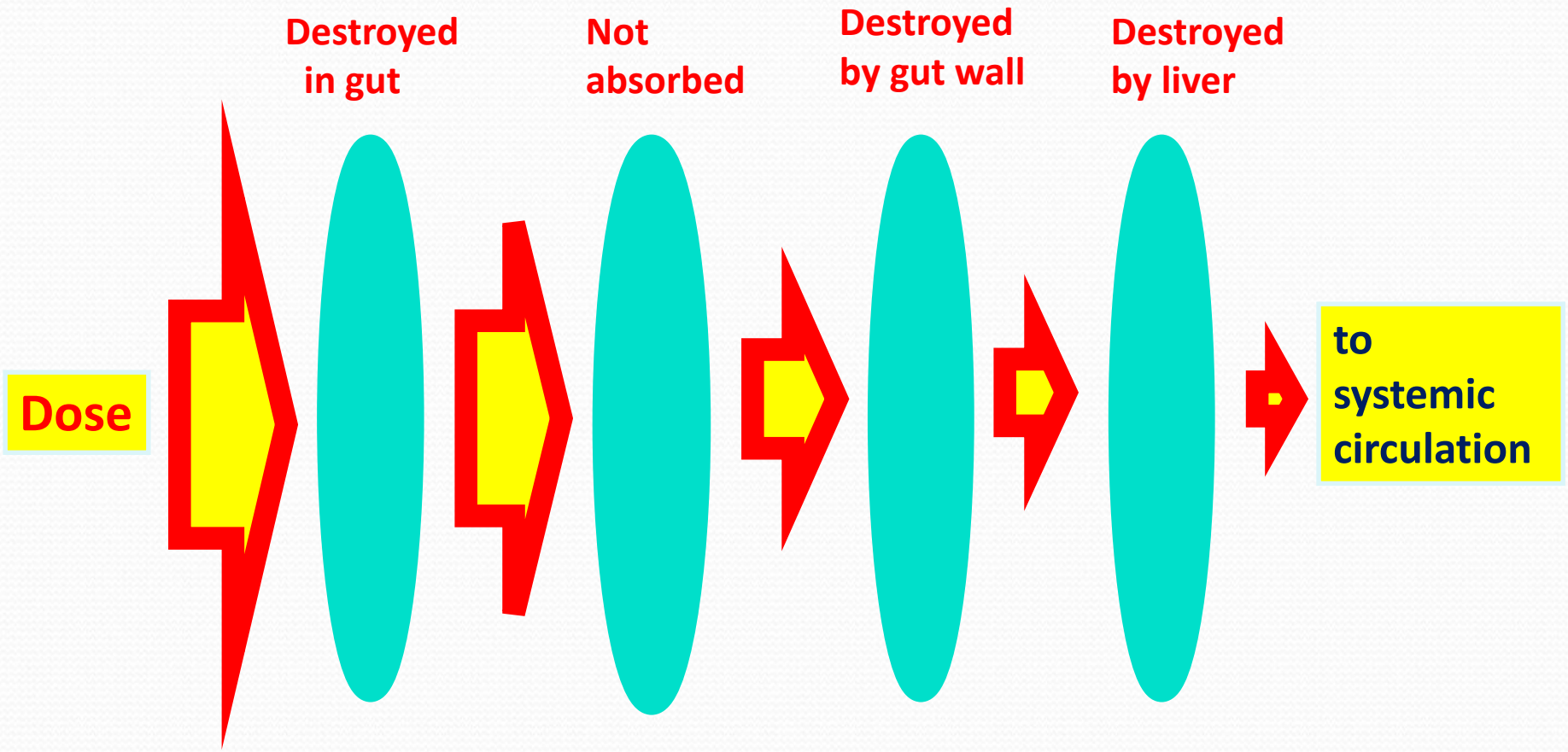
for I.V: 100%

for **non I.V**: ranges from 0 to 100%

e.g. lidocaine bioavailability 35% due to destruction in gastric acid and liver metabolism

Labelled as "F"

Bioavailability

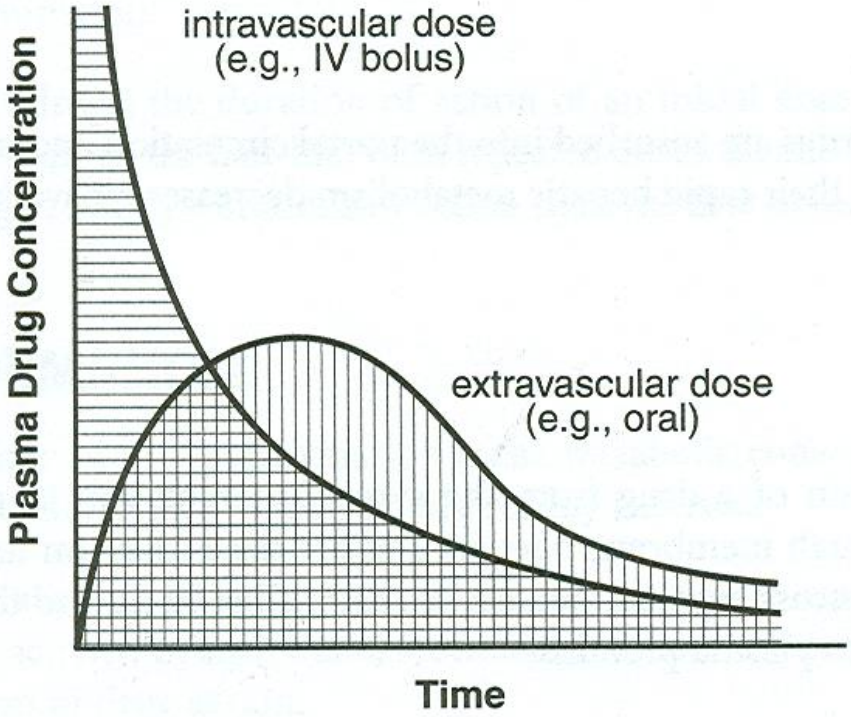


How is bioavailability measured?

- Drug plasma levels are measured at different time points following various routes of administration
- Plasma levels are plotted against time
- Area under the curve (AUC) is measured
- If oral and IV doses are the same, then

$$\mathbf{F = AUC_{oral} / AUC_{iv}}$$

Bioavailability (f)



Measure of the fraction of a dose that reaches the systemic circulation. By definition, intravascular doses have 100% bioavailability, f = 1.

$$f = \frac{AUC_{PO}}{AUC_{IV}}$$

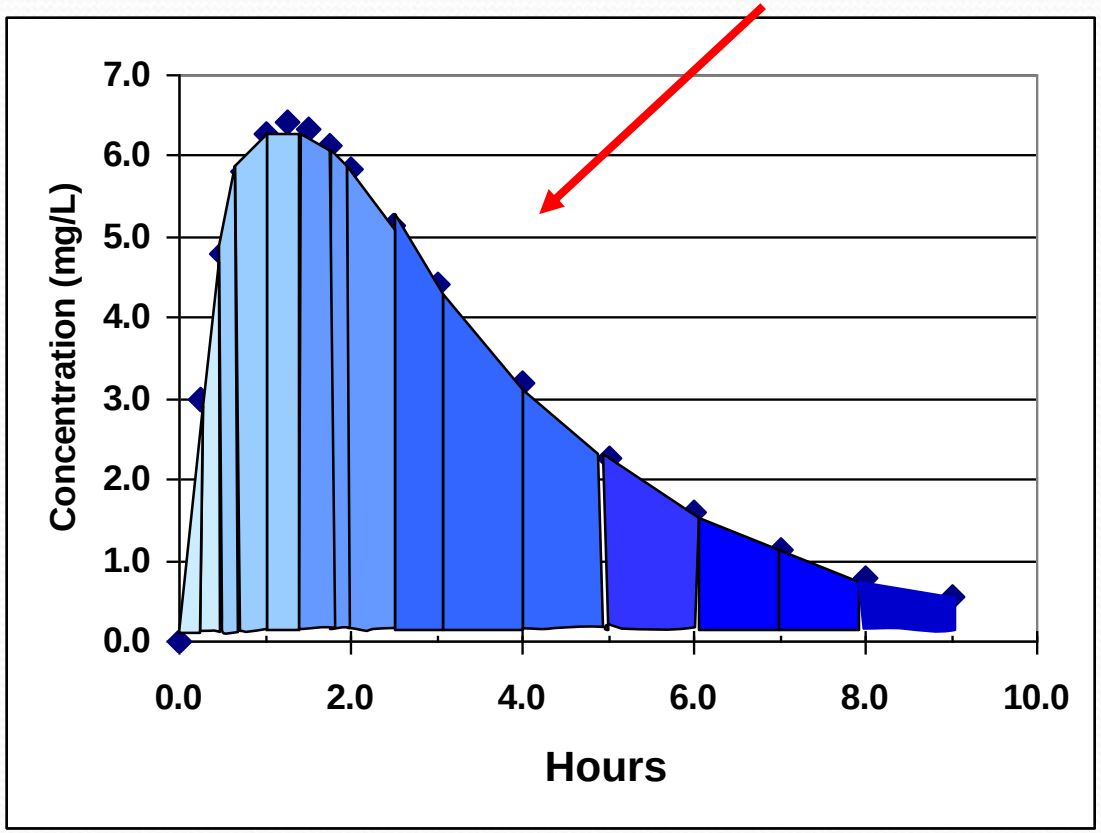
Figure I-1-4. Area Under the Curve for an IV Bolus and Extravascular Doses

Parameters for Estimating Bioavailability

Measures of Extent:
Area Under the Curve [AUC]

Is AUC a good measure of the extent of absorption?

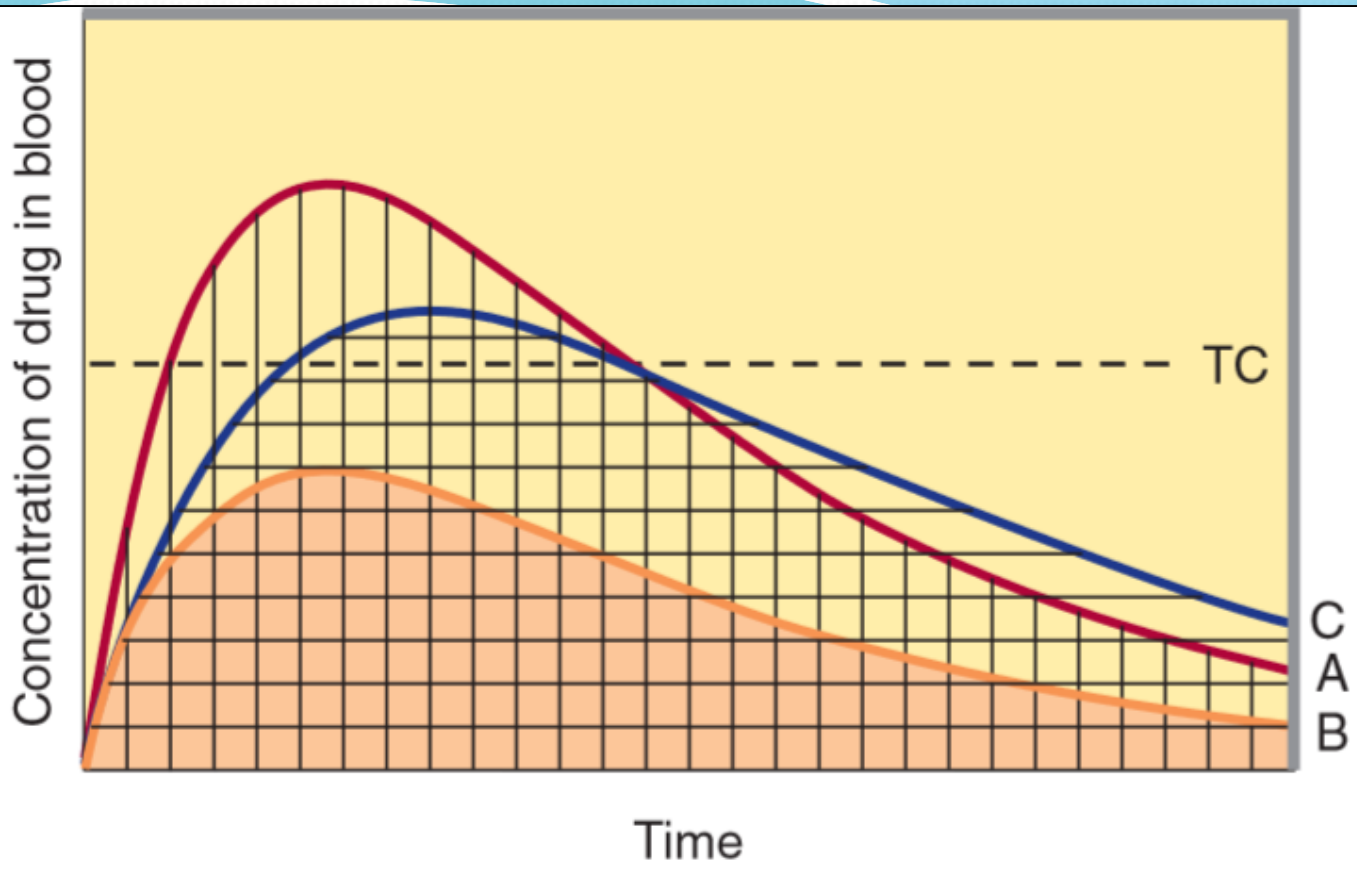
Yes ! ....



Even based on trapezoidal rule AUC is a good measure of extent

Other parameters
T max
C max

Parameter	Description	Indicates
C max	Peak plasma concentration	Rate of absorption
T max	Time to attain the Peak plasma concentration	Rate of absorption
AUC (mg-hr/ml)	Area under the curve of plasma concentration versus time curve	Extent of absorption

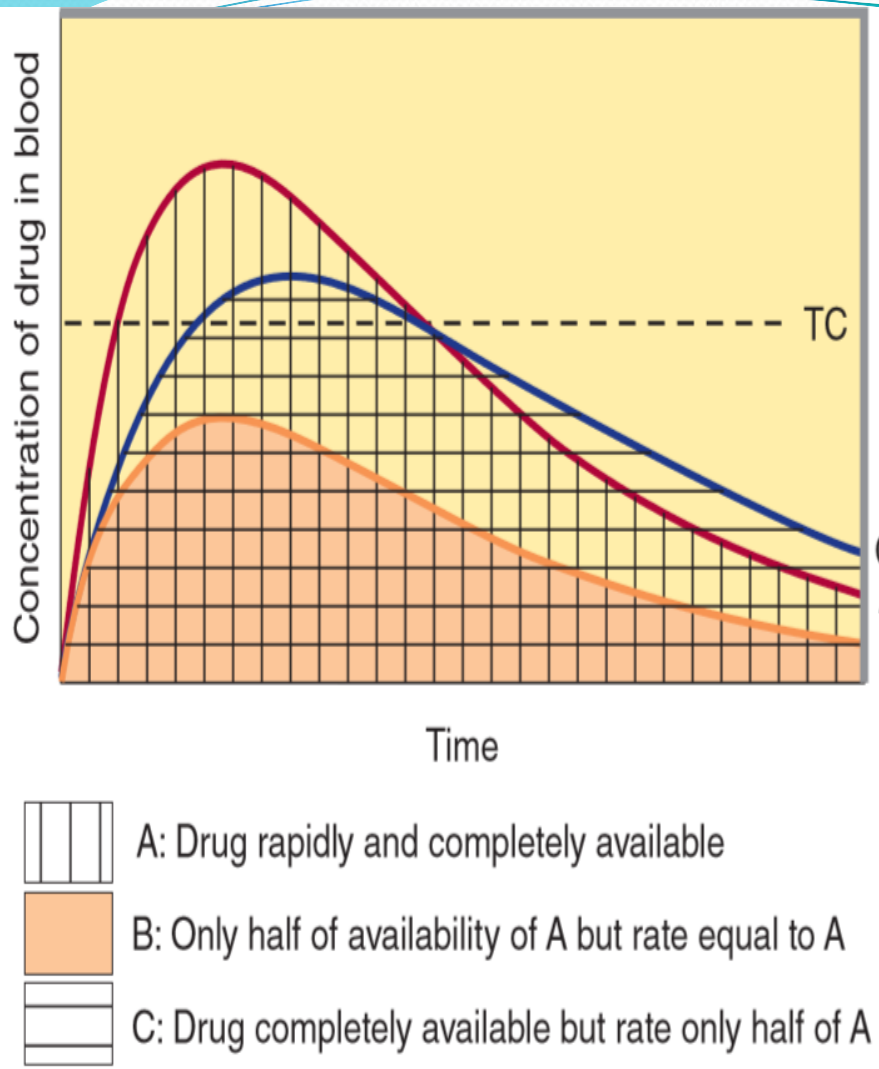


A: Drug rapidly and completely available

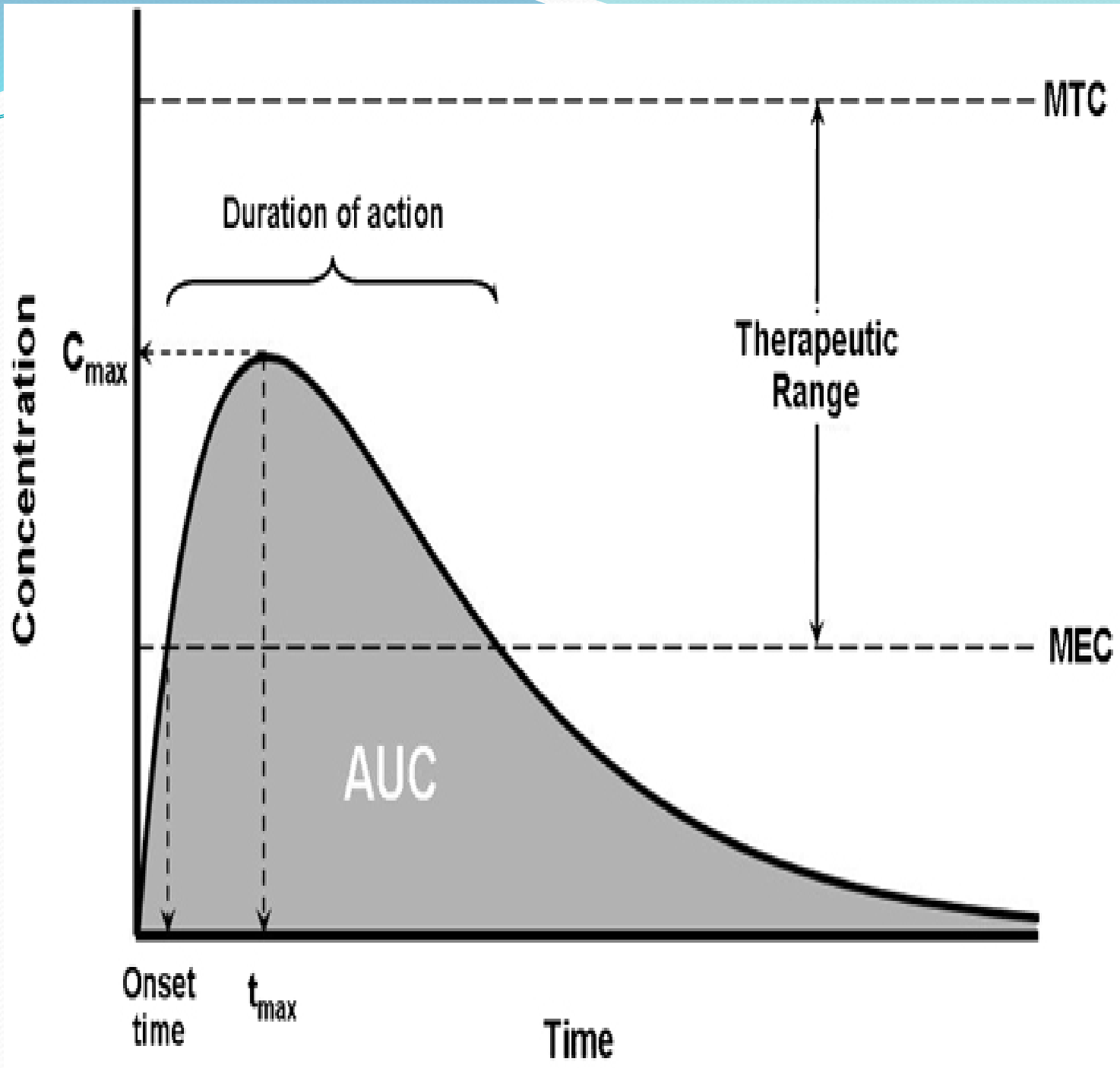
B: Only half of availability of A but rate equal to A

C: Drug completely available but rate only half of A

Rate of Absorption



- Dosage form B would require twice the dose to attain blood concentrations equivalent to those of dosage form A.
- Dosage form A would reach its target concentration earlier than from dosage form C.
- Concentrations from A would also reach a higher level and remain above the target concentration for a longer period.
- Differences in rate of absorption may become important for drugs given as a single dose, such as a hypnotic used to induce sleep.


MTC
Duration of action
Therapeutic Range
Concentration
C_{max}
MEC
AUC
Onset time
t_{max}
Time

Absolute vs. Relative

- Absolute bioavailability : when the systemic availability of the drug administered orally is determined in comparison to its i.v. administration.

- Relative bioavailability : when the systemic availability of the drug administered orally is compared with that of an oral standard of the same drug.

