# *Absorption of Drugs (mechanisms & factors controlling)*

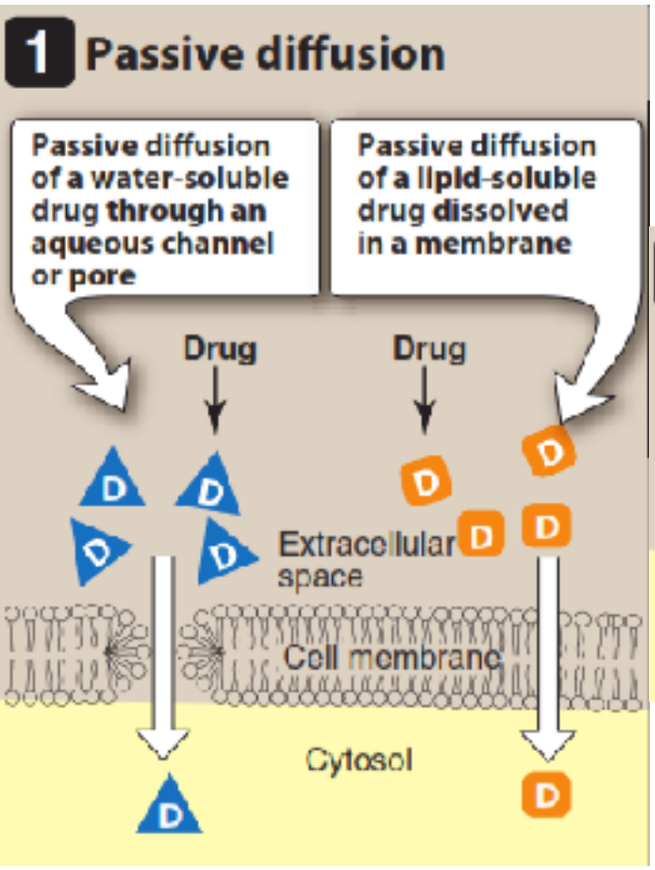
➢ *The transfer of D from site of administration to blood stream via several mechanisms*

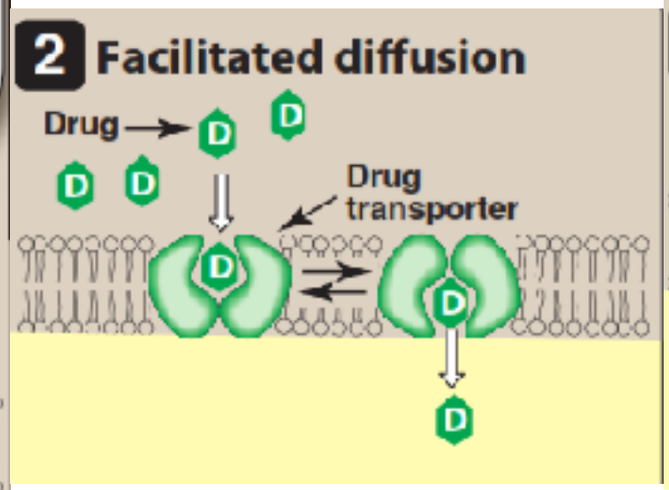
➢ *Rate & Efficiency*

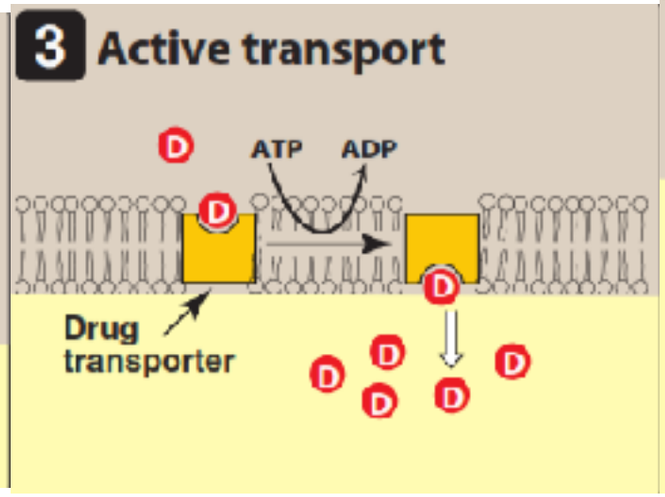
➢ *Mechanisms of absorption of drugs from GIT*