Relative bioavailability

If a drug cannot be given IV route ,then its bioavailability can be determined by comparing the AUC of test drug with the AUC of standard preparation of the same drug by administering both the drugs orally

FACTORS AFFECTING ORAL BA

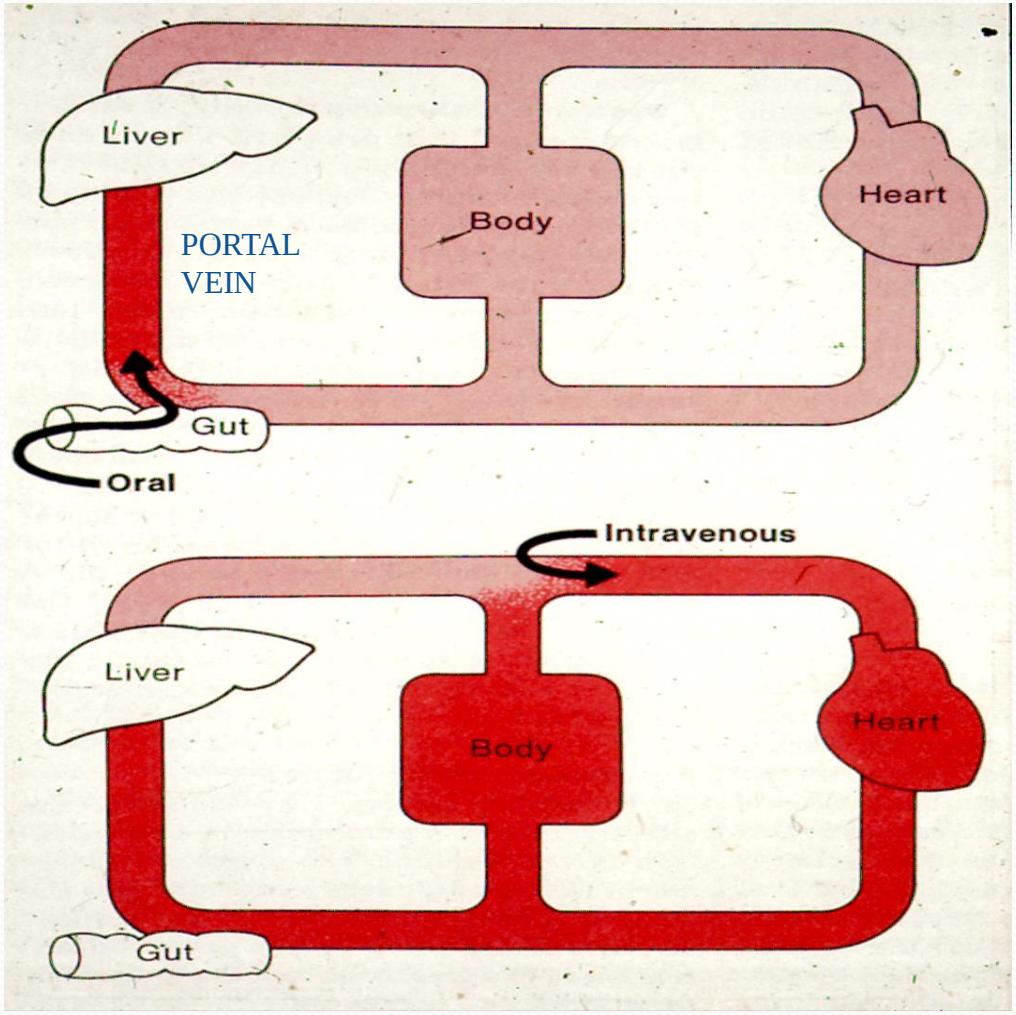
1.Biological factors

All the factors affecting oral absorption will affect bioavailability

Which are the factors….

- Lipid solubility
- Ionization status of the drug
- Area of absorbing surface
- Blood circulation
- Gastric motility/gastric emptying
- Presence of food and other drugs
- Disease states

2. FIRST-PASS METABOLISM/Presystemic elimination



If food decreases the rate **but not** the extent of absorption of a particular drug from the GIT ,then taking the drug with food will result in a **smaller**

a. Area under the plasma drug concentration time curve .
b. Maximal plasma drug concentration
c. Time at which the maximal plasma drug concentration occurs
d. Fractional bioavailability
e. Total clearance

If food decreases the rate **but not** the extent of absorption of a particular drug from the GIT ,then taking the drug with food will result in a **smaller**

a. Area under the plasma drug concentration time curve .
b. **Maximal plasma drug concentration**
c. Time at which the maximal plasma drug concentration occurs
d. Fractional bioavailability
e. Total clearance

Why?

If rate of drug absorption is reduced, then maximal drug concentration will be less ,

because more time will be available for drug distribution and elimination while the drug is being absorbed .

$$CL = \frac{\text{Rate of elimination}}{C} \qquad (1)$$

$$\begin{aligned} \text{Rate of elimination} &= Q \cdot C_A - Q \cdot C_V \\ &= Q(C_A - C_V) \end{aligned} \qquad (2)$$

$$CL_{organ} = Q\left[\frac{C_A - C_V}{C_A}\right] = Q \cdot E \qquad (3)$$

expression $(C_A\text{-}C_V)/C_A$ in can be referred to as the *Extraction ratio (E)* of the drug

$$E = \frac{CL}{Q}$$

First-pass Effect cont.

Magnitude of first pass hepatic effect:

Extraction ratio (ER)

$$ER = \frac{CL_{liver}}{Q}$$

where Q is hepatic blood flow (usually about 90 L per hour).

Systemic drug bioavailability (F) may be determined from the extent of absorption (f) and the

F = f x (1 -ER)

Drug –Morphine

- Almost completely absorbed (f= 1) ,no loss in gut
- But the liver extracts Morphine
- ER= $\frac{\text{Morphine clearance}}{\text{hepatic blood flow}} = \frac{60\text{L/h/70 kg}}{90\text{L/h/70 kg}} = 0.67$

Its oral bioavailability is

$F = f \times (1 - ER)$

$F = 1 \times (1 - 0.67)$

$F = 0.33$

$F = 33\%$

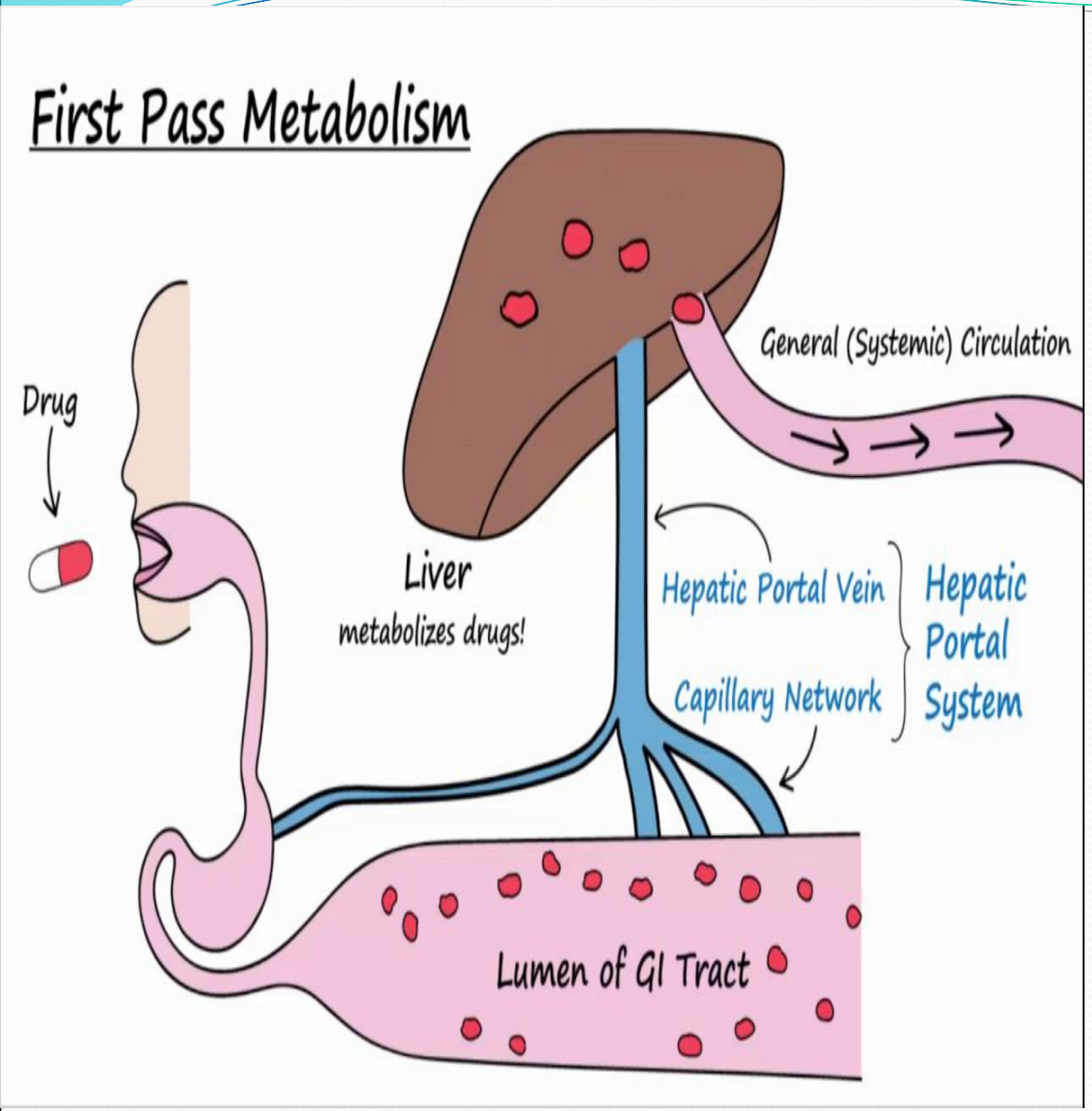
Clinical Significance of drugs with extensive 1st pass

- Should be given by parenteral route
- Interindividual variation significant
- Hepatic disease-high concentration of drugs with low TI
- Oral bioavailability may increase if two or more drugs compete for the 1st pass metabolism

Clinical significance

- Drugs that generate active metabolites the difference in oral and parenteral dose ,may not be so much

Diazepam has both the properties that it is slowly and completely metabolized and also generates active metabolites

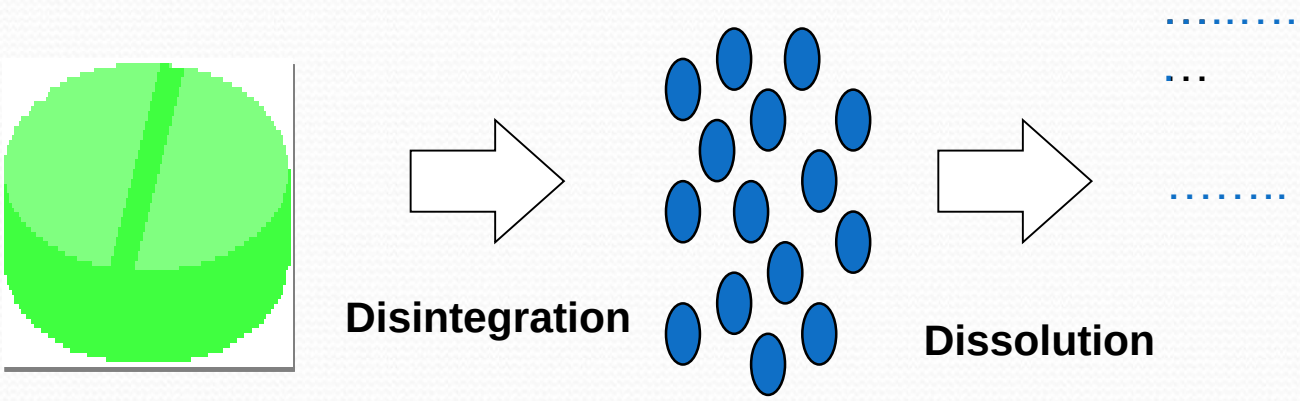


Drugs with high first pass metabolism

"NILL By Mouth"

N	Nitrates
I	Imipramine
L	Lignocaine
B	Beta blockers Highest : Propranolol
M O	Morphine

3.Pharmaceutical factors



A .Formulation/dosage form

B. Drugs in microfined form-griseofulvin,digoxin

B. Excipients and adjuvant used

Advantage of a particular brand

- Different brands differ in their bioavailability
- Drugs with narrow therapeutic index

- ✓ phenytoin toxicity
- ✓ digoxin overdosage
- ✓ Oral anticoagulants
- ✓ Antidiabetics
- ✓ Corticosteroids

4.Other factors……..

Genetic influences

Bioavailability variation assumes practical significance

- low safety margin (digoxin,phenytoin)
- dosage needs precise control (oral hypoglycemics, oral anticoagulants).
- responsible for success or failure of an antimicrobial regimen.

BIOEQUIVALENCE

Two preparations of a drug are considered bioequivalent if they show comparable bioavailability and similar times to achieve peak blood concentration

Two related drugs with a significant difference in bioavailability are said to be bioinequivalent

The drug administration route demonstrating the slowest onset of action is

A. inhalation

B. transdermal

C. intramuscular

D. sublingual

Drug absorption is NOT affected by which of the following?

A. drug ionization

B. blood flow

C. formulation

D. half-life

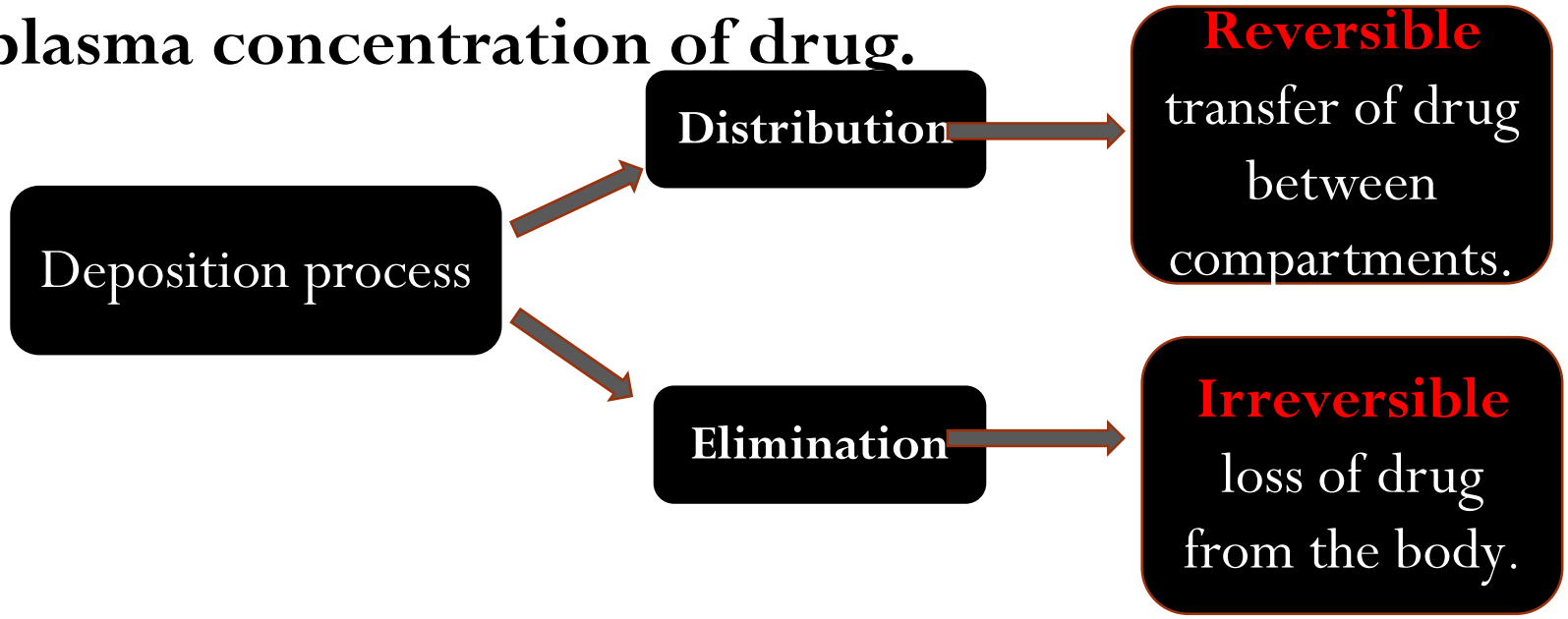
DRUG DISTRIBUTION

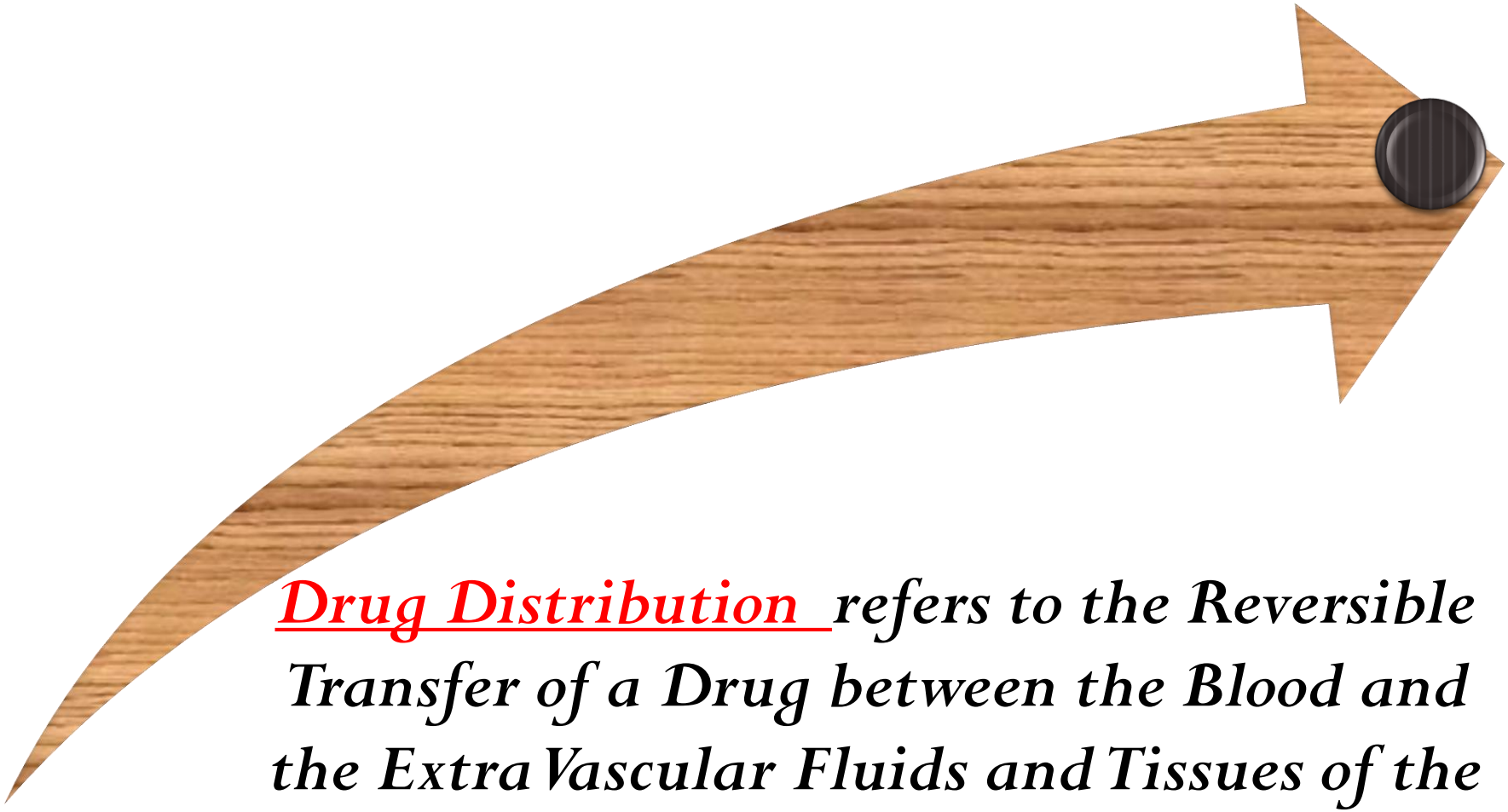
Contents

- Introduction
- Definition
- Factors affecting distribution of drug
- Reservoirs of drugs
- Body fluids
- Volume of distribution(Vd)
- Redistribution of drug

Introduction

Once a drug enter into a blood stream the drug is subjected to a numbers of processes called as DEPOSITION PROCESSES that tend to lower the plasma concentration of drug.





Drug Distribution *refers to the Reversible Transfer of a Drug between the Blood and the Extra Vascular Fluids and Tissues of the body*

(for example, fat, muscle, and brain tissue).

Distribution is a **Passive Process**,

for which the

driving force is the concentration gradient between the blood and extravascular Tissues

- The Process occurs by the diffusion of Free Drug until equilibrium is established.

DISTRIBUTION

passage of drug from the circulation to the tissue & site of its action.

Extent of distribution of drug depends on

- ✓**Lipid solubility**
- ✓**Ionization at physiological pH**
- ✓**Extent of binding to plasma & tissue proteins**
- ✓**Blood flow to the organ**
- ✓**Differences in regional blood flow**
- ✓**Disease like CHF, cirrhosis**

Drug distribution is influenced by:

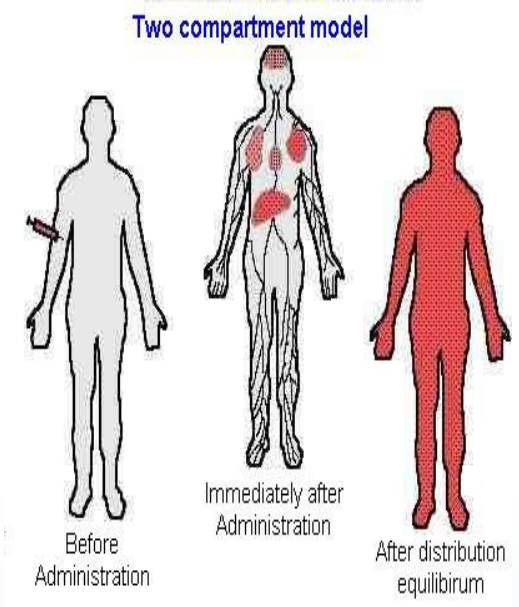
a) **Blood flow to target tissues**

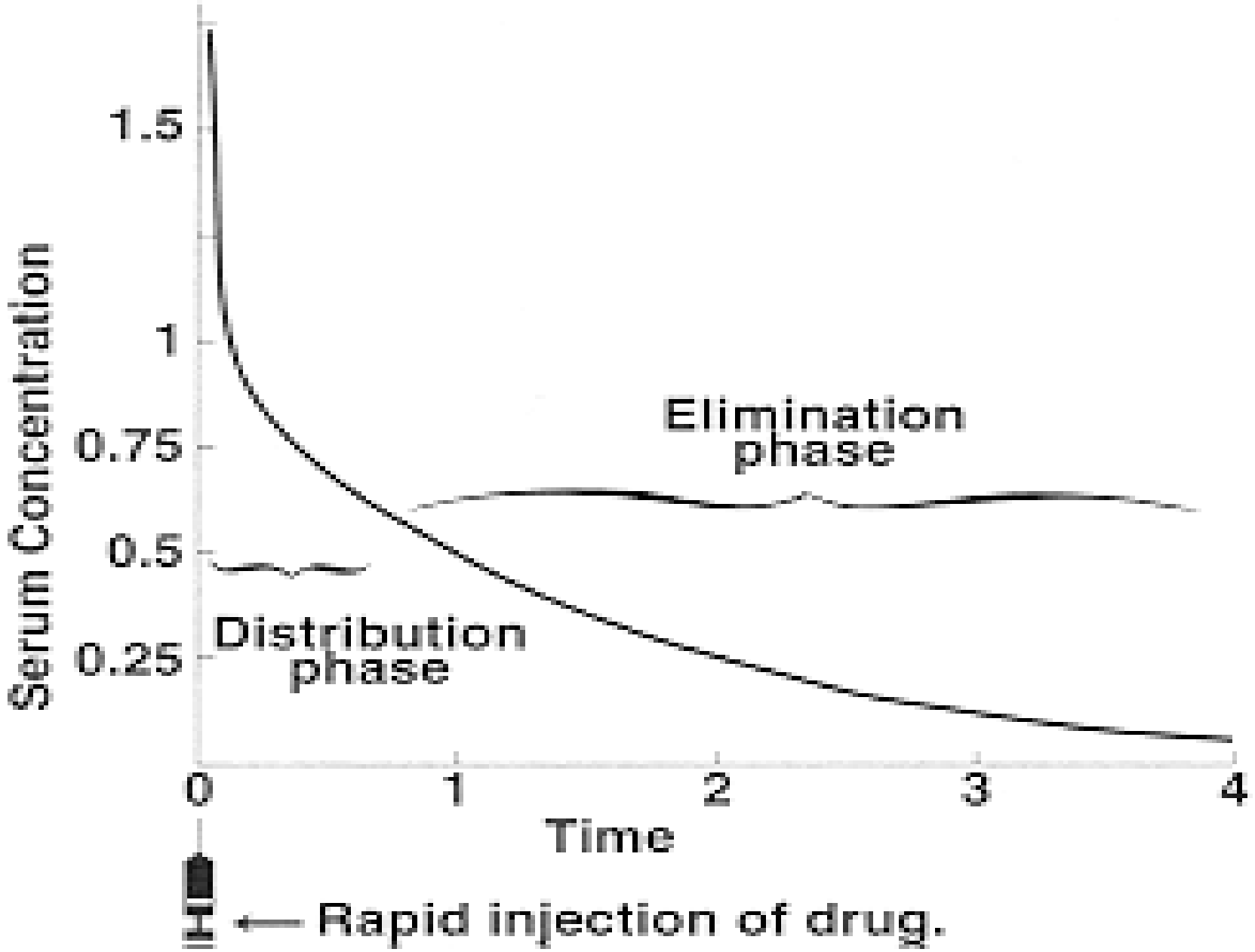
b) **Ability of drug to exit blood vessels**

- typical capillary - no barrier
- blood-brain barrier = tight junctions between endothelial cells (only lipid soluble)
- placental barrier - only lipid soluble pass freely

C) **Ability to enter cells**

must be lipid soluble, or have transporter




Serum Concentration
1.5
1
0.75
0.5
0.25
Elimination phase
Distribution phase
0
1
2
3
4
Time
Rapid injection of drug.

Two phases – 1st & 2ND Phase

1st phase

- **Rapid**
- **Limited distribution**
- **Delivery to highly perfused organs- liver,kidney ,brain**

2nd phase

- **Min to hrs to reach equilibration.**

- **Involves far larger fraction of body mass(muscle, most viscera, skin, fat)**

Drug Distribution Factors

Blood Flow

The rate at which a drug reaches different organs and tissues will depend on the blood flow to those regions

Equilibration is rapidly achieved with heart, lungs, liver, kidneys and brain where blood flow is high.

Skin, bone, and fat equilibrate much more slowly.

Body fluids:

TOTAL BODY WATER(TBW)
(42 L in 70 kg man)
60% of body weight

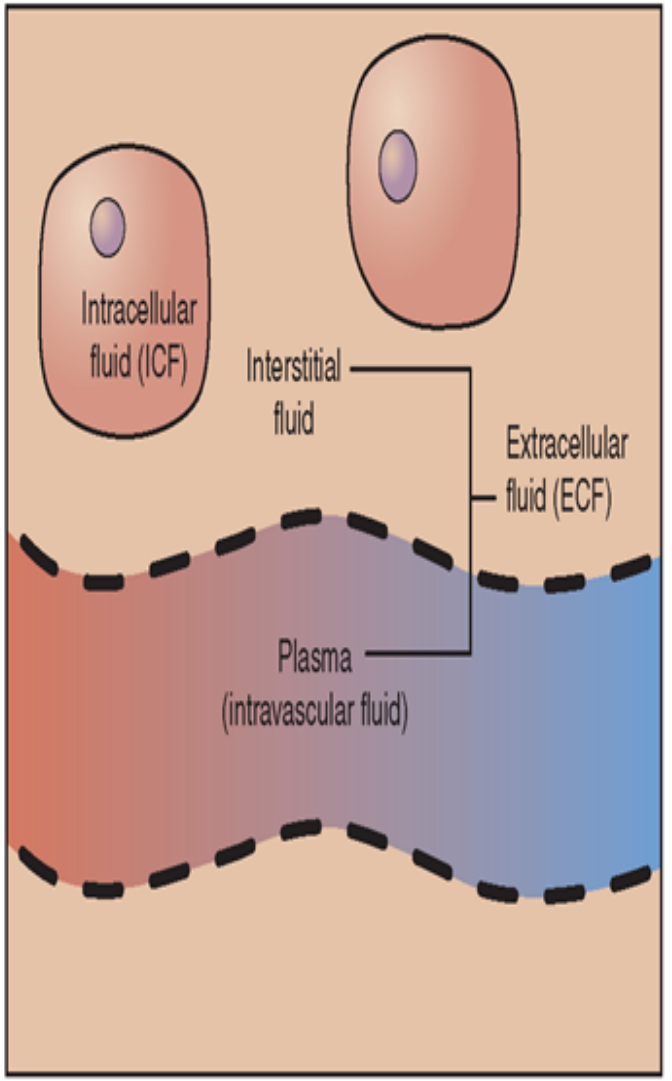
14 L
ECF
(20 % of BW)

28 L
ICF
(40 % of BW)

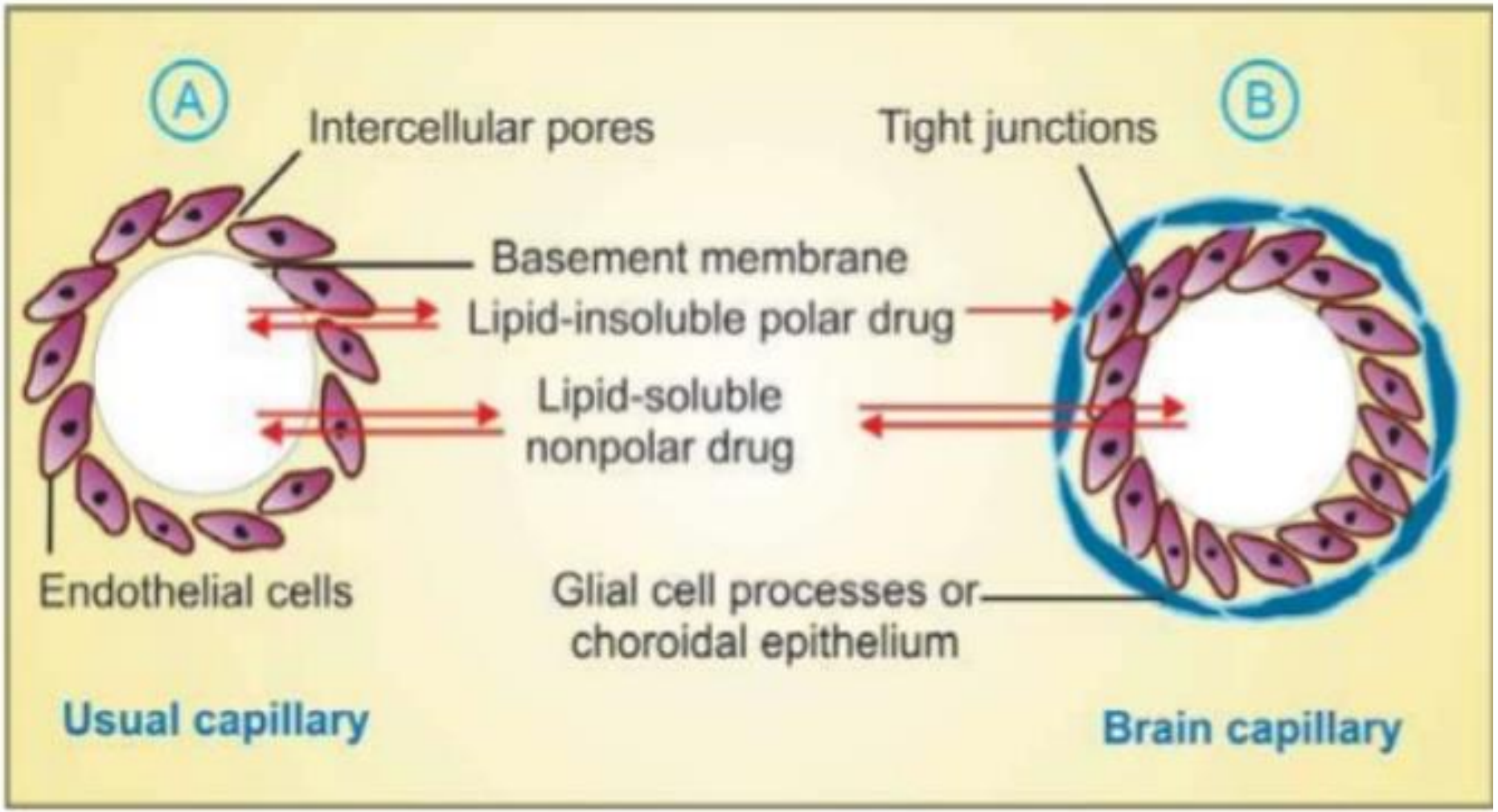
10.5L
INTERSTITIAL
FLUID(3/4th
of ECF)

3 L
(PLASMA)
(1/4th of ECF)

0.5 L
TRANSCELLU
LAR FLUID



1.Blood brain barrier:



Only lipid soluble non ionized drugs penetrate the brain easily.

- **volatile anaesthetics , ultrashort acting barbiturates, narcotic analgesics ,dopamine precursors and sympathomimetics.**

Water soluble ionized drug fail to penetrate BBB

E.g. **dopamine, serotonin ,streptomycin etc.**

- A solute may enter to brain via

1} Passive diffusion through the lipoidal barrier

2} Active transport of essential nutrients like sugars and amino acids.

- **Efflux Carriers** :

- MDR1 (P-gp) and

organic anion–transporting polypeptide(OATP) present in the brain capillary endothelial cells.

-capable of **removing a large number of chemically diverse drugs from the cell.**

- **limit access of the drug to the tissue expressing the efflux transporter.**

- Relatively restricted pharmacological access to the **brain** and other tissues such as the **testis,** where drug concentrations may be below those necessary to achieve a desired effect despite **adequate blood flow it is due to efflux carriers.**
- Second-generation antihistamines, such as **Loratadine**, achieve far lower brain concentrations than do agents such as diphenhydramine and thus are non-sedating.
- **Loperamide,** a potent, systemically active opioid with no significant absorption from the gut and does not cross the blood brain barrier(because of efflux by p - glycoprotein).

- **Blood-brain barrier disruption** has emerged as a,

strategy in the treatment of certain brain tumors such as primary CNS lymphomas (Angelov et al., 2009). The goal of this treatment is to enhance delivery of chemotherapy to the brain tumor while maintaining cognitive function that is often damaged by conventional radiotherapy.

- **Meningeal and encephalic inflammation** increase local permeability and allow polar antibiotics like ampicillin ,penicillin G to penetrate the BBB.

c) Placental barrier

- It is present between maternal and fetal blood vessels.
- The transfer of drugs across the placenta is of critical importance because drugs may cause anomalies in the developing fetus.
- Important general determinants in drug transfer across the placenta:

  -Lipid solubility,

  - extent of plasma binding, and

  - degree of ionization of weak acids and bases.
- Placenta= lipid in nature;

it allows the transfer of **non polar lipid soluble substances** mainly by a process of **passive diffusion**.

- The fetal plasma is slightly more acidic than that of the mother (pH 7.0–7.2 vs. 7.4), so that ion trapping of basic drugs occurs.
- Transfer of substances:

passive diffusion – non polar ,unionized, lipid soluble substances.

e.g., general anaesthetics,sedative hypnotics

active transport – amino acids and glucose.

pinocytosis – maternal immunoglobulins.

carrier mediated transport – ionized or water soluble drugs and essential nutrients.

Important point.....

Distribution of a drug not uniform throughout the body because **different tissues** receive the drug from plasma at **different rates** and to **different extents.**

Multi compartment model

The body is a container in which a drug is distributed - but the body is not homogeneous

(plasma; extracellular fluid; intracellular fluid; + special areas (fetus, brain)

Volume of Distribution

Volume of distribution (V_D), also known as **Apparent volume of distribution** is used to quantify the distribution of a drug between plasma and the rest of the body after oral or parenteral dosing.

It is called as Apparent Volume / Imaginary volume

It is defined as the volume in which the amount of drug appears to be distributed if concentration throughout the body is same as that of plasma

Apparent volume of distribution

If body is considered a single homogenous compartment then the distribution volume (Vd) of a drug is the volume in which it appears to be distributed (apparent) ,if concentration throughout body was same to that in plasma

Volume of distribution (Vd) (In litres for average 70 Kg adult human)

Warfarin	7
heparin	5
Aspirin	11
Sulphamethoxazole	14
Digoxin	510
Chloroquine	13,000
Imipramine	1600

Small vol. Mainly stays in plasma little in tissues.

Medium vol. Similar conc in plasma and tissues

Large vol. Mainly in tissues, little in plasma.

Which of the following statements is incorrect ?

a) A drug may produce different action in different doses .

b) Systemic effects are not always produced on oral administration

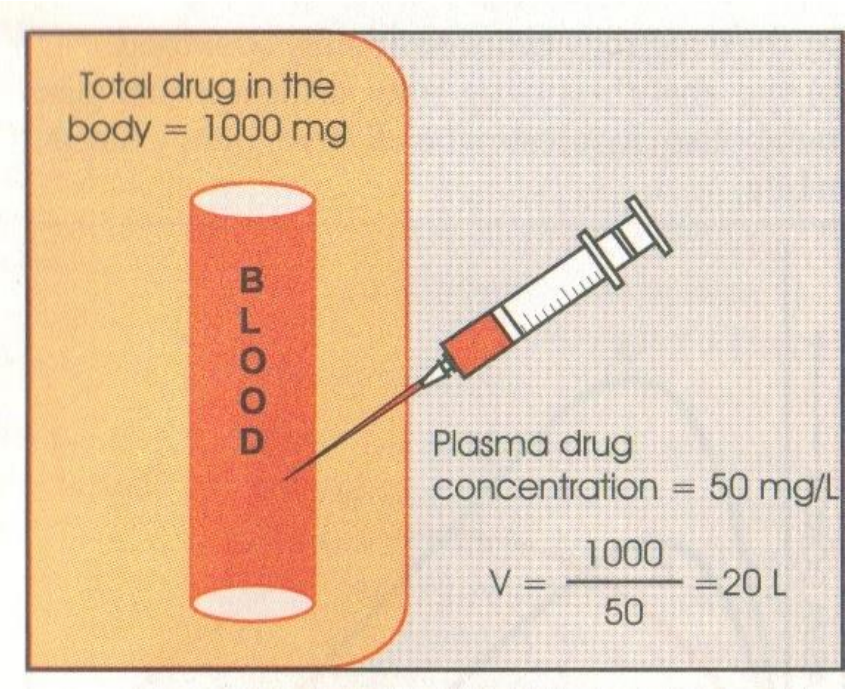
c) A drug can produce vomiting without crossing the BB barrier

d) A drug can produce vomiting only after crossing BB barrier

Apparent volume of distribution (Vd)

Presuming that the body behaves as a Single homogeneous compartment with volume V into which drug gets immediately & uniformly distributed:

$$Vd = \frac{\text{Dose administered IV}}{\text{Plasma concentration}}$$



Practice calculation

A dose of analgesic (50mg) is administered IV and a blood sample is taken shortly afterwards. The initial concentration of analgesic in the blood sample is 5 $\mu g.ml^{-1}$.

Calculate the volume of distribution of the analgesic (in Litres).

Solution

Mixed units!

$$V = D/C_0$$

$$= 50\ mg / 5\ \mu g.ml^{-1}$$

$$= 50{,}000\ \mu g / 5\ \mu g.ml^{-1}$$

$$= 10{,}000\ ml$$

$$= 10\ Litre$$

V d is expressed in litres

EXPLANATION

- The drug is present in the blood /plasma as well as in the tissue fluids +within the ICF
- It has to be visualized that all these fluids ,Plasma +tissue fluid +ICF are continuous, ie extension of plasma
- If a drug concentrates in adipose tissue, but one has to imagine that conc of the drug is same throughout the body and the volume of fluid has enlarged physically to accommodate the fact that the adipose tissue concentration is excessive

-Vd as an apparent volume may be appreciated by comparing the volumes of distribution of drugs such as **digoxin** or **chloroquine** with some of the physical volumes of the body.

- Examples:

1) if 500 µg of the cardiac glycoside digoxin were added into the body of 70 kg subject;

-a plasma concentration = 0.75 µg / L would be observed.

V = 500 µg/ 0.75 µg/L = <u>667 L</u>

-volume of distribution for digoxin of about 667 L, or a value about 15 times greater than the total-body volume of a 70-kg man.

- In fact, digoxin distributes preferentially to muscle and adipose tissue and binds to its specific receptors, **the Na+,K+-ATPase**, leaving a very small amount of drug in the plasma to be measured.

- A drug's volume of distribution therefore can reflect the extent to which it is present in **extravascular tissues** and not in the plasma.

2) the value of V for the highly lipophilic antimalarial **chloroquine** is some **15,000 L,** whereas the volume of total-body water is about 42 L in a 70-kg male.

Chloroquine
=highest Vd
(15000 L/ 70 kg)

Drugs(extensively bound to plasma proteins) that are completely retained within the vascular compartment, would have a minimum possible volume of distribution eg, **0.04 L/kg body weight or 3 L/70 kg for a drug that is restricted to the plasma compartment.**

Plasma protein binding

1. Following absorption into systemic circulation, most drugs are transported in a protein – bound form
2. Binding protein different for acidic and basic drugs.
3. Some drugs are highly protein bound, others not
4. Protein bound forms of the drug acts as a drug reservoir
5. Pharmacological activity mediated by the unbound fraction of the drug
6. Also called silent receptors

Plasma protein binding

7. Bound fraction is not available for action but dissociates from the protein once the concentration of free drug decreases

8. In hypoalbuminemia, binding may be reduced and high concentration of free drug may be attained (e.g. phenytoin).

PLASMA PROTEIN- DRUG BINDING

Protein	Molecular Weight (Da)	concentration (g/L)	Drugs that bind
Albumin	65,000	3.5–5.0	Acidic drugs,aspirin,phenytion, penicillins
α1- acid glycoprotein	44,000	0.04 – 0.1	Basic drugs - propranolol, imipramine , and lidocaine .
Lipoproteins	200,000–3,400,000	.003-.007	Basic lipophilic drug Eg- chlorpromazine
α1 globulin	59000	.015-.06	Steroid , thyroxine
α2 globulin	13400		Vit. –A,D,E,K

Drugs extensively bound to plasma proteins are largely restricted to the vascular compartment and have low Vd
(e.g. warfarin – 99% bound and its Vd is less

Drugs sequestrated in other tissues have high Vd e.g. digoxin ,propranolol,chloroquine

Therefore, in case of poisoning,
drugs with large Vd are not easily removed by haemodialysis.

Disease	Influence on plasma protein	Influence on protein drug binding
Renal failure (uremia)	↓ albumin content	Decrease binding of acidic drug, basic drug unaffected
Hepatic failure	↓ albumin synthesis	Decrease binding of acidic drug ,binding of basic drug is normal or reduced depending on AAG level.
Inflammatory state (trauma , burn, infection)	↑ AAG levels	Increase binding of basic drug , acidic drug unaffected

Displacement interactions and toxicity

- One drug can bind to many sites on the albumin molecule
- More than one drug can bind to the same site

Displacement interactions

Consequences...

1. kernicterus – displacement of bilirubin by NSAID'S drugs
2. Displacement of digoxin by quinidine
3. Aspirin displaces sulfonylureas
4. Aspirin displaces methotrexate

Redistribution

✓ Highly lipid soluble drugs when given by i.v. or by inhalation initially get distributed to organs with high blood flow, e.g. brain, heart, kidney etc.

✓ Later, less vascular but more bulky tissues (muscles,fat) take up the drug and plasma concentration falls and drug is withdrawn from these sites.

✓ If the site of action of the drug was in one of the highly perfused organs, redistribution results in termination of the drug action.

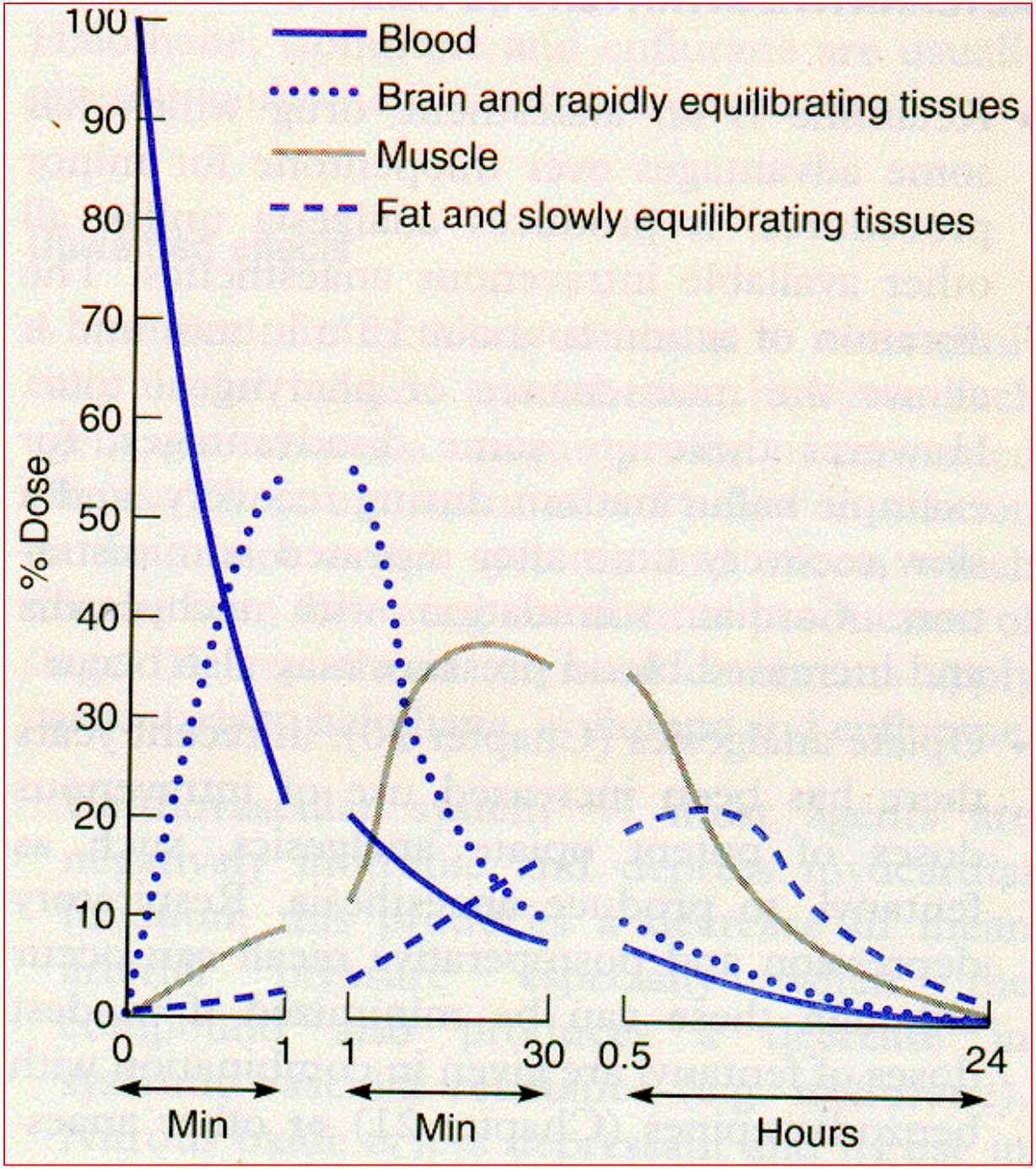
✓ Greater the lipid solubility of the drug, faster is its redistribution.