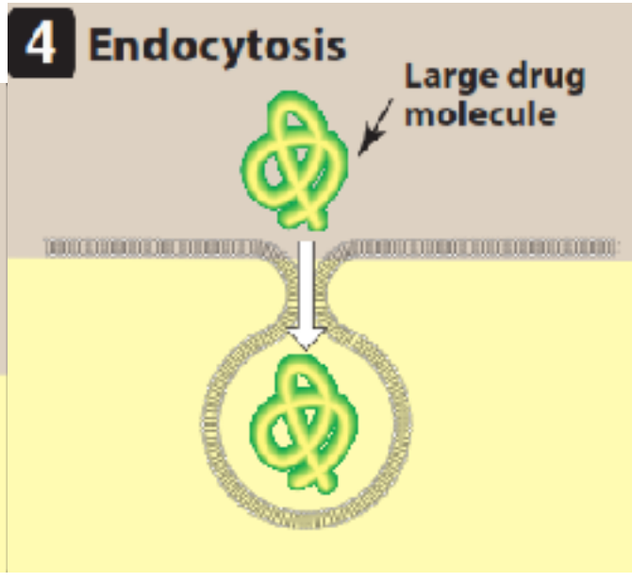
- ❖ *Passive diffusion*
- ❖ *Facilitated diffusion*
- ❖ *Active transport*
- ❖ *Endocytosis & exocytosis*

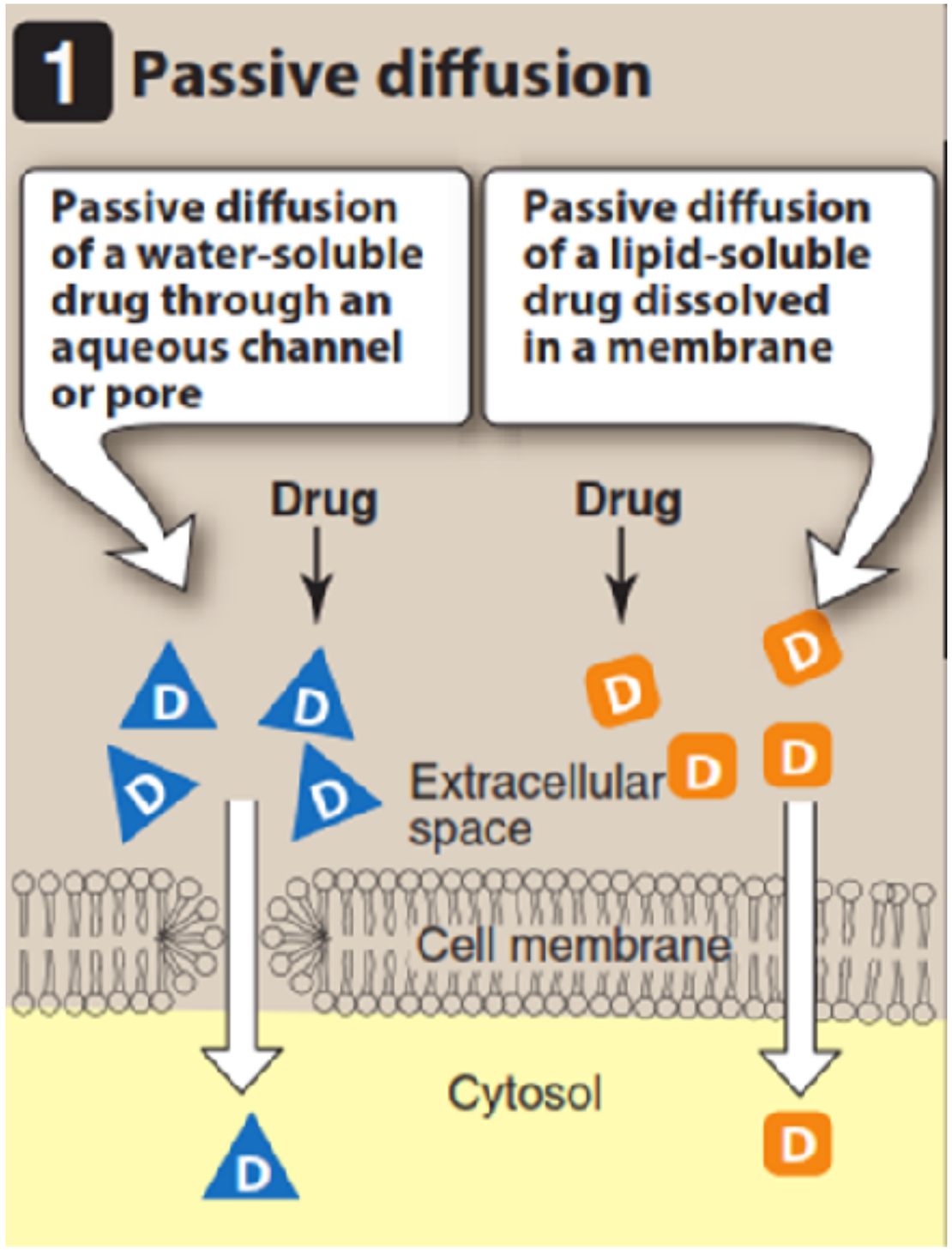
# *Mechanisms of absorption of drugs from GIT*