Tissue storage.

Drugs may also accumulate in specific organs or get bound to specific tissue constituents, e.g:

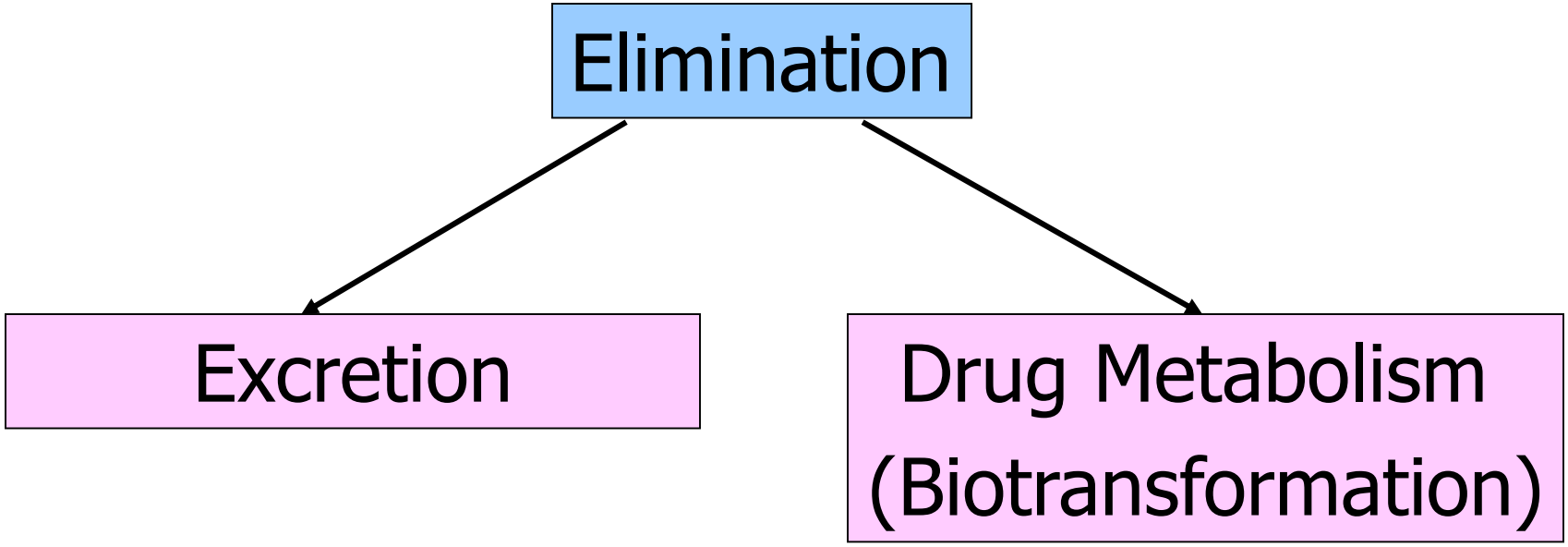
1. Heart and skeletal muscles – digoxin (*to muscle proteins)*
2. Liver – chloroquine, tetracyclines, digoxin
3. Kidney – digoxin, chloroquine
4. Thyroid gland – iodine
5. Brain – chlorpromazine, isoniazid,
6. Retina – chloroquine (to nucleoproteins)
7. Iris – ephedrine, atropine (to melanin)
8. Bones and teeth – tetracyclines, heavy metals
9. Adipose tissues – thiopental, ether, minocycline,DDT

Thiopental (thiopentone) -redistribution In muscle and fat



Elimination

The irreversible removal of the parent drugs from the body



-Definition

-Importance Of Biotransformation

-First pass Metabolism and biotransformation – what is the difference

-Phase-1 Reactions

-Cytochrome P450 Enzymes

-Phase-2 Reactions

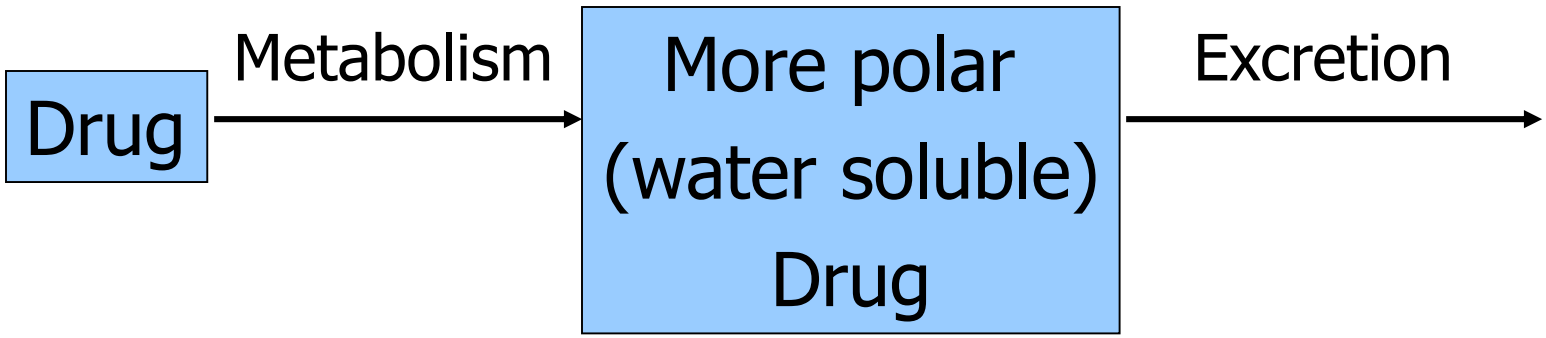
-Drug Metabolizing Enzymes

-Non Enzymatic Biotransformation

-Factors affecting drug metabolism

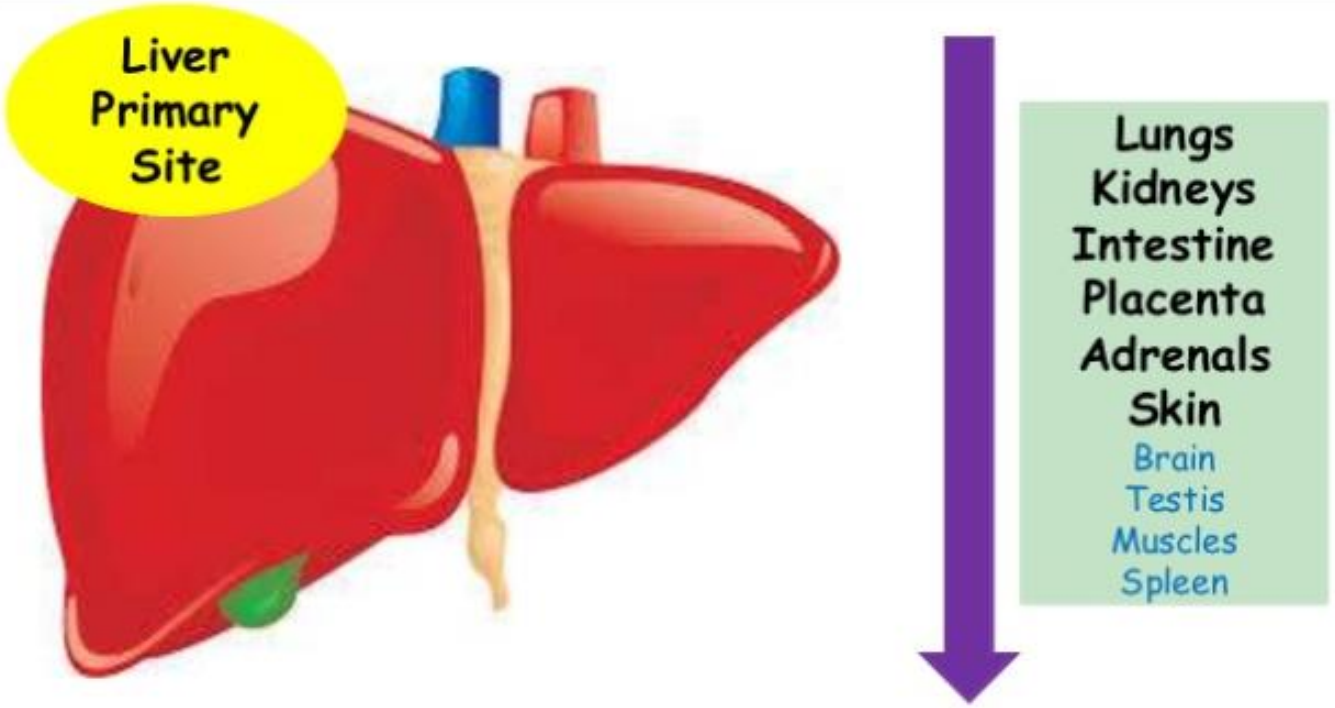
Drug Metabolism

- The chemical modification of drugs with the overall goal of getting rid of the drug
- Enzymes are typically involved in metabolism

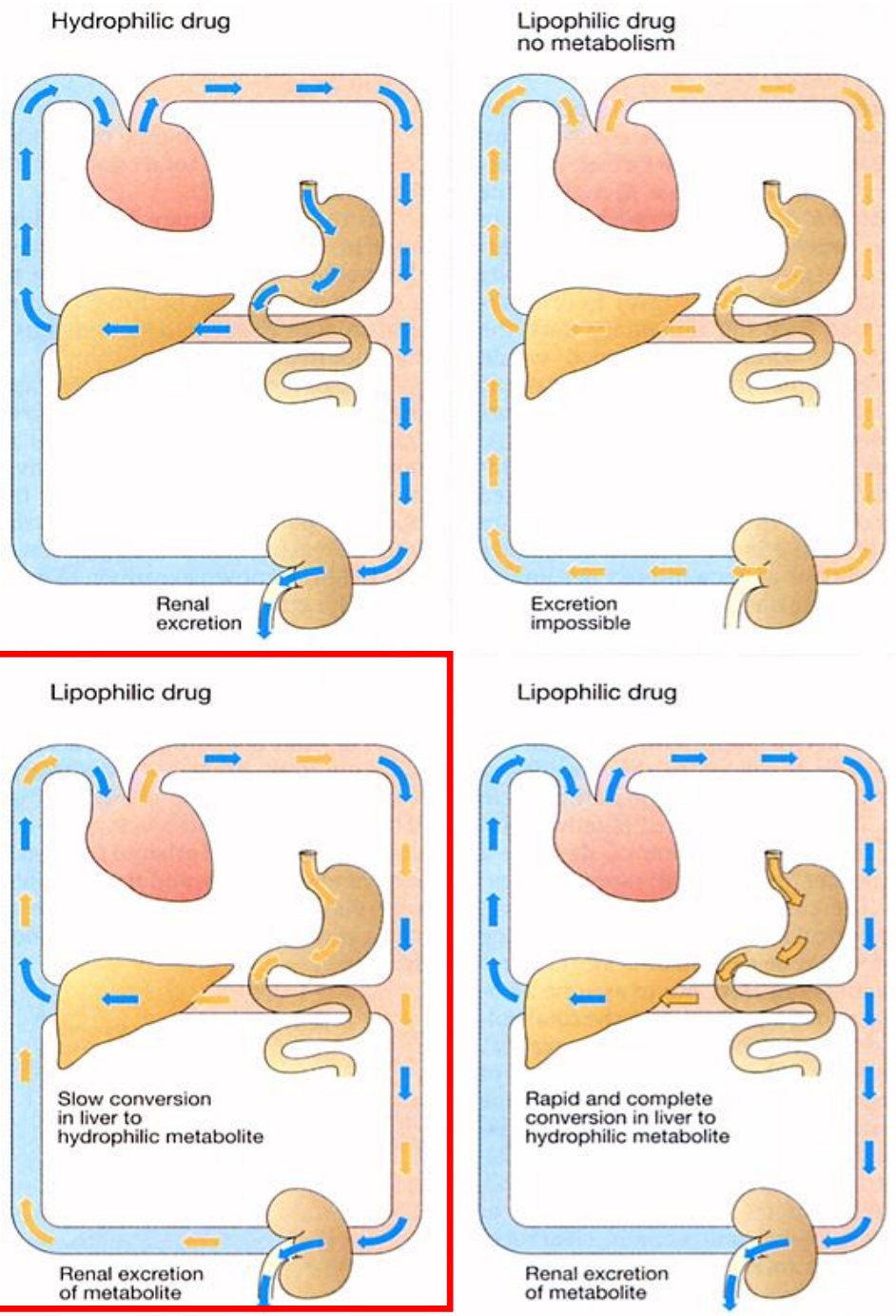


liver considered as the **"metabolic clearing house"** for both endogenous chemicals & xenobiotics as it is rich in metabolizing enzymes.

- Metabolism occur other other than liver is called **extra hepatic metabolism**.
- **lesser importance** as lower level of metabolizing enzymes present in such tissues.

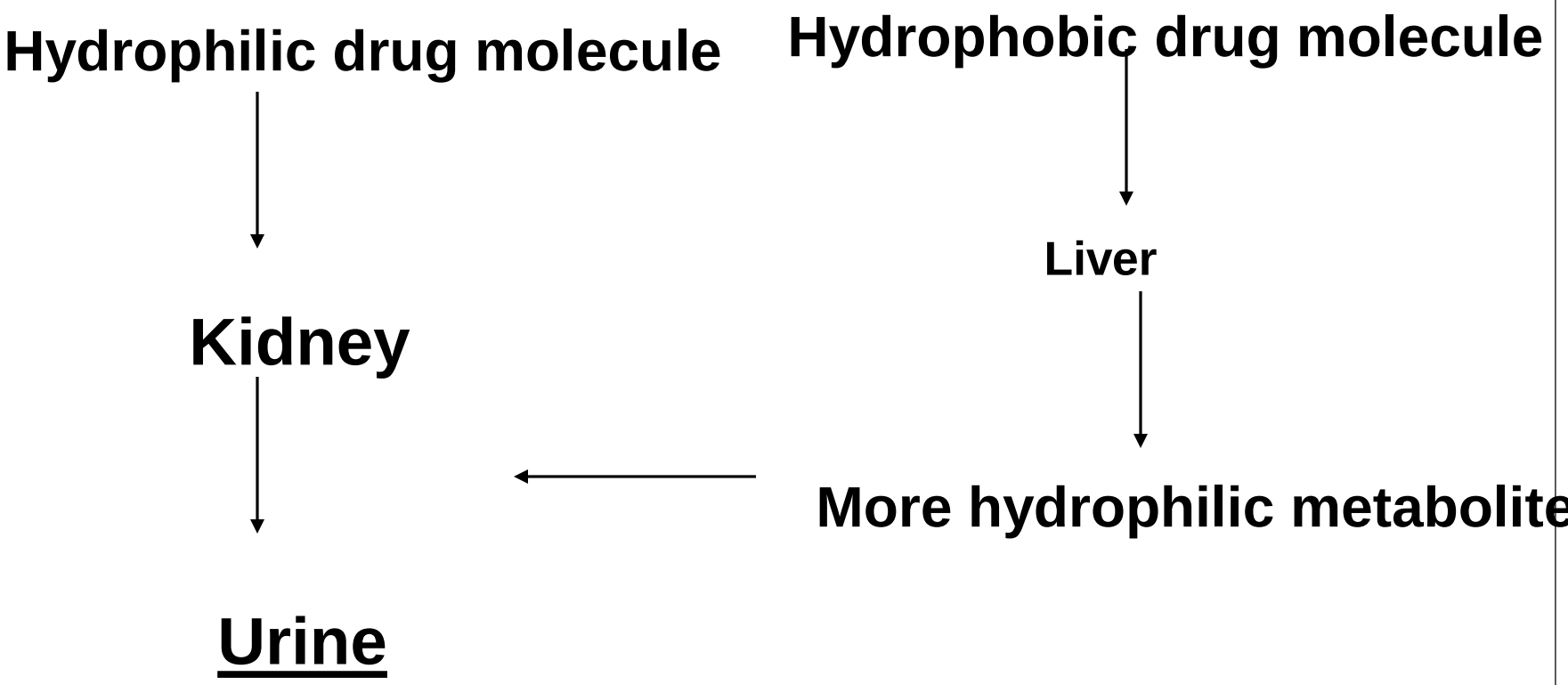


Drug Metabolism

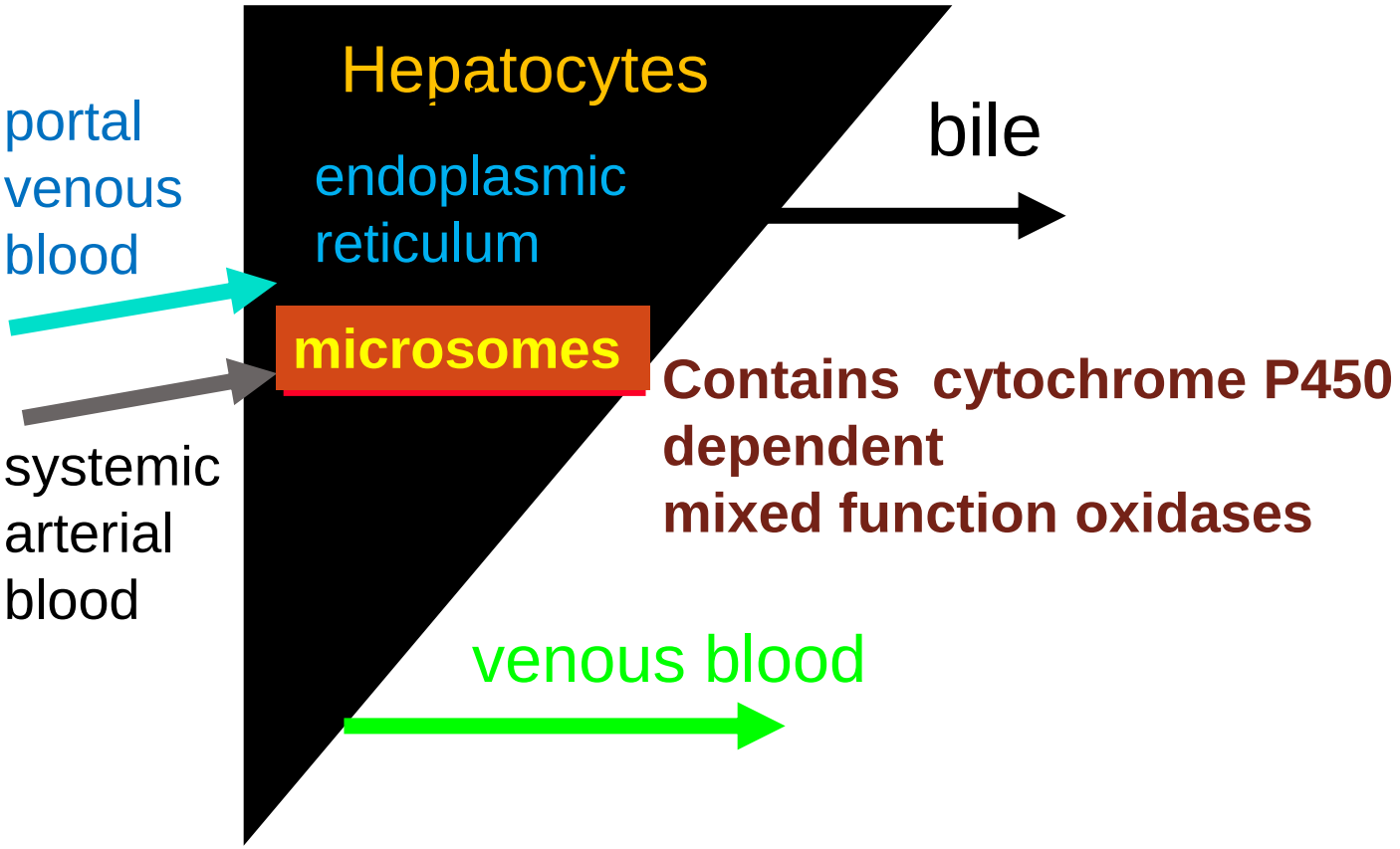


Drug elimination : Kidney

Typical pathways:



The liver


Hepatocytes
portal venous blood
endoplasmic reticulum
bile
microsomes
Contains cytochrome P450 dependent mixed function oxidases
systemic arterial blood
venous blood

Consequences Of Metabolism

1. **Inactivation**. Most drugs & their active metabolites are converted to less active or inactive metabolites

applies to most drugs.

2. Conversion of one pharmacologically *active* to another *active* substance ,this has the effect of prolonging drug action

Active drug	*Active metabolite*
amitriptyline	nortriptyline
codeine	morphine
chloroquine	hydroxychloroquine
diazepam	oxazepam
spironolactone	canrenone

3.Activation of inactive drug. Few drugs (so called prodrugs) are inactive as such.

Need conversion in the body to one or more active metabolites (enalapril, perindopril).

The prodrug-advantages:

- ✓ **Their active forms may be more stable**
- ✓ **Can have better bioavailability**

Inactive substance	Active metabolite(s)	Comment
aciclovir	aciclovir triphosphate	s , Drug for herpes infection
colecalciferol	calcitriol and alfacalcidol	highly active metabolites of vitamin D_3; s
cyclophosphamide	phosphoramide mustard	another metabolite, acrolein, causes the bladder toxicity; s
perindopril	perindoprilat	less risk of first dose hypotension (applies to all ACE inhibitors except captopril)
levodopa	dopamine	levodopa, but not dopamine, can cross the blood-brain barrier
sulindac	sulindac sulphide	possibly reduced gastric toxicity
sulfasalazine	5-aminosalicylic acid	used in ulcerative colitis
zidovudine	zidovudine triphosphate	drug for AIDS

Some more examples...

- **Dipivefrine** → **Epinephrine**
- **Bacampicillin** → **Amipicillin**
- **Prednisone** → **Prednisolone**
- **a- methyldopa** → **a-methyl norepinephrine**

PHASES OF DRUG METABOLISM

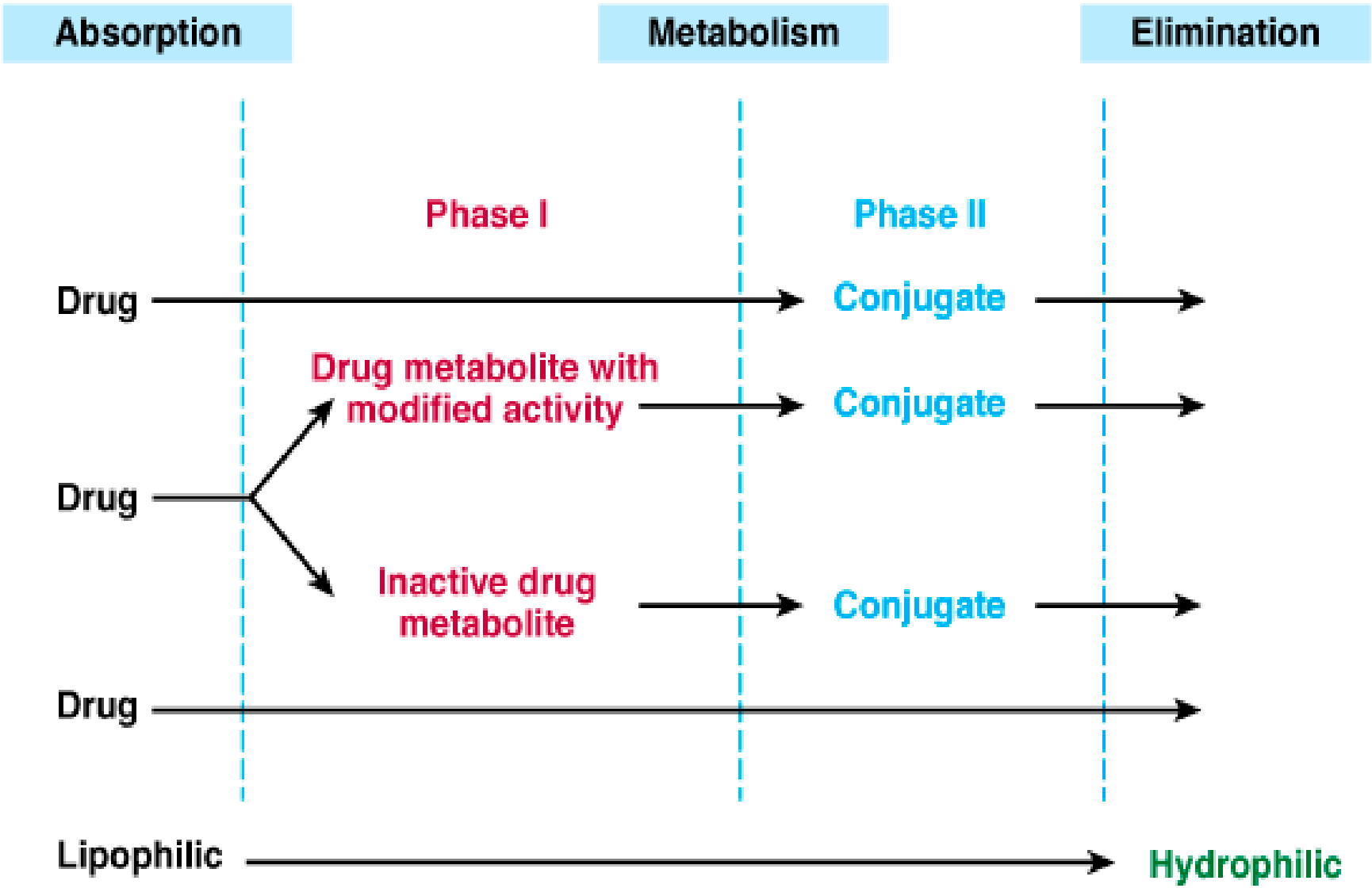
PHASE – I REACTION	PHASE - II REACTION
1.Nonsynthetic reaction	1.Synthetic reaction
2.Introduction of functional group (-OH, -NH2,-SH,-O -,-COOH)	2.Conjugates phase 1 metabolite with glucuronic acid,sulfate,acetyl, methyl groups.
3.Mainly microsomal	3.Microsomal, Mitochondrial & Cytoplasmic
4.Metabolites formed may be smaller, polar/non-polar Active/Inactive	4.Metabolites formed are usually larger,polar,water soluble &Inactive

The Most Important Enzymes

- Microsomal cytochrome P450 monooxygenase family of enzymes, which oxidizes drugs
- Act on **structurally unrelated** drugs
- Also called mixed function oxidases
- Metabolise the **widest** range of

drugs.

Biotransformation reactions can be classified into two phases: I (non synthetic) and II (synthetic, conjugation).



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

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Phase 1

- These reactions usually convert the parent drug to a more polar metabolite by introducing or unmasking a functional group.(-OH,-NH2,-SH)

Role of drug transporters in metabolism

- metabolism of drugs from often requires the transport of compounds into hepatocytes via the **organic anion transporting polypeptide (OATP) and the organic cation transporter (OCT) family of proteins.**
- **These transporters** are particularly relevant for the metabolism (HMG-CoA) reductase inhibitors (statins)

- The clearance of pravastatin is dependent on the transporter OATP1B1, which transports the drug into hepatocytes.
- Drug uptake into hepatocytes via OATP1B1 is the rate-limiting step in the clearance of pravastatin.
- The uptake of pravastatin by the liver also provides a potential advantage by keeping the drug out of the systemic circulation, from which it could be taken up by **muscle cells and thereby cause toxic effects such as rhabdomyolysis**.

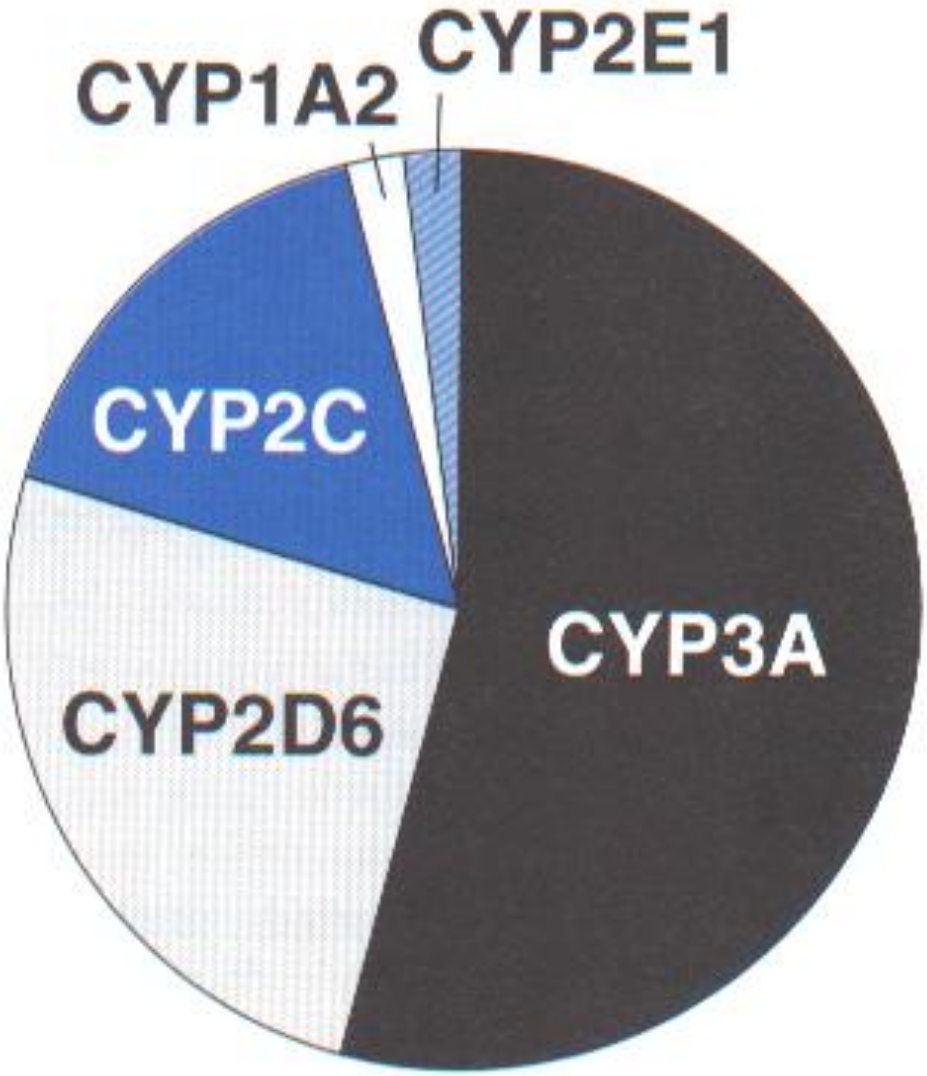
CYP-450 Families

- **Twelve CYP gene families have been identified in humans, and the categories are based upon protein sequence homology**
- **Most of the drug metabolizing enzymes are in CYP 1, 2, & 3 families .**
- **Two or more enzymes can catalyze the same type of oxidation → broad substrate specificity.**
- **CYP3A4 responsible for metabolism of many drugs; its presence in the GI tract is responsible for poor oral bioavailabilty of many drugs**

- ✓The name cytochrome P450 is derived from the spectral properties of this hemoprotein.
- ✓ In its reduced (ferrous) form, it binds carbon monoxide to give a complex that absorbs light maximally at 450 nm.

CYP Nomenclature

- **Families - CYP plus numeral (>40% homology of amino acid sequence, eg. CYP(1,2,3,4…..)**
- **Subfamily - 40-55% homology of amino acid sequence; eg. CYP1A (A,B,C….)**
- **Individual isoenzyme again allotted numeral (1,2,3,4…..)**


CYP1A2
CYP2E1
CYP2C
CYP3A
CYP2D6

✓The majority of enzymes concerned with human metabolism belong to families CYP 1, 2 and 3.

✓CYP 3A4/5 carry out biotransformation of largest number (30–50%) of drugs.

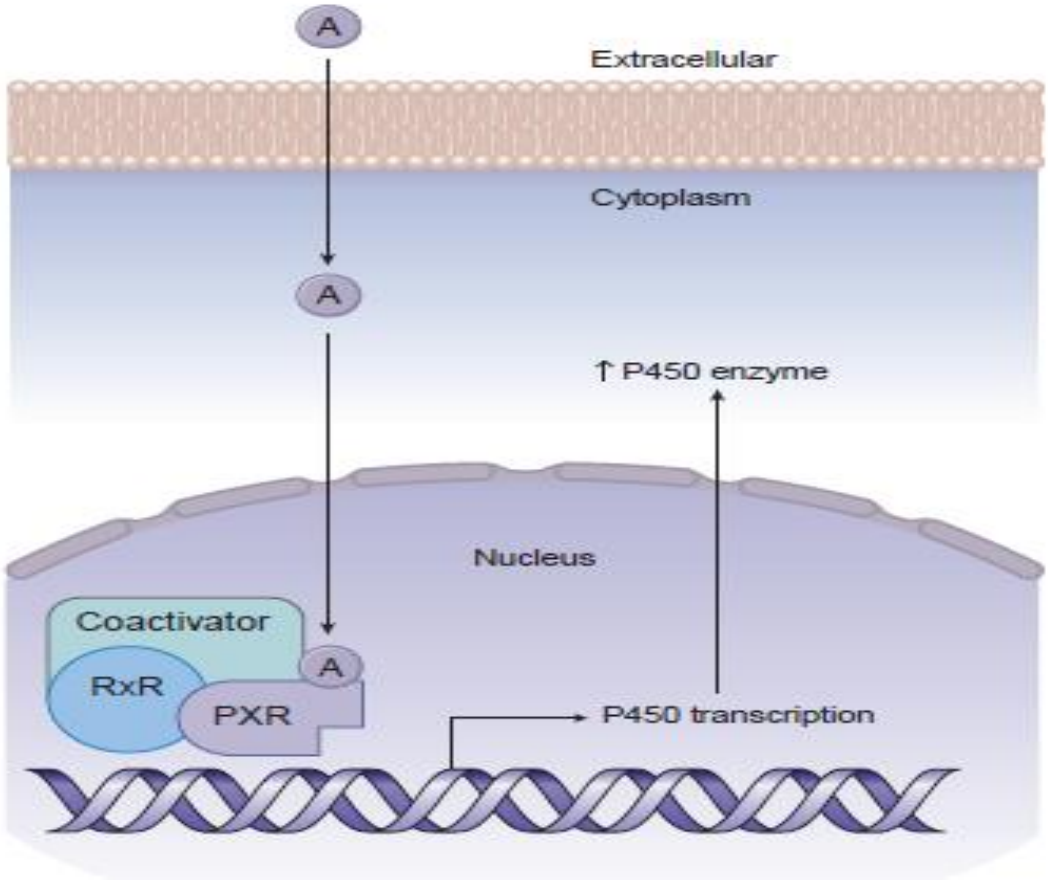
✓Inhibition of CYP 3A4 by erythromycin, clarithromycin, ketoconzole,itraconazole, verapamil, diltiazem and *grape fruit juice*

✓Rifampicin, phenytoin,carbmazepine, phenobarbital are inducers of the CYP 3A4.

- CYP3A4 and several other isoforms are inducible – prolonged drug application enhances expression& activity of enzyme in liver

- Induction may lead to accelerated metabolism of multiple drugs (not just the inducer itself). Example: Rifampicin or phenytoin → accelerated inactivation of contraceptive agents

- The primary mechanism of P450 enzyme induction is an increase in the expression of the enzyme chiefly through increased transcription
- Drugs, environmental pollutants, industrial chemicals, and even foodstuffs can enter hepatocytes and bind to several different xenobiotic receptors, such as the pregnane X receptor(PXR)(CYP3A), constitutively active/ androstane receptor (CAR), and aryl hydrocarbon receptor (AhR)(CYP1A) ,PPAR-α(CYP4A)
- Drugs, environmental pollutants bind to several different xenobiotic receptors
- These are nuclear hormone receptors

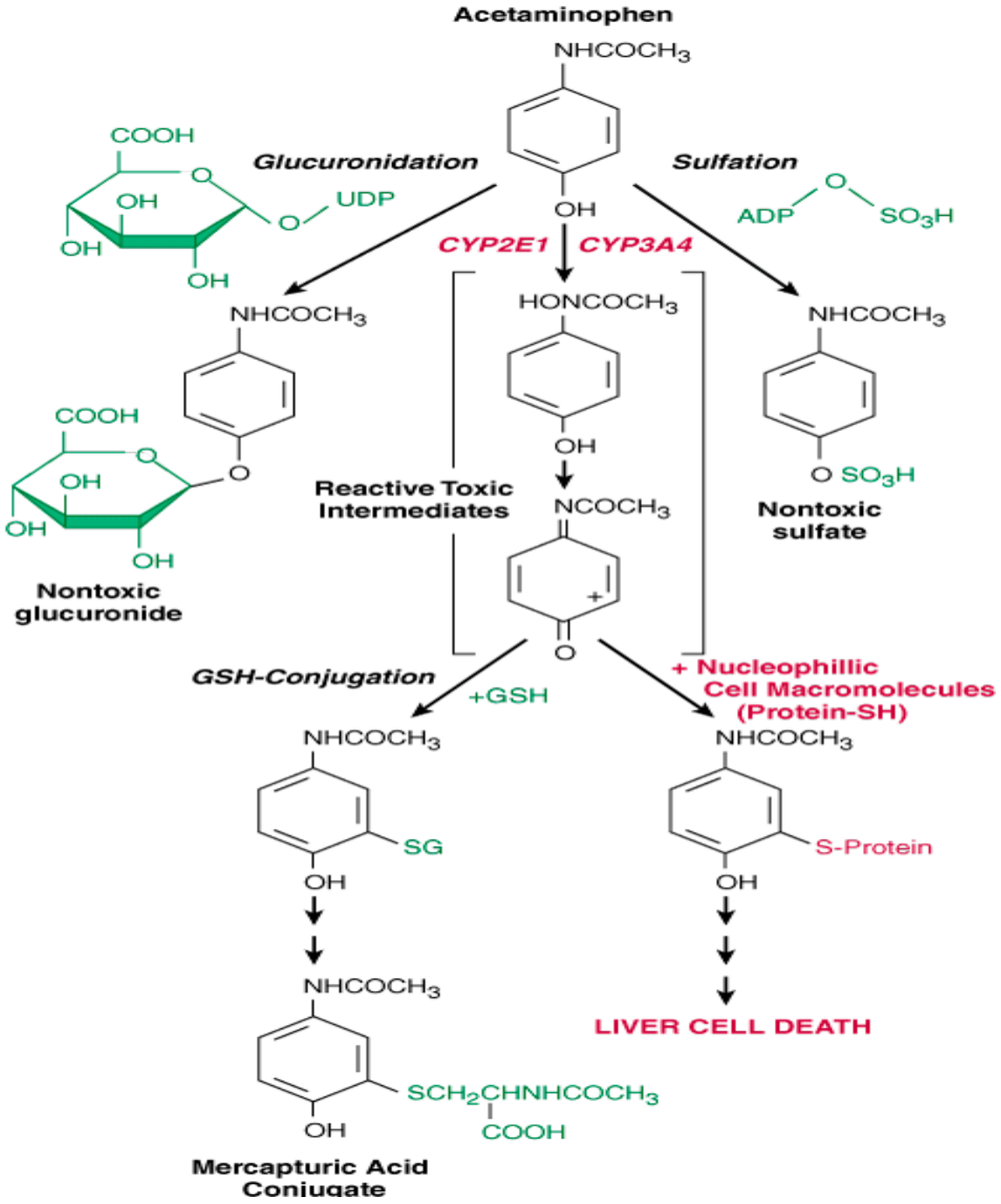


- ✓ On binding of its particular ligand ,PXR,CAR and PPAR-α ,Each forms **heterodimers** with another nuclear receptor ,the retinoid X Receptor (RXR).
- ✓ This heterodimer in turn binds to response elements within the promoter regions of specific P450 GENES TO INDUCE GENE EXPRESSION

- barbecued meats
- Barbiturates
- Brussels sprouts
- carbamazepine
- DDT (dicophane, and other insecticides)
- ethanol (chronic use)
- Nevirapine
- **phenobarbital**
- **Phenytoin**
- **primidone**
- rifampicin
- St John's Wort
- tobacco smoke

Multiple consequences of induction

- ✓ Auto induction
- ✓ Induction of coadministered drug – rifampin with HIV therapy
- ✓ Generation of toxic metabolites


Acetaminophen
NHCOCH3
OH
Glucuronidation
UDP
COOH
O
OH
OH
OH
Sulfation
ADP
O
SO3H
CYP2E1
CYP3A4
NHCOCH3
HONCOCH3
NHCOCH3
COOH
O
OH
OH
OH
O
Nontoxic glucuronide
Reactive Toxic Intermediates
OH
NCOCH3
+
O
O SO3H
Nontoxic sulfate
GSH-Conjugation
+GSH
+ Nucleophillic Cell Macromolecules (Protein-SH)
NHCOCH3
NHCOCH3
SG
S-Protein
OH
OH
NHCOCH3
LIVER CELL DEATH
SCH2CHNHCOCH3
COOH
OH
Mercapturic Acid Conjugate

Induction-relevance to drug therapy

1) Clinically important drug-drug (and drug-herb *interactions,)*

in failure of oral contraceptives, loss of anticoagulant control

1) *Disease may result. Antiepilepsy drugs accelerate the breakdown of dietary and endogenously formed vitamin* D, producing an inactive metabolite resulting in osteomalacia.

2) *Tolerance to drug therapy may result in and provide an explanation for suboptimal treatment*

3) *Variability in response to drugs is increased. Enzyme induction caused by heavy alcohol drinking or heavy* smoking may be an unrecognised cause for failure of therapy

4) *Drug toxicity may occur. A patient who becomes enzyme induced by taking rifampicin is more likely to develop* ,liver toxicity after paracetamol overdose by increased production of a hepatotoxic metabolite.