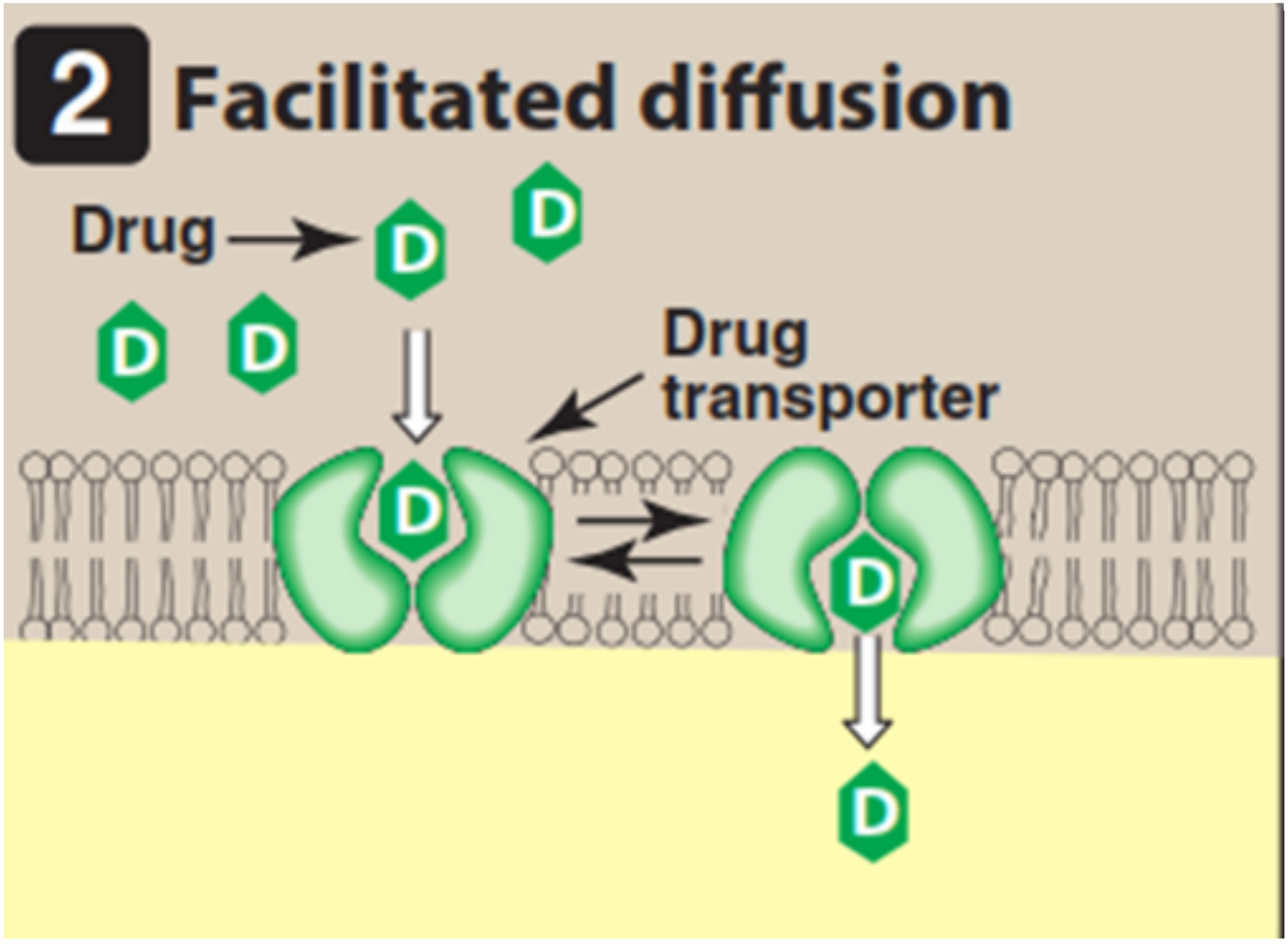


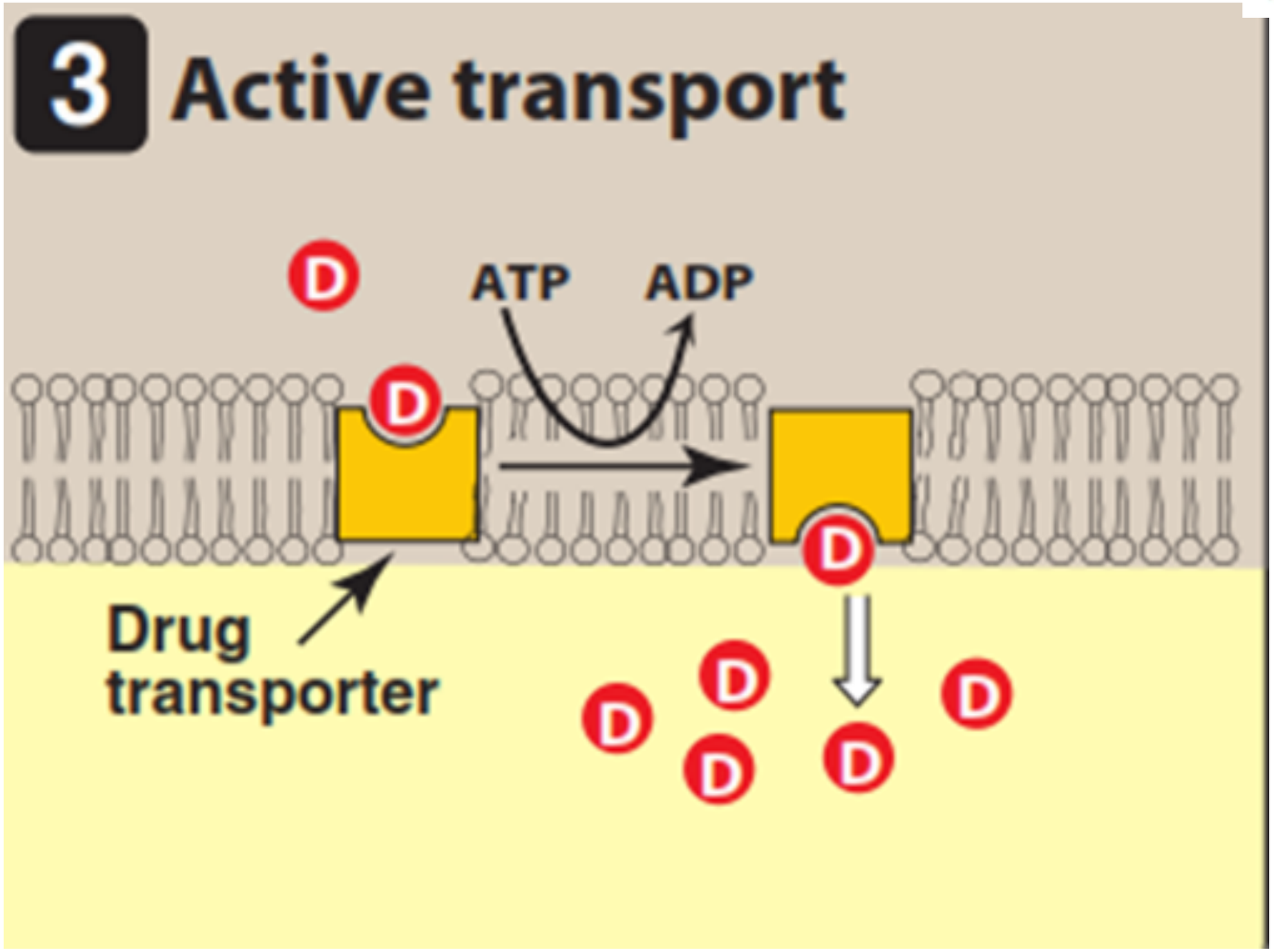



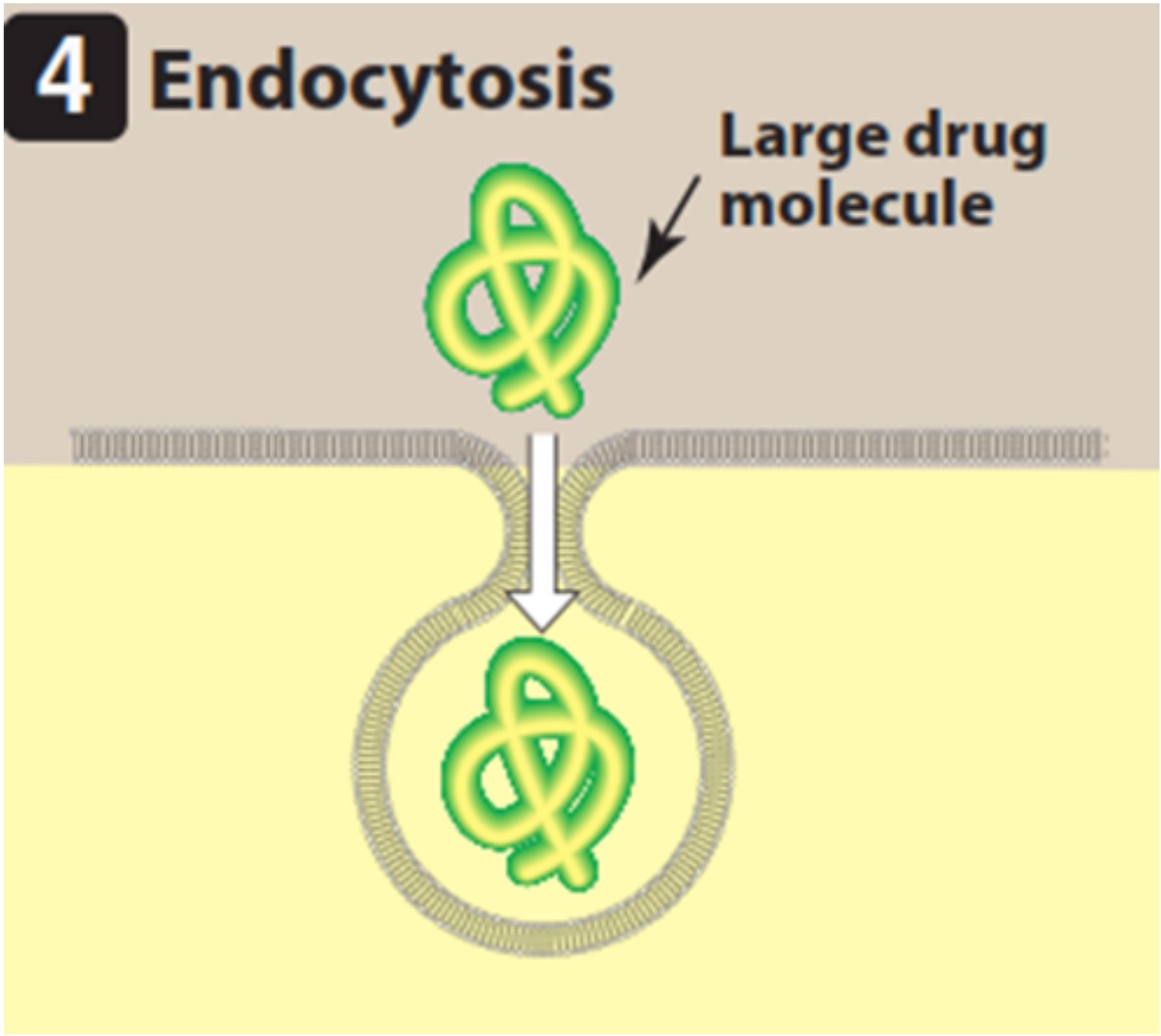




1 Passive diffusion
Passive diffusion of a water-soluble drug through an aqueous channel or pore
Passive diffusion of a lipid-soluble drug dissolved in a membrane
Drug
Drug
D
Extracellular space
Cell membrane
Cytosol