Cytochrome P450 Enzyme inhibition

- Can result in toxicity of object drug, whose metabolism is inhibited
- Clinically significant inhibition of drug metabolism occurs in case of drugs having affinity for the same isoenzyme especially if metabolized by saturation kinetics
- Cimetidine,
- Ketoconazole
- Fluoxetine
- Erythromycin
- HIV protease inhibitors

Nonsynthetic reactions/phase I

i. **Oxidation**

- ✓ **Involves addition of oxygen/removal of hydrogen**
- ✓ **Barbiturates, phenothiazines, ibuprofen, paracetamol, steroids, benzodiazepines**
- ✓ **About 95% carried out by cytochrome P 450 enzyme system**

- **Oxidation/Reduction Reactions**
- Oxidation reactions involve membrane-associated enzymes expressed within the endoplasmic reticulum (ER) of hepatocytes
- They catalyze these phase I reactions, are oxidases; majority of these enzymes are **heme protein mono-oxygenases of the cytochrome P450 class.**
- **Cytochrome**P450 enzymes also known as microsomal mixed-function oxidases

Non P450 OXIDATIVE PATHWAY

- Alcohol dehydrogenase pathway
- Monoamine oxidase pathway

ii. **Reduction:** Alcohol, warfarin, Chloramphenicol,

iii. **Hydrolysis:**,

This is cleavage of drug molecule by taking up a molecule of water

Ester hydrolysis: aspirin, procaine

Ester + H_2O ---------- Acid + Alcohol

Amide hydrolysis: procainamide, lidocaine, indomethacin

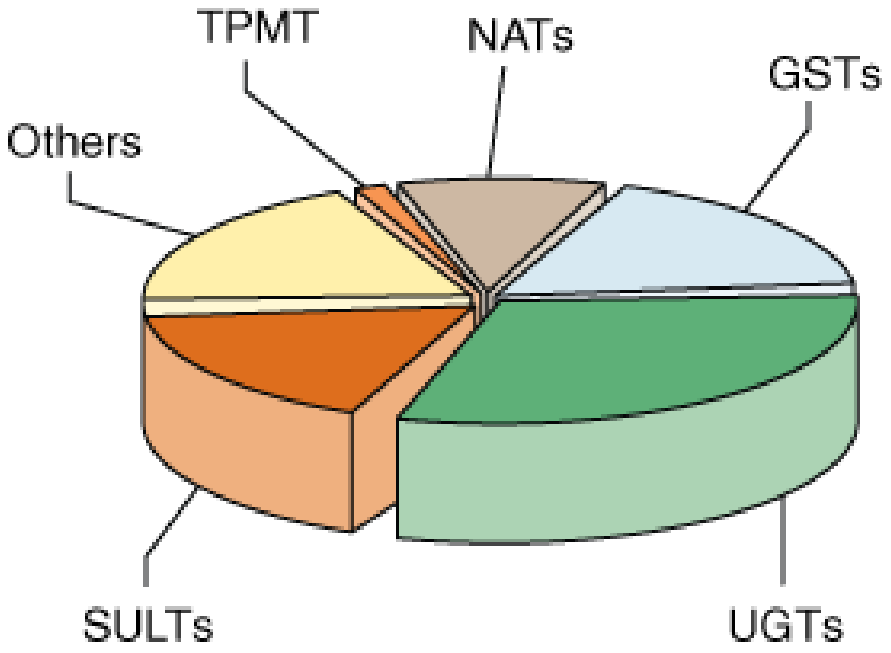
Epoxide hydrolysis : carbamazepine

IV. Cyclization: proguanil

V. Decyclization: barbiturate, phenytoin

SYNTHETIC REACTIONS/PHASE 2

- Parent drugs or their phase I metabolites undergo coupling / conjugation reactions with an endogenous substance to yield **drug conjugates.**
- Conjugates- polar - readily excreted& often inactive
- Such enzymes may be located in microsomes or in cytosol



B

GLUCORONIDE CONJUGATION

UDP – glucuronyl transferase conjugates the drug molecule with a glucuronic acid moiety

Developmental deficiency of this enzyme at birth puts infant at a risk of neonatal jaundice and kernicterus

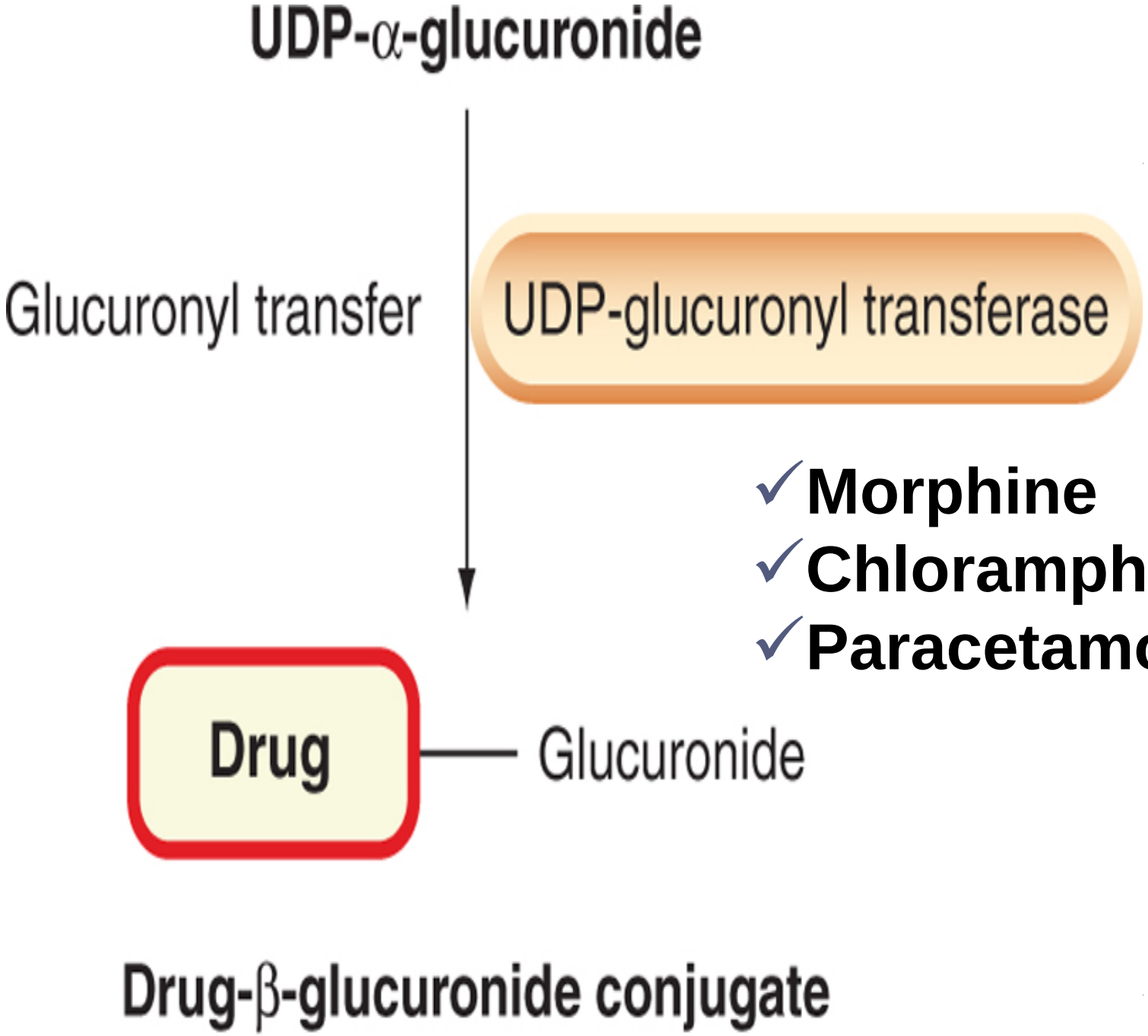
Barbiturates induce this enzyme

Morphine

Chloramphenicol

Aspirin

Diazepam



- ✓ **Morphine**
- ✓ **Chloramphenoicol**
- ✓ **Paracetamol**

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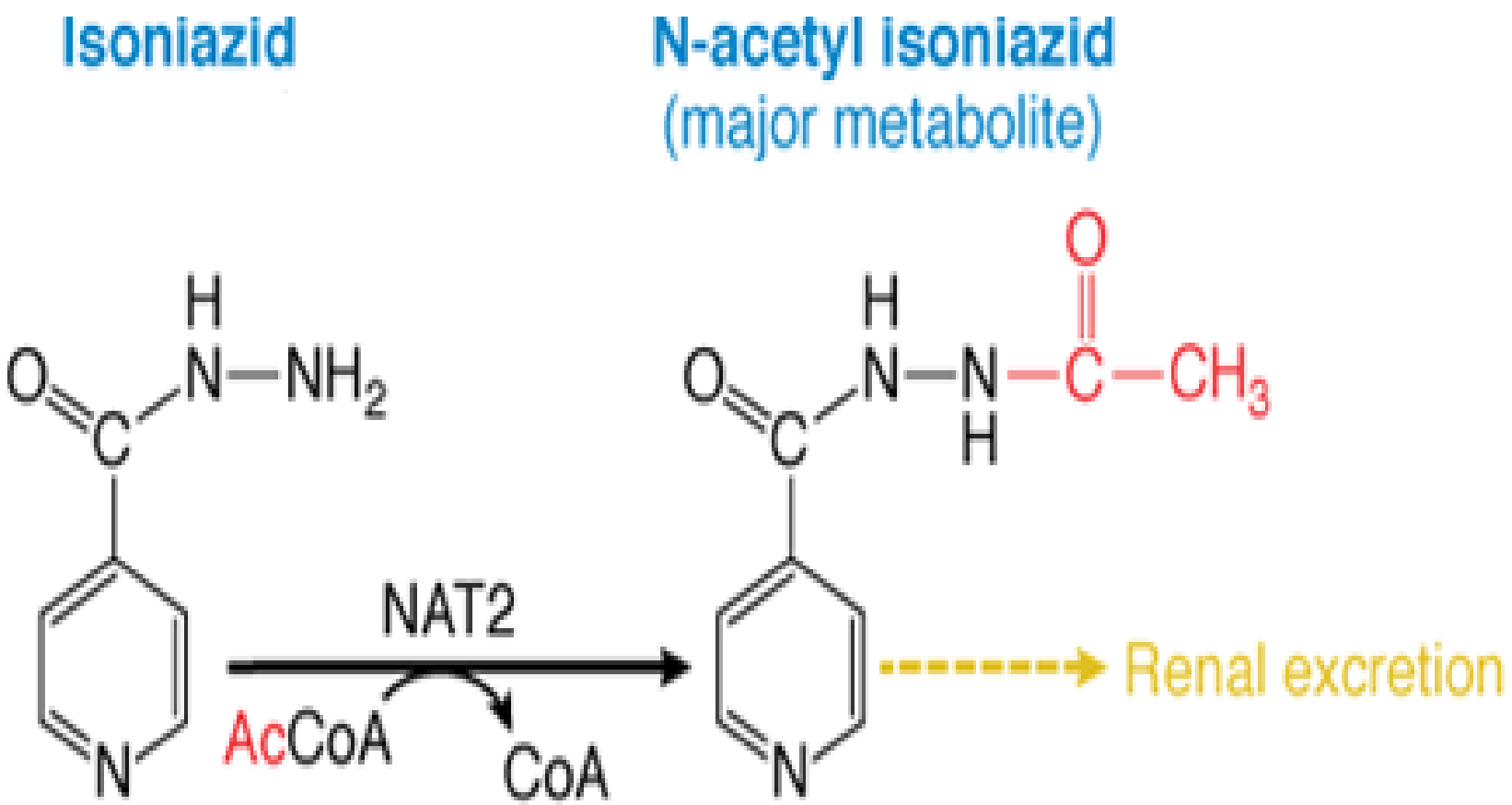
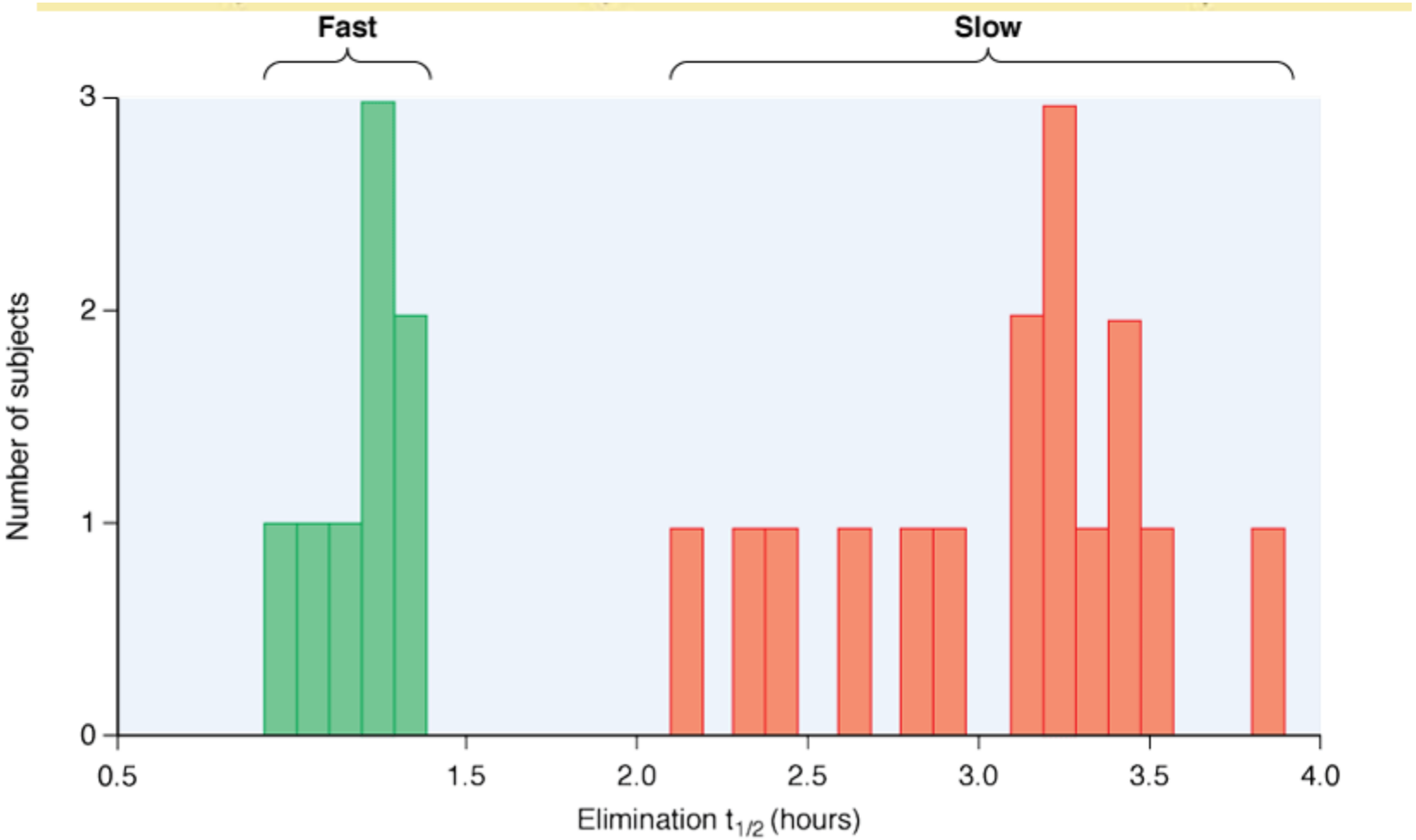
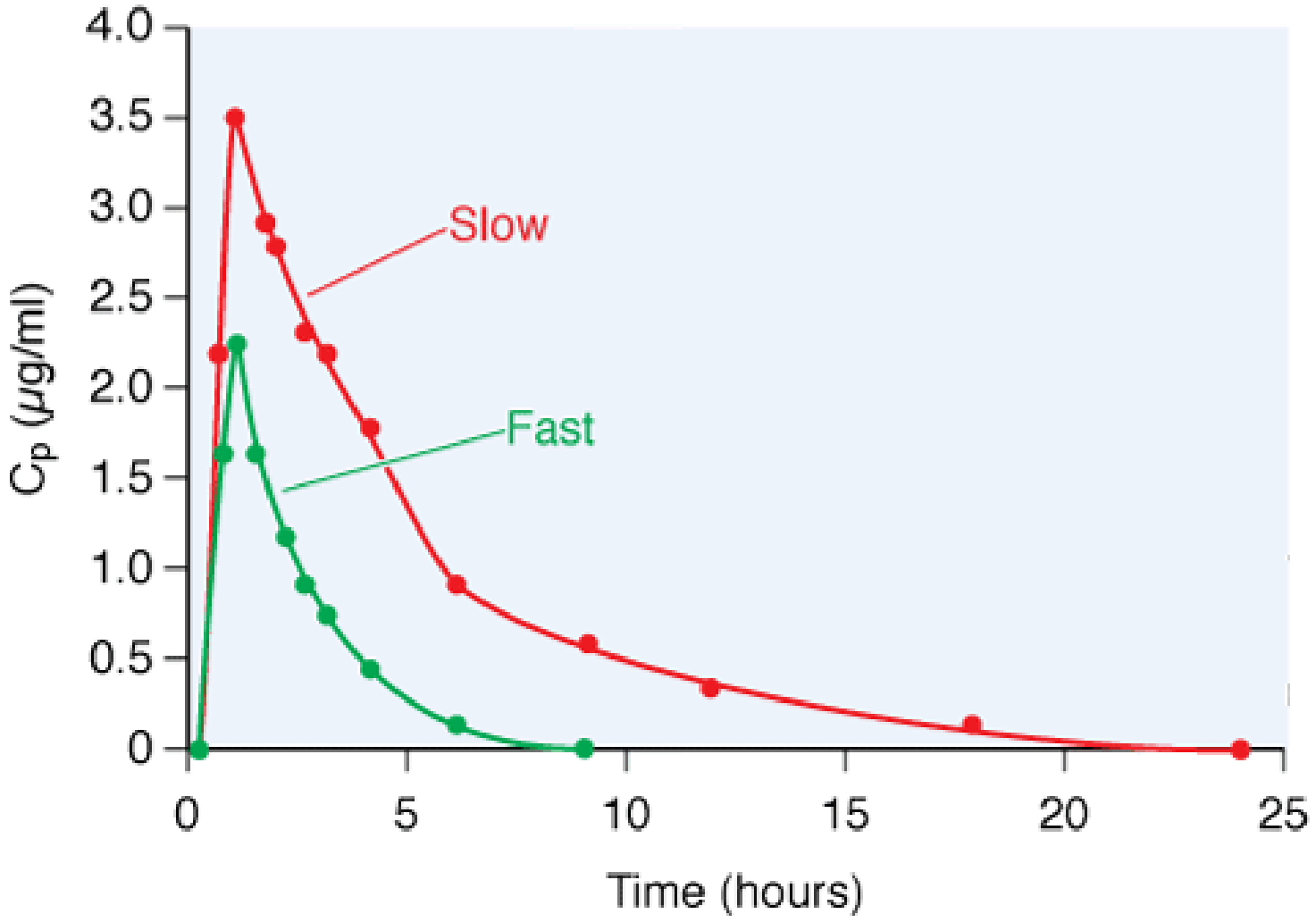
N-Acetyltransferase

- ✓ Catalyze to a drug molecule the conjugation of an acetyl moiety derived from acetyl coenzyme A
- ✓ Shows genetic polymorphism –slow and fast acetylators


Isoniazid
N-acetyl isoniazid
(major metabolite)
NAT2
AcCoA
CoA
Renal excretion

Multi-modal distribution of INH clearance due to NAT2 polymorphisms





Fast acetylation is found in Inuit ,Japanese, **Asians**
Slow acetylation predominant phenotype in most Scandinavians, Jews, and North African whites.

Methylation

- Catalyse the methyl conjugation of drugs, hormones and neurotransmitters
- COMT enzyme responsible for biotransformation of dopamine and norepineprine
- N-methylation –Norepinephrine to epinephrine
- S- methylation by enzyme thiopurine methyl tranferase (TPMT)
- Severe bone marrow depression with normal doses of 6-mercaptopurine

SULPHOTRANSFERASES

- Metabolizes and inactivates .
- Acetaminophen, minoxidil, steroid hormones

GLUTATHIONE CONJUGATION

Carried out by glutathione –S- transferase

Minor pathway

Inactivates toxic drug intermediates

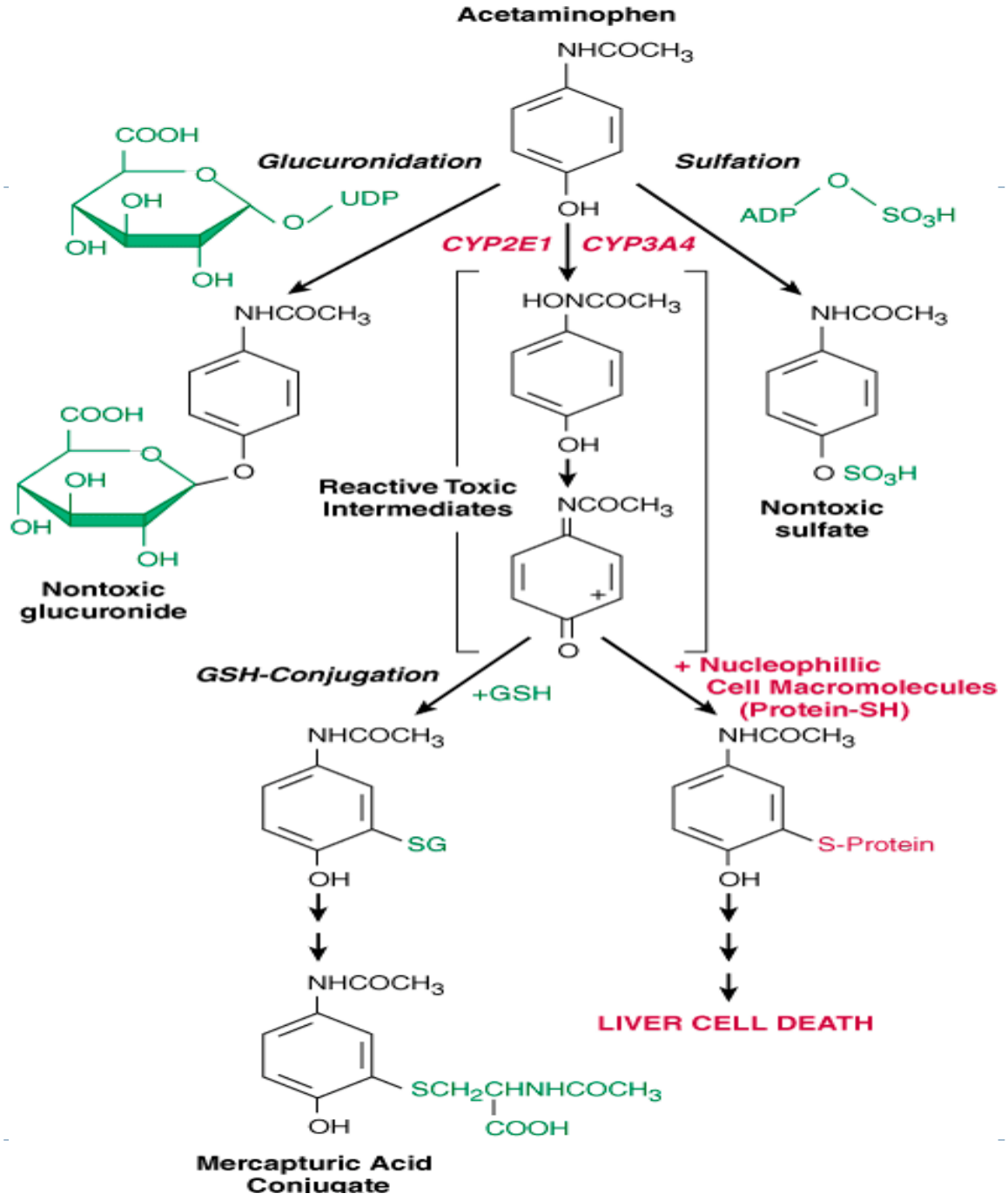

Acetaminophen
NHCOCH3
OH
Glucuronidation
UDP
COOH
OH
OH
OH
Sulfation
ADP
O
SO3H
CYP2E1
CYP3A4
NHCOCH3
COOH
OH
OH
OH
O
Nontoxic glucuronide
HONCOCH3
OH
NCOCH3
O
Reactive Toxic Intermediates
NHCOCH3
O SO3H
Nontoxic sulfate
GSH-Conjugation
+GSH
+ Nucleophillic Cell Macromolecules (Protein-SH)
NHCOCH3
SG
OH
NHCOCH3
S-Protein
OH
LIVER CELL DEATH
NHCOCH3
SCH2CHNHCOCH3
COOH
OH
Mercapturic Acid Conjugate