2 Facilitated diffusion
Drug
D
D
D
D
Drug transporter
D
D
D


3 Active transport
D
ATP
ADP
D
D
Drug
transporter
D
D
D
D
D


4 Endocytosis
Large drug molecule

# *Factors Influencing Absorption*

*1- Effect of pH*

*2- Blood flow*

*3- Surface area*

*4- Contact time*

*5- Expression of P-gp*

$$AH \rightleftharpoons A^- + H^+$$

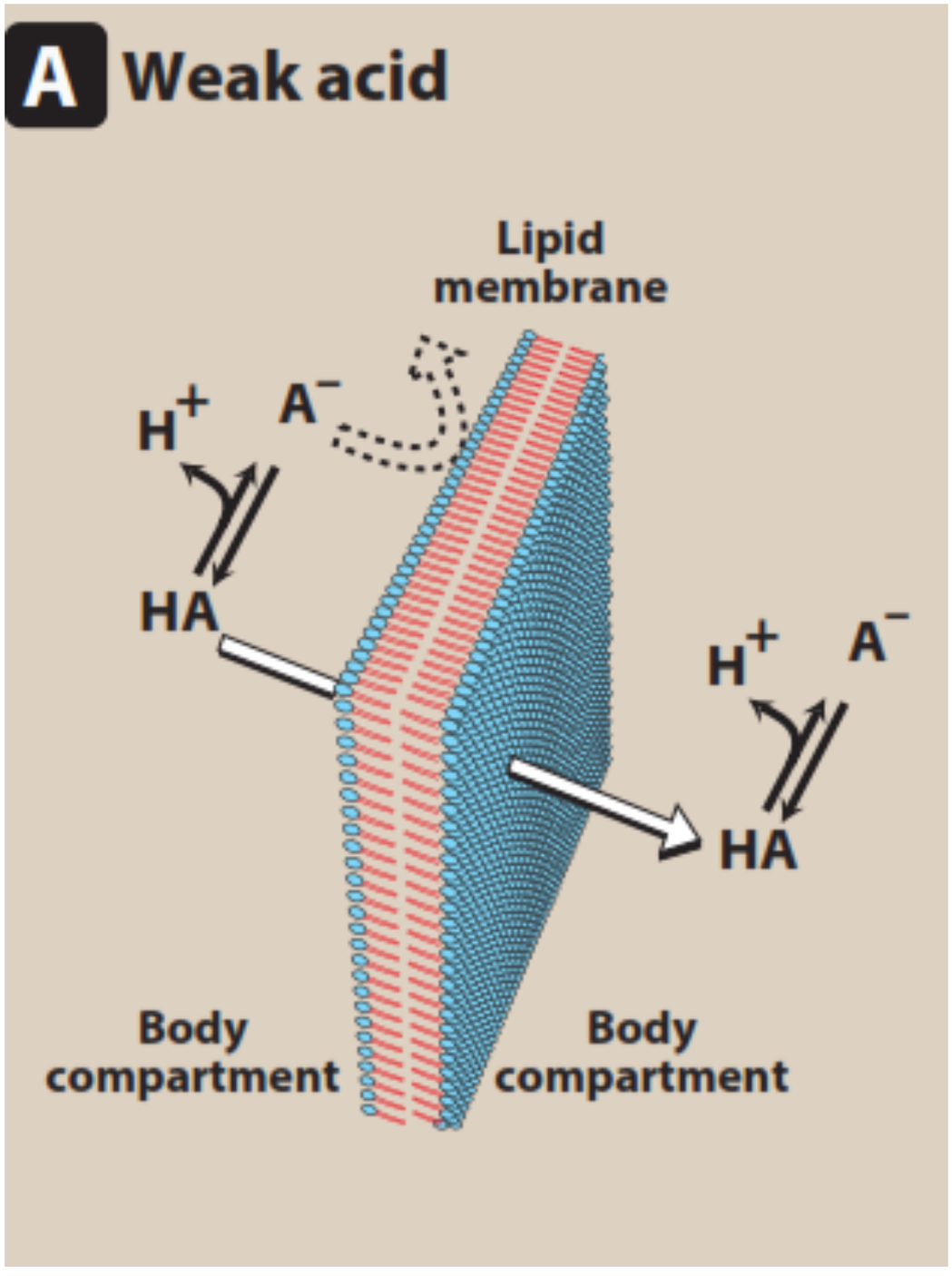
$$BH^+ \rightleftharpoons B + H^+$$

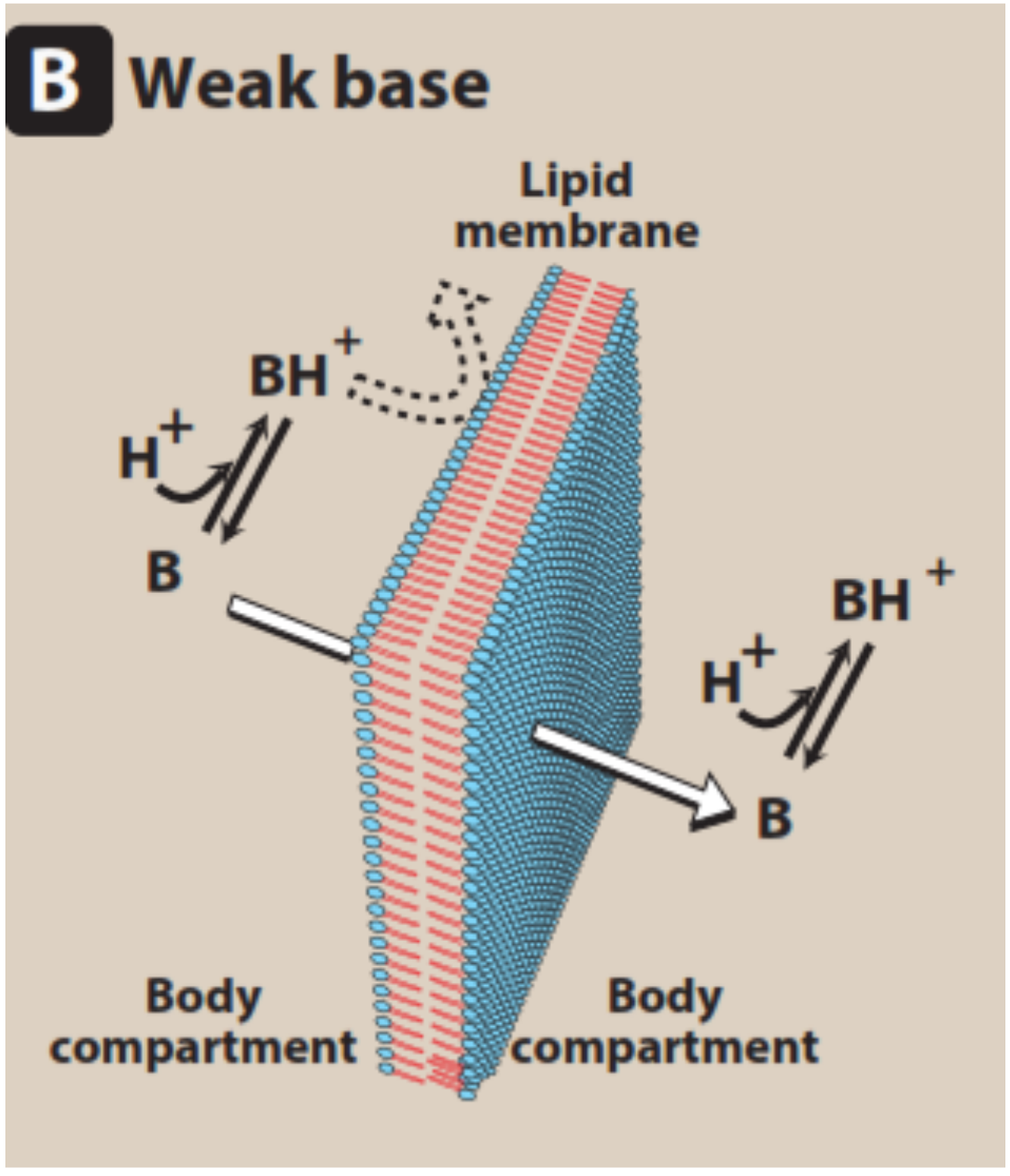
- In the case of weak acids and weak bases the ability to move from aqueous to lipid or vice versa varies with the pH of the medium.

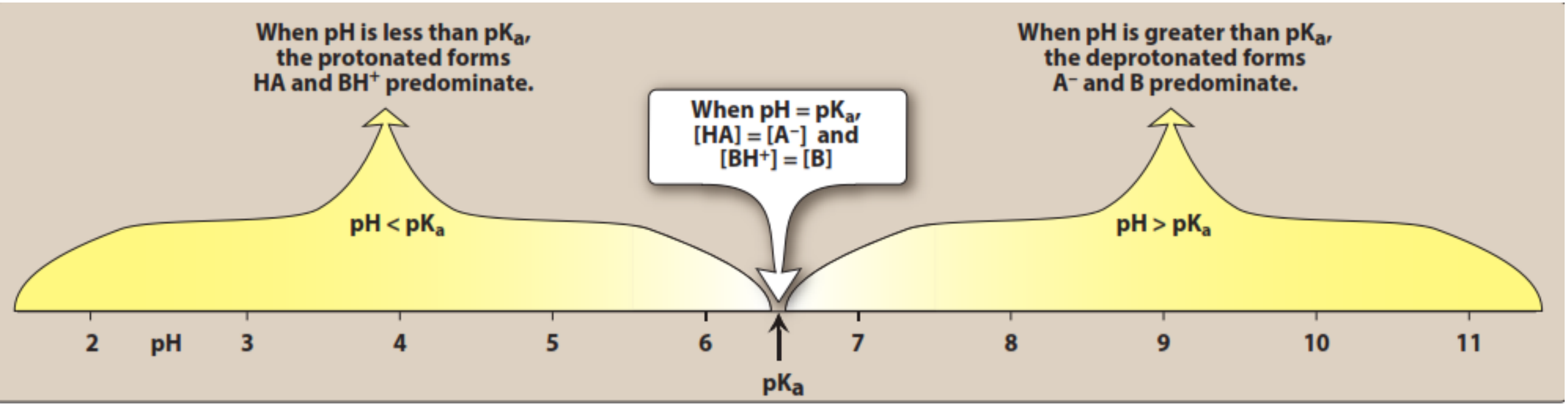
- Henderson-Hasselbalch equation (can be use to predict the effect of pH change on ABSORPTION):