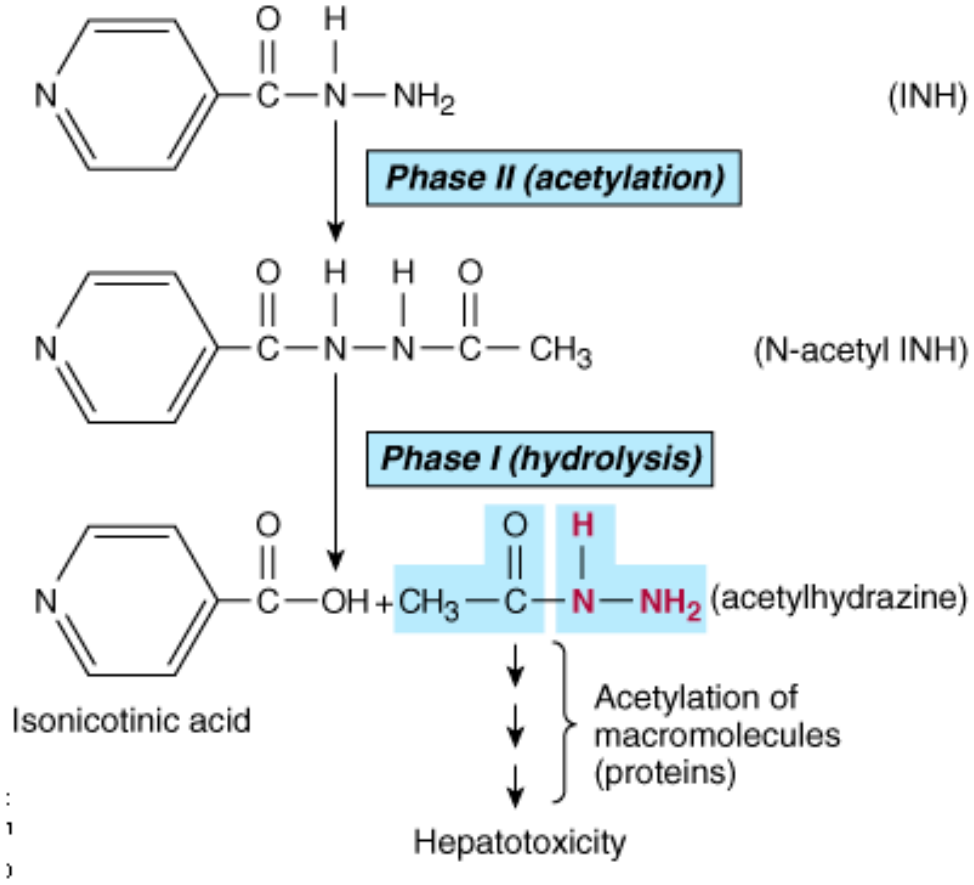
Table 6–1

Xenobiotic Metabolizing Enzymes

ENZYMES	REACTIONS
Phase 1 "oxygenases"	
Cytochrome P450s (P450 or CYP)	C and O oxidation, dealkylation, others
Flavin-containing monooxygenases (FMO)	N, S, and P oxidation
Epoxide hydrolases (mEH, sEH)	Hydrolysis of epoxides
Phase 2 "transferases"	
Sulfotransferases (SULT)	Addition of sulfate
UDP-glucuronosyltransferases (UGT)	Addition of glucuronic acid
Glutathione-S-transferases (GST)	Addition of glutathione
N-acetyltransferases (NAT)	Addition of acetyl group
Methyltransferases (MT)	Addition of methyl group
Other enzymes	
Alcohol dehydrogenases	Reduction of alcohols
Aldehyde dehydrogenases	Reduction of aldehydes
NADPH-quinone oxidoreductase (NQO)	Reduction of quinones

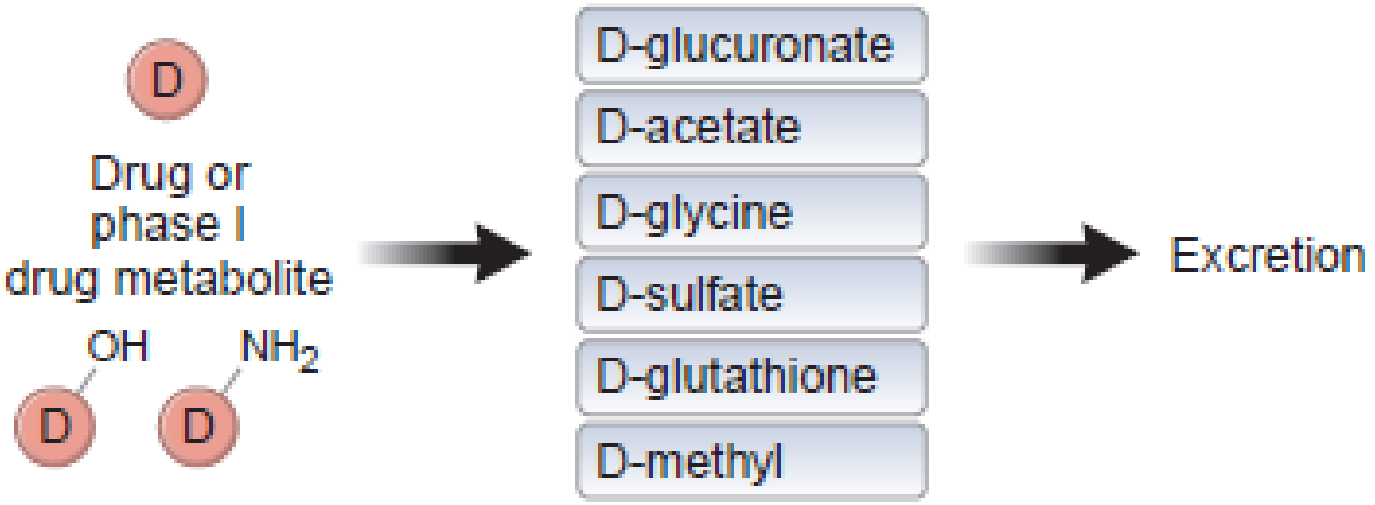
mEH and sEH are microsomal and soluble epoxide hydrolase. UDP, uridine diphosphate; NADPH, reduced nicotinamide adenine dinucleotide phosphate.

Drug conjugations were once believed to represent terminal inactivation events and as such have been viewed as "true detoxification" reactions



1. **Isoniazid gets converted to a toxic metabolite**

2. **sulfation activates the orally active prodrug minoxidil into a very efficacious vasodilator**
3. **morphine-6-glucuronide is more potent than morphine itself.**


D
Drug or
phase I
drug metabolite
OH
NH2
D
D
D-glucuronate
D-acetate
D-glycine
D-sulfate
D-glutathione
D-methyl
Excretion

Conjugation	Endogenous Reactant	Transferase (Location)
Glucuronidation	UDP glucuronic acid	UDP glucuronyl transferase (microsomes)
Glutathione conjugation	Glutathione (GSH)	GSH-*S*-transferase (cytosol, microsomes)
Glycine conjugation	Glycine	Acyl-CoA glycine transferase (mitochondria)
Sulfation	Phosphoadenosyl phosphosulfate	Sulfotransferase (cytosol)
Acetylation	Acetyl-CoA	*N*–Acetyltransferase (cytosol)

In drug metabolism ,hepatic cytochrome P- 450 system is responsible for :

a)Phase I reactions only

b) Phase II Reactions only

c) Both phase I and Phase II

d) Converting hydrophilic metabolites to lipophilic metabolites

Other (non-microsomal)reactions

- Hydrolysis in plasma by esterases (suxamethonium by cholinesterase)
- Alcohol and aldehyde dehydrogenase in cytosolic fraction of liver (ethanol)
- Monoamine oxidase in mitochondria (tyramine, noradrenaline, dopamine, amines)
- Xanthine oxidase (6-mercaptopurine, uric acid production)
- enzymes for particular drugs (tyrosine hydroxylase, dopa-decarboxylase etc)

Drug metabolism may confer the following changes to the parent drug

a) **Inactivation of drugs**
b) **Conversion of inactive forms into pharmacologically active forms**
c) **Conversion of drug into free radicals**
d) **All of the above**

In a patient on normal therapeutic dose of codeine the risk of toxicity is possible in individuals who exhibits the following genetic polymorphism for CYP2D6

a) Deficient or subnormal activity of CYP2D6
b) Normal CYP2D6 activity
c) Exaggerated CYP2D6 activity
d) None of the above

- **Genetic polymorphism:**

PHASE-I: CYP2D6

DRUG	PHENOTYPE	EFFECT
codeine	PM	dec. analgesic effect.
	UM	inc. respiratory depression
tramadol	PM	inc. seizure risk
nortriptyline	PM	Increased . ADR
	UM	dec. therapeutic effect.

Of the following ,the agent predominantly metabolized by glucuronide conjugation is:

a. Morphine
b. Chloroamphenicol
c. Acetaminophen
d. All of the above

Diseases Affecting Drug Metabolism

- Alcoholic hepatitis
- Alcoholic cirrhosis
- Hemochromatosis
- Chronic active hepatitis
- Biliary cirrhosis
- Viral/drug-induced hepatitis

Impair hepatic drug-metabolizing enzymes

Cardiac disease

By limiting blood flow to the liver, impairs disposition of those drugs

- ✓ Lidocaine
- ✓ Amitriptyline
- ✓ Meperidine
- ✓ Propoxyphene
- ✓ Isoniazid
- ✓ Propranolol
- ✓ Labetalol
- ✓ Verapamil

metabolism is flow-limited

- Hypothyroidism ↑es the half-life of antipyrine, digoxin, methimazole, and some beta blockers, whereas hyperthyroidism has opposite effect.
- release of inflammatory mediators, cytokines, and nitric oxide associated with bacterial or viral infections, cancer, or inflammation impairs drug metabolism by inactivating P450s and enhancing their degradation.

Answer in one word

1. This drug is acetylated slowly in Caucasians than in most Asians.

Isoniazid

2.This is a commonly used drug that may inhibit the hepatic microsomal enzyme responsible for warfarin metabolism

Cimetidine

3. This drug has higher 1st pass metabolism in men than in women

Ethanol

EXCRETION OF DRUGS

Some basic facts…..

- Drugs are eliminated from the body either unchanged by the process of excretion or converted to metabolites.
- Excretory organs, eliminate polar compounds more efficiently than substances with high lipid solubility.
- Lipid-soluble drugs thus are not readily eliminated until they are metabolized to more polar compounds.

Organs of excretion

- **Kidney** :most important organ for excreting drugs & their metabolites.
- Substances excreted in **feces** are either unabsorbed orally ingested drugs or drug metabolites transported by liver into the bile
- Excretion of drugs in **breast milk** is important because excreted drugs are potential sources of unwanted pharmacological effects in the nursing infant (Buhimschi and Weiner, 2009).
- Excretion from the **lung** is important mainly for the elimination of anesthetic gases

- **Lungs:** Eliminate volatile anesthetics and alcohol.
- **Milk:** Eliminates anticancer drugs, Chloramphenicol, tetracyclines & benzodiazepines.
- **Bile:** Eliminates erythromycin, rifampicin, morphine and carbenoxolone.

- **Saliva:** iodine, lithium ,rifampin & lead.

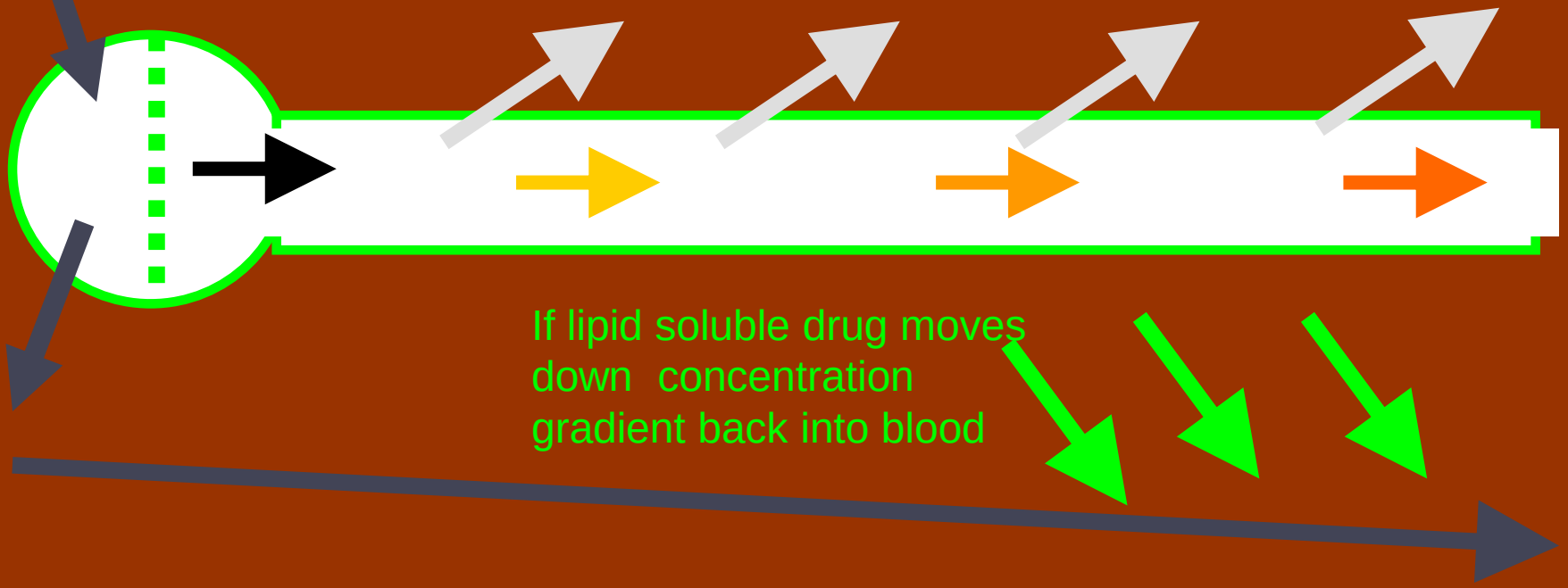
Effect of lipid solubility and pH

ionized drug is less lipid soluble

Glomerular

blood flow; filtrate

99% of GF is re-absorbed;
concentration of drug rises in tubule



If lipid soluble drug moves down concentration gradient back into blood

Re-absorption

Renal Excretion

- Renal blood flow comprises about 25% of total systemic blood flow, ensuring that the kidneys are continuously exposed to any drug found in the blood.
- The afferent arteriole introduces both free (unbound) drug and plasma protein-bound drug into the glomerulus.
- Typically, only the free drug form is filtered into the renal tubule.

GLOMERULAR FILTRATION

- ✓It Is non selective , unidirectional process
- ✓Ionized or unionized drugs are filtered, except those that are bound to plasma proteins.
- ✓Driving force for GF is hydrostatic pressure of blood flowing in capillaries.
- ✓**GLOMERULAR FILTRATION RATE:**

  Out of 25% of cardiac out put or 1.2 liters of blood/min that goes to the kidney via renal artery only 10% or 120 to 130ml/min is filtered through glomeruli. The rate being called as glomerular filtration rate.(GFR).

Glomerular filtration

✓**The rate at which a drug** enters the glomerular filtrate depends on the concentration of free drug in plasma water and on it molecular weight.

✓Substances that have a MW > 50 000 excluded from the glomerular filtrate while those of MW< 10 000 (which includes almost all drugs) pass easily through the pores of the glomerular membrane.

ACTIVE TUBULAR SECRETION

- Occurs in proximal tubule.
- carrier mediated process requiring energy for transportation of against conc. gradient
- Two separate classes of nonspecific transporters identified which operate in the proximal tubules(OATP,OCT)
- Efflux transporters P-glycoprotein & MRP-2 located in the luminal membrane of proximal tubular cells.
- If renal clearance of a drug is>120 ml/min additional tubular secretion can be assumed to be occuring.

Two secretion mechanisms are identified

System for secretion of organic acids

E.g. Penicillin, salicylates,uricacid,Probenecid, methotrexate

System for organic base

morphine, furosemide,amiloride,cimetidine,quinine

Tubular transport mechanisms are not well developed at birth

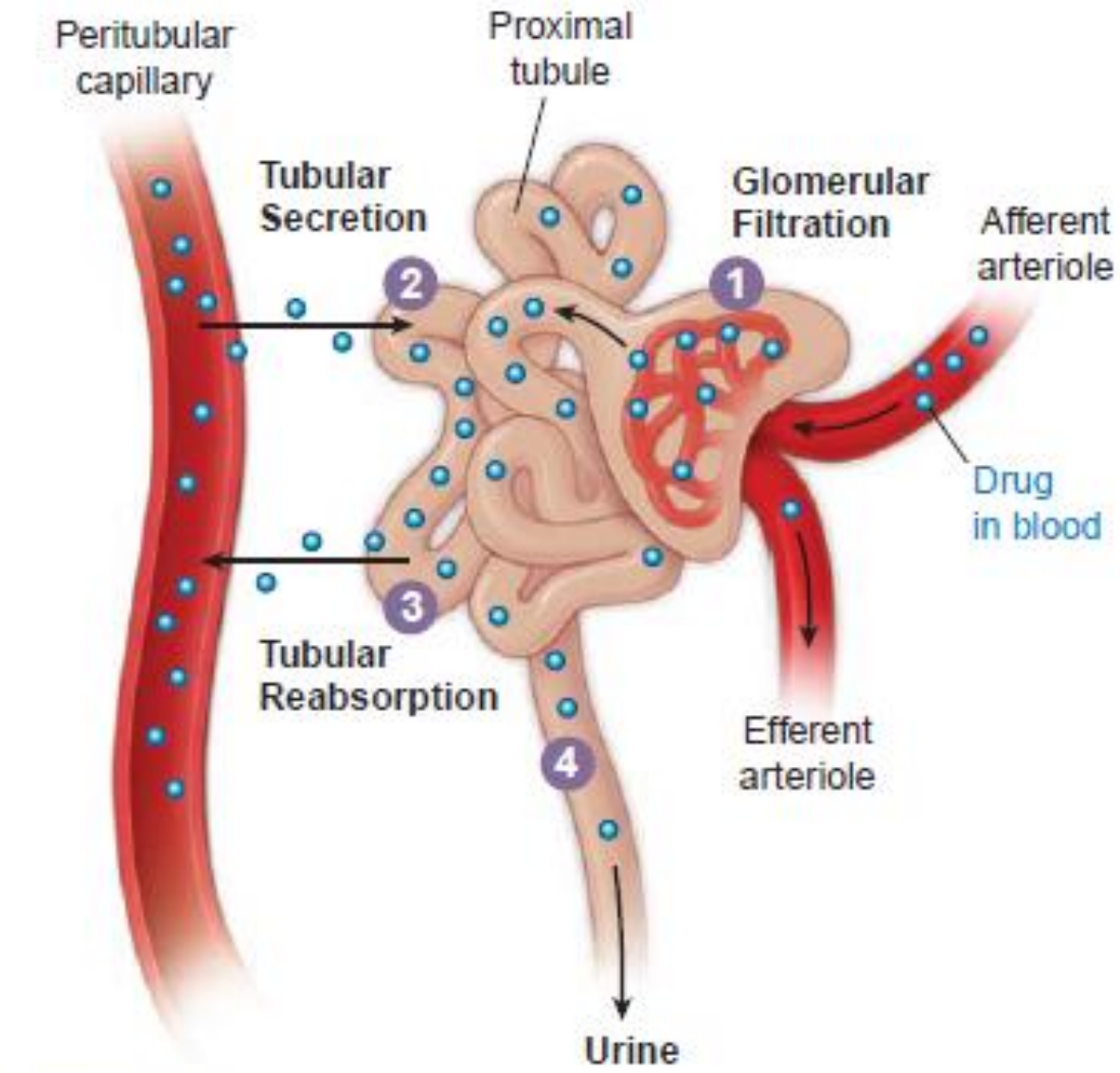
TUBULAR REABSORPTION

- It occurs after the glomerular filtration of drugs,
- takes place all along the renal tubules.
- Reabsorption results in ↑in T1/2 of the drug.

The glomerular filtrate contains drug at the same concentration as it is free in the plasma, but the fluid is concentrated progressively as it flows down the nephron so that a gradient develops, **drug in the tubular fluid becoming more concentrated** than in the blood perfusing the nephron.

Renal tubular reabsorption.

- tubular epithelium- properties of a lipid membrane
- the extent to which a drug diffuses back into the blood will depend on its lipid solubility, i.e. on its pKa in the case of an electrolyte, and on the pH of tubular fluid.


Peritubular capillary
Proximal tubule
Tubular Secretion
Glomerular Filtration
Afferent arteriole
2
1
Drug in blood
3
Tubular Reabsorption
Efferent arteriole
4
Urine

Faecal excretion of drugs

- Apart from unabsorbed fraction of orally administered drug,most of the drug in faeces is derived from bile

- **Biliary excretion. In the liver there is one active** transport system for acids and one for bases, in addition,there is a system that transports un-ionised molecules,e.g. digoxin, into the bile.

- Small molecules tend to be reabsorbed by the bile canaliculi and in general only compounds that have a molecular weight greater than 300 are excreted in bile.

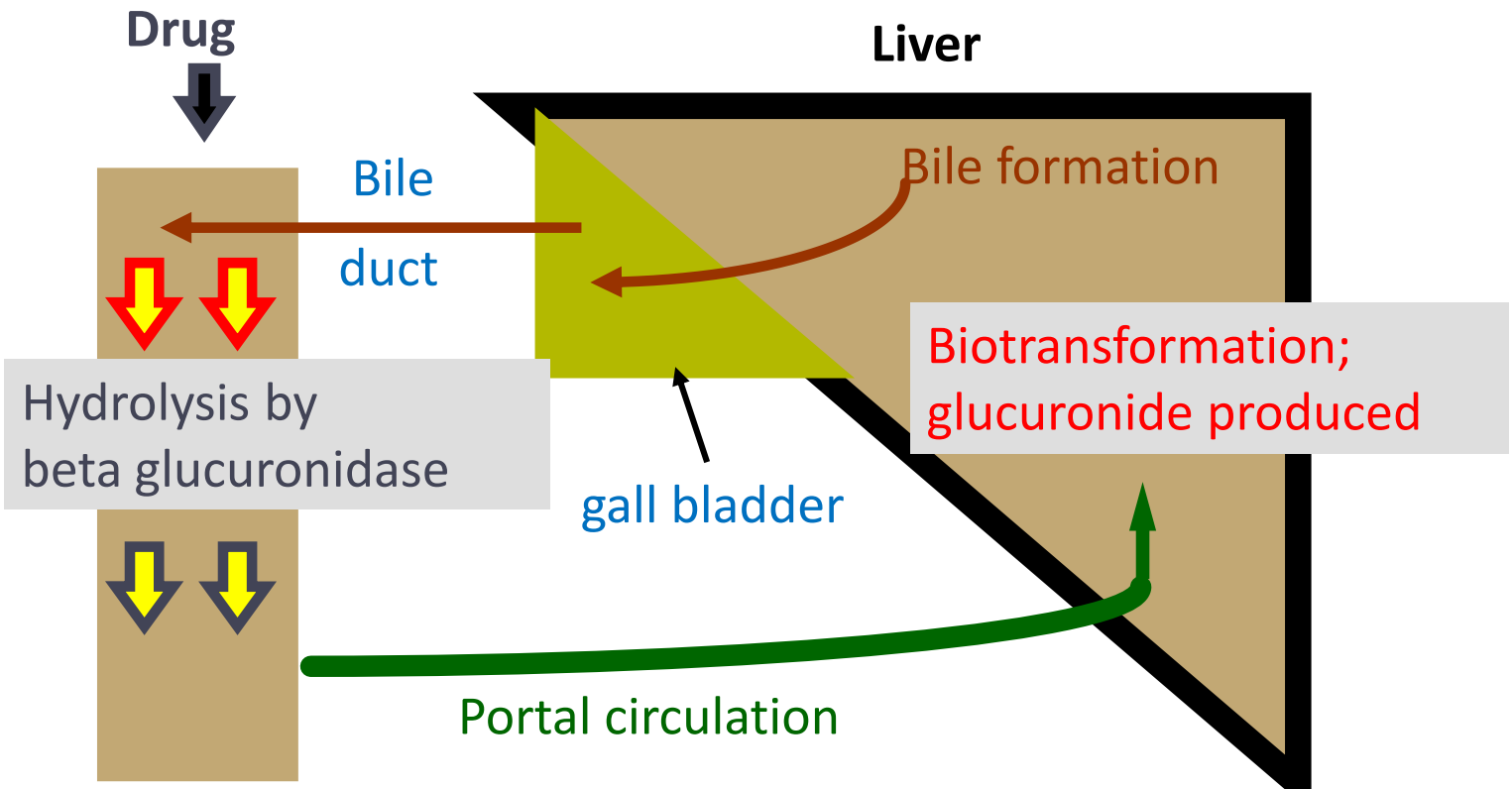
Some drugs are secreted from the liver into the bile by members of the ATP binding cassette (ABC) superfamily of transporters, which includes seven families of proteins.

THE ENTEROHEPATIC CIRCULATION

EC is important in conservation of Vitamins, Folic acid and hormones.

Some drugs undergoing EC are cardiac glycosides, rifampicin and chlorpromazine.

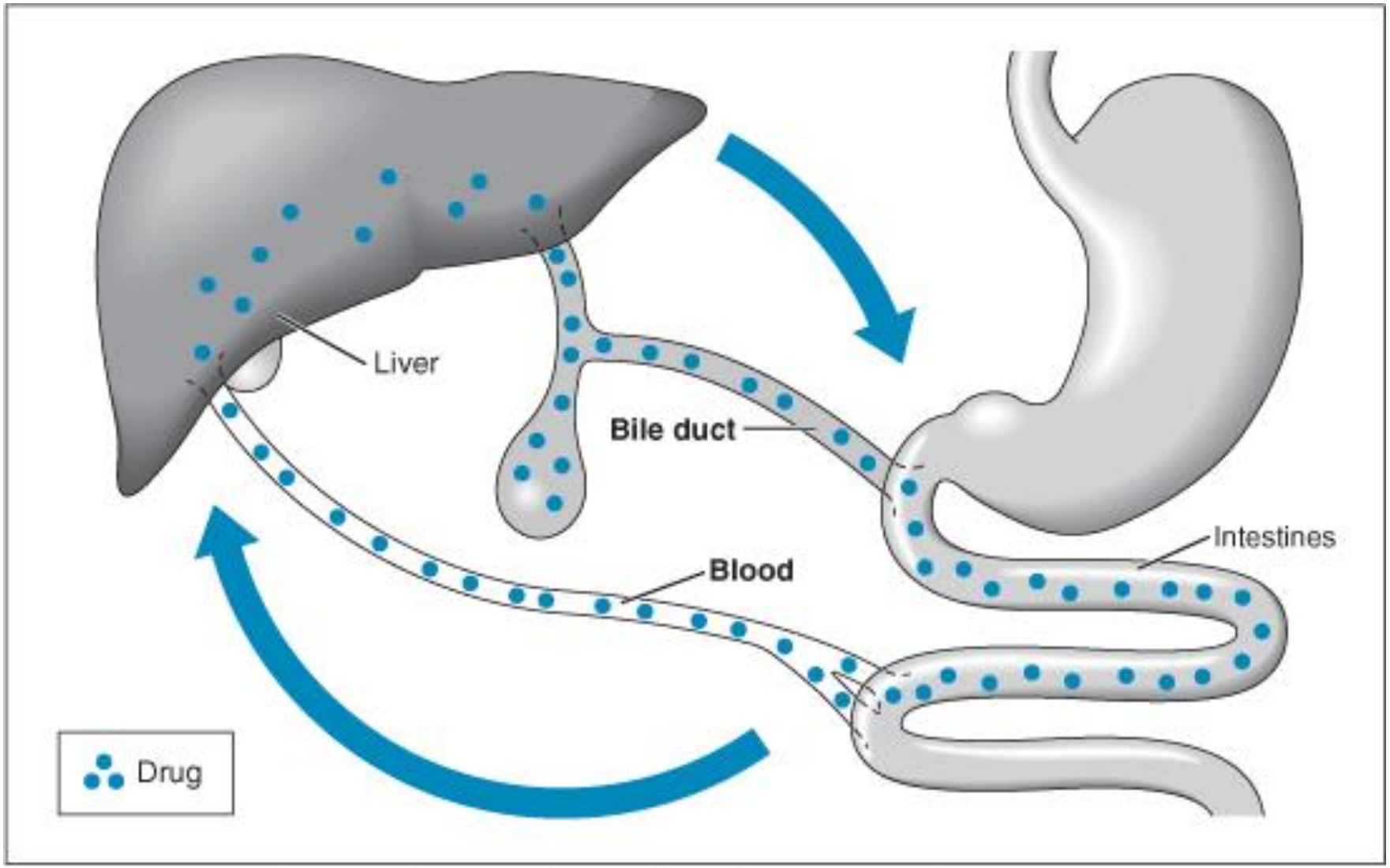
The enterohepatic shunt



Rifampicin, Ethinylestadiol, morphine

Biliary excretion- drugs with mwts >300 excreted in to bile

Enterohepatic cycling-



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PULMONARY EXCRETION

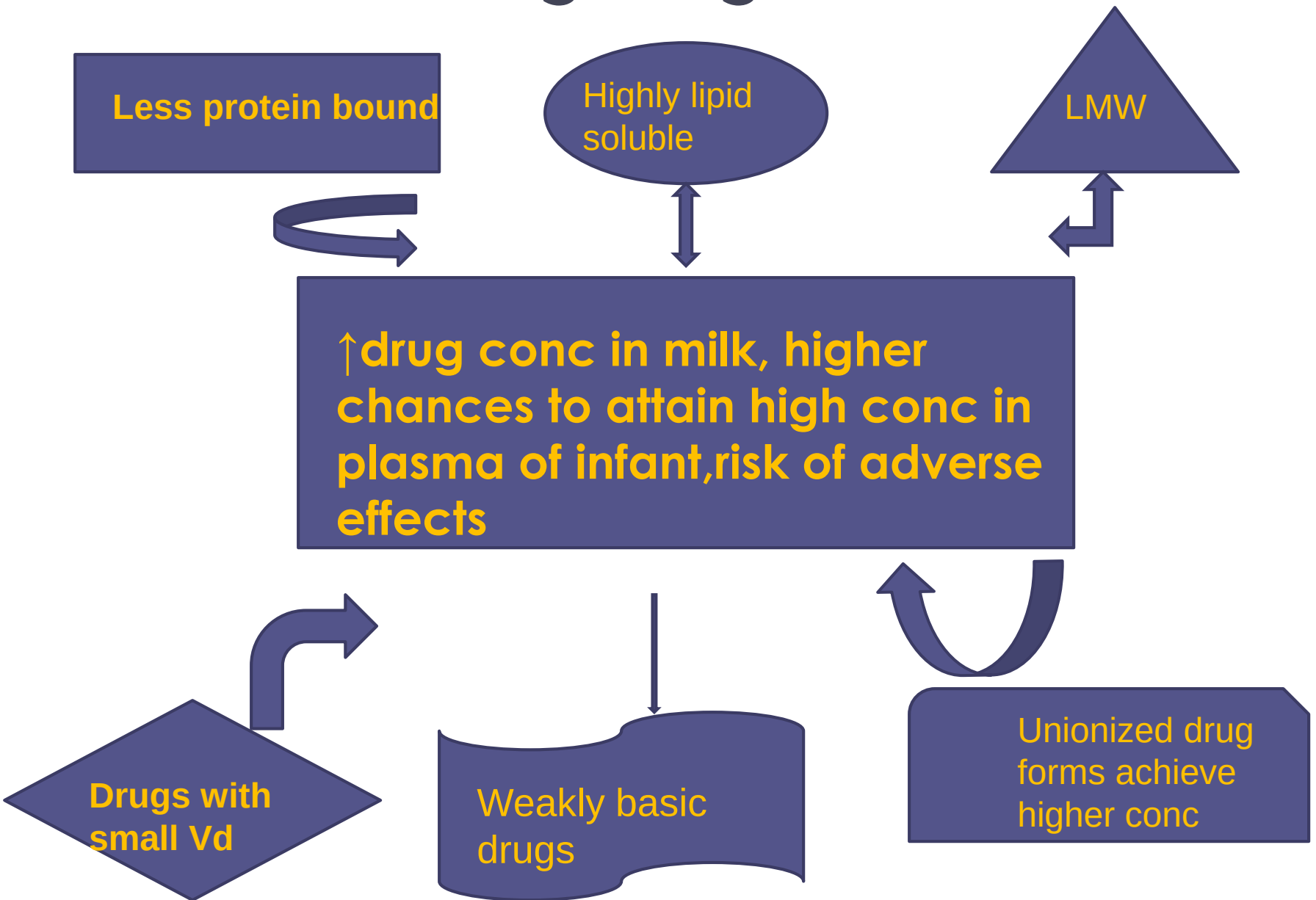
Gaseous and volatile substances such as general anesthetics (Halothane) are eliminated through lungs by simple diffusion.

Intact gaseous drugs are excreted but not metabolites. Alcohol which has high solubility in blood and tissues are excreted slowly by lungs.

SALIVARY EXCRETION

- ✓The pH of saliva varies from 5.8 to 8.4.
- ✓Unionized lipid soluble drugs are excreted passively.
- ✓ The bitter after taste in the mouth of a patient is indication of drug excreted.
- ✓Some basic drugs inhibit saliva secretion and are responsible for mouth dryness.
- ✓Compounds excreted in saliva are Lithium, Phenytoin,Rifampicin,digoxin,penicillins, tetracyclins

Factors affecting drug transfer into milk



MAMMARY EXCRETION

- 0.5 to 1 litre of milk is secreted /day in lactating mothers.
- Excretion of drug in milk important as it gains entry in breast feeding infants.
- pH of milk varies from6.4to7.6.
- Free un-ionized and lipid soluble drugs diffuse passively.
- Highly plasma bound drug like Diazepam is less secreted in milk.
- Since milk contains proteins. Drugs excreted can bind to it.

All of the following factors may cause increased excretion of a drug into milk EXCEPT

a. Large volume of distribution
b. High lipid solubility
c. Poor protein binding
d. Alkaline nature

21. The greater proportion of the dose of a drug administered orally will be absorbed in the small intestine. However, on the assumption that passive transport of the nonionized form of a drug determines its rate of absorption, which of the following compounds will be absorbed to the least extent in the stomach?

a. Ampicillin ($pK_a = 2.5$)
b. Aspirin ($pK_a = 3.0$)
c. Warfarin ($pK_a = 5.0$)
d. Phenobarbital ($pK_a = 7.4$)
e. Propranolol ($pK_a = 9.4$)

Thankyou all for a patient hearing

WISHING A VERY HAPPY DIWALI AND NEW YEAR WISHES TO ALL OF YOU

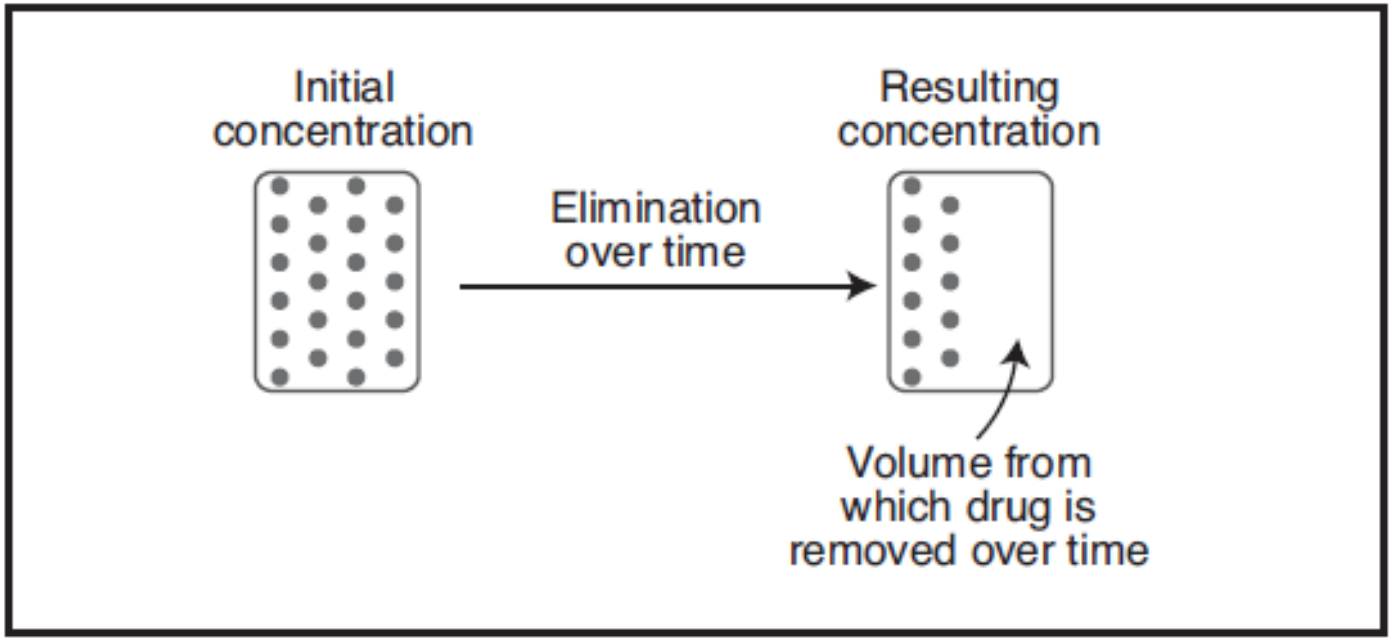
CLEARANCE

Defined as a theoretical volume of plasma from which the drug is completely removed in unit time .

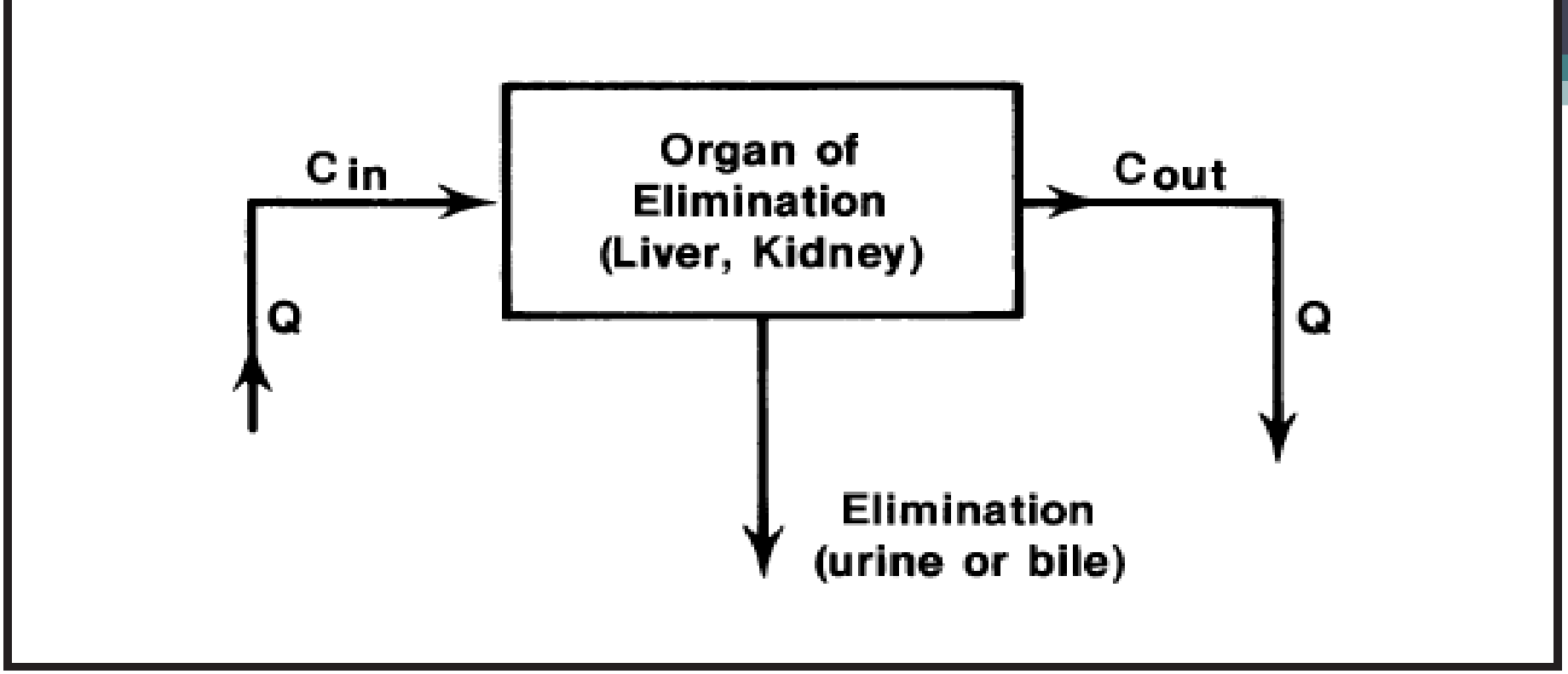
$$CL = \frac{\text{Rate of elimination}}{C}$$

when clearance is constant, the rate of drug elimination is directly proportional to drug concentration

- Clearance (expressed as volume/time) describes the removal of drug from a volume of plasma in a given unit of time



Clearance may be viewed as the volume of plasma from which drug is totally removed over a specified period.



Model for organ clearance of a drug.

organ clearance = blood flow × extraction ratio

Clearance of drug by several organs is additive

$$CL_{renal} = \frac{\text{Rate of elimination}_{kidney}}{C}$$

$$CL_{liver} = \frac{\text{Rate of elimination}_{liver}}{C}$$

$$CL_{other} = \frac{\text{Rate of elimination}_{other}}{C}$$

$$CL_{systemic} = CL_{renal} + CL_{liver} + CL_{other}$$

$$CL = \frac{\text{Rate of elimination}}{C}$$

$$\begin{aligned} \text{Rate of elimination} &= Q \cdot C_A - Q \cdot C_V \\ &= Q(C_A - C_V) \end{aligned}$$

$$CL_{organ} = Q\left[\frac{C_A - C_V}{C_A}\right] = Q \cdot E$$

expression (*CA-CV)/CA* in can be referred to as the *Extraction ratio (E)* of the drug

Q stands for Blood flow to the organ

Knowing the extraction ratio (E_H) for a drug across the liver it is possible to predict the maximum oral availability (*F*max) , assuming that hepatic elimination follows first-order processes:

$$F_{max} = 1 - E_H = 1 - (CL_{hepatic} / Q_{hepatic})$$

- PROCEEDING TO KINETICS OF ELIMINATION

Alkalinization of urine hastens the excretion of :

A)Weakly basic drugs

B)Weakly acidic drugs

C)Strong electrolytes

D)Nonpolar drugs

Diffusion of drugs across cell membrane :

A)Is dependent upon metabolic activity of the cell

B)Is competitively inhibited by chemically related drugs

C)Is affected by extent of ionization of drug molecules

D)Exhibits saturation kinetics

The most important factor governing absorption of a drug from intact skin is :

A)Molecular weight of the drug

B)Site of application

C)Lipid solubility of the drug

D)Nature of the base used in formulation

What kind of substances can't permeate membranes by passive diffusion?

A- Lipid-soluble

B- Non-ionized substances

C- Hydrophobic substances

D- Hydrophilic substances

Which route of drug administration most likely leads to the first-pass effect?

a) Sublingual

b) Oral

c) Intravenous

d) Intramuscular

Which of the following factor does not influence the oral bioavailability of the drugs

A-Metabolism by gut wall enzymes

B-Decomposition by hydrolytic gut enzymes

C-Chelation with existing food in stomach

D-Plasma half life

Reasons for taking a drug history from patients

- Are a cause of disease. Abrupt Withdrawal can cause disease. benzodiazepines, antiepilepsy drugs.
- Conceal disease, e.g. adrenal steroid.
- interact causing adverse effect/ therapeutic failure.
- Can give diagnostic clues, e.g. ampicillin causing rash in infectious mononucleosis
- Cause false results in clinical chemistry tests
- Assists choice of drugs in the future.
- Can leave residual effects after administration has ceased, e.g. chloroquine, amiodarone.
- Drugs available for independent patient self medication are increasing in range and importance.