**Acid: $pH = pKa + \log [A^-]/[HA]$**

**Base: $pH = pKa + \log [B]/ [HB^+]$**


A Weak acid
Lipid membrane
H+
A−
HA
H+
A−
HA
Body compartment
Body compartment


B Weak base
Lipid membrane
BH+
H+
B
BH+
H+
B
Body compartment
Body compartment


When pH is less than $pK_a$, the protonated forms HA and $BH^+$ predominate.
When pH = $pK_a$, [HA] = $[A^-]$ and $[BH^+]$ = [B]
When pH is greater than $pK_a$, the deprotonated forms $A^-$ and B predominate.
pH < $pK_a$
pH > $pK_a$
2
pH
3
4
5
6
7
8
9
10
11
$pK_a$

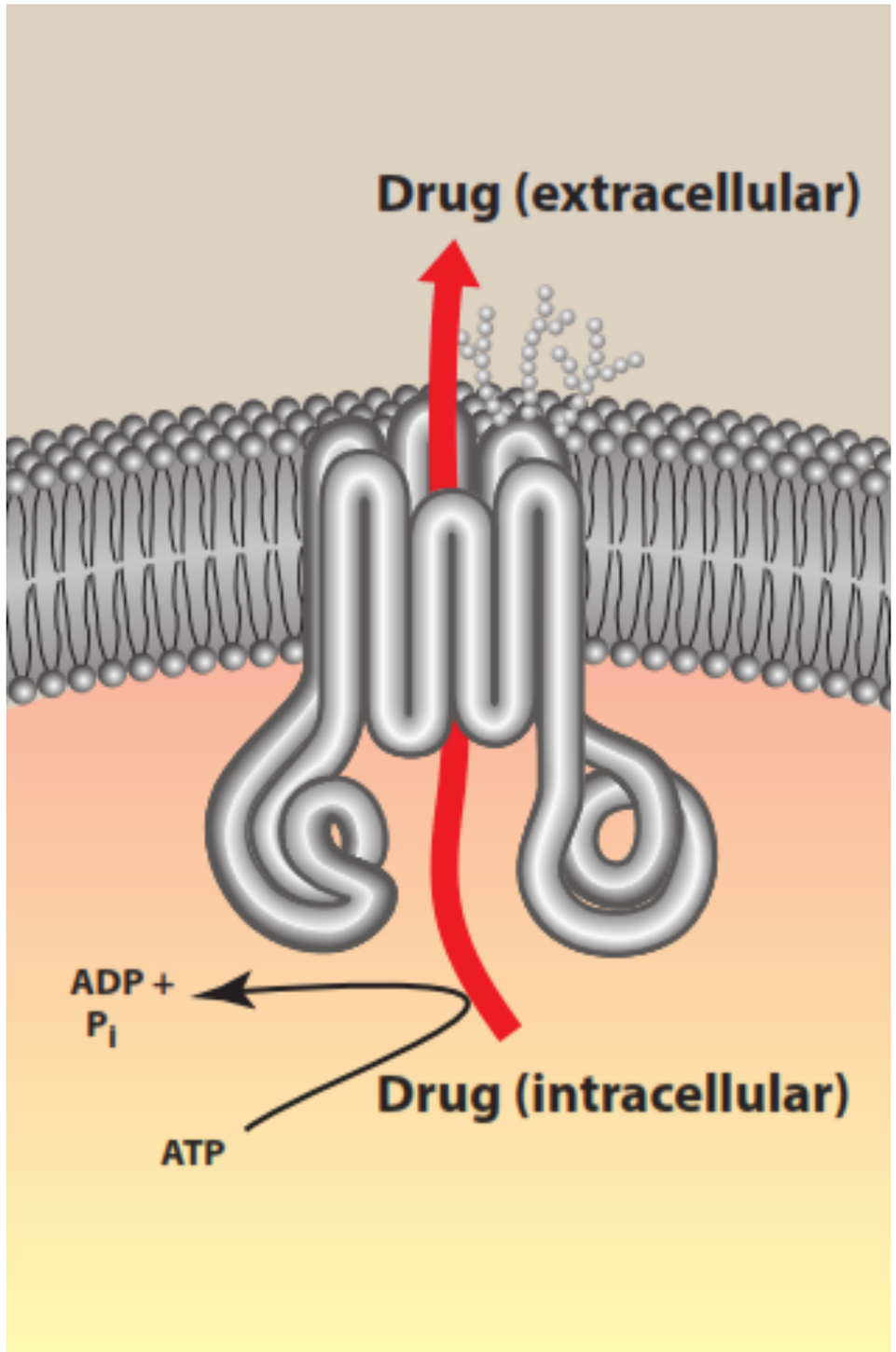
# *Factors Influencing Absorption (cont.)*

*2- Blood flow*

*3- Surface area*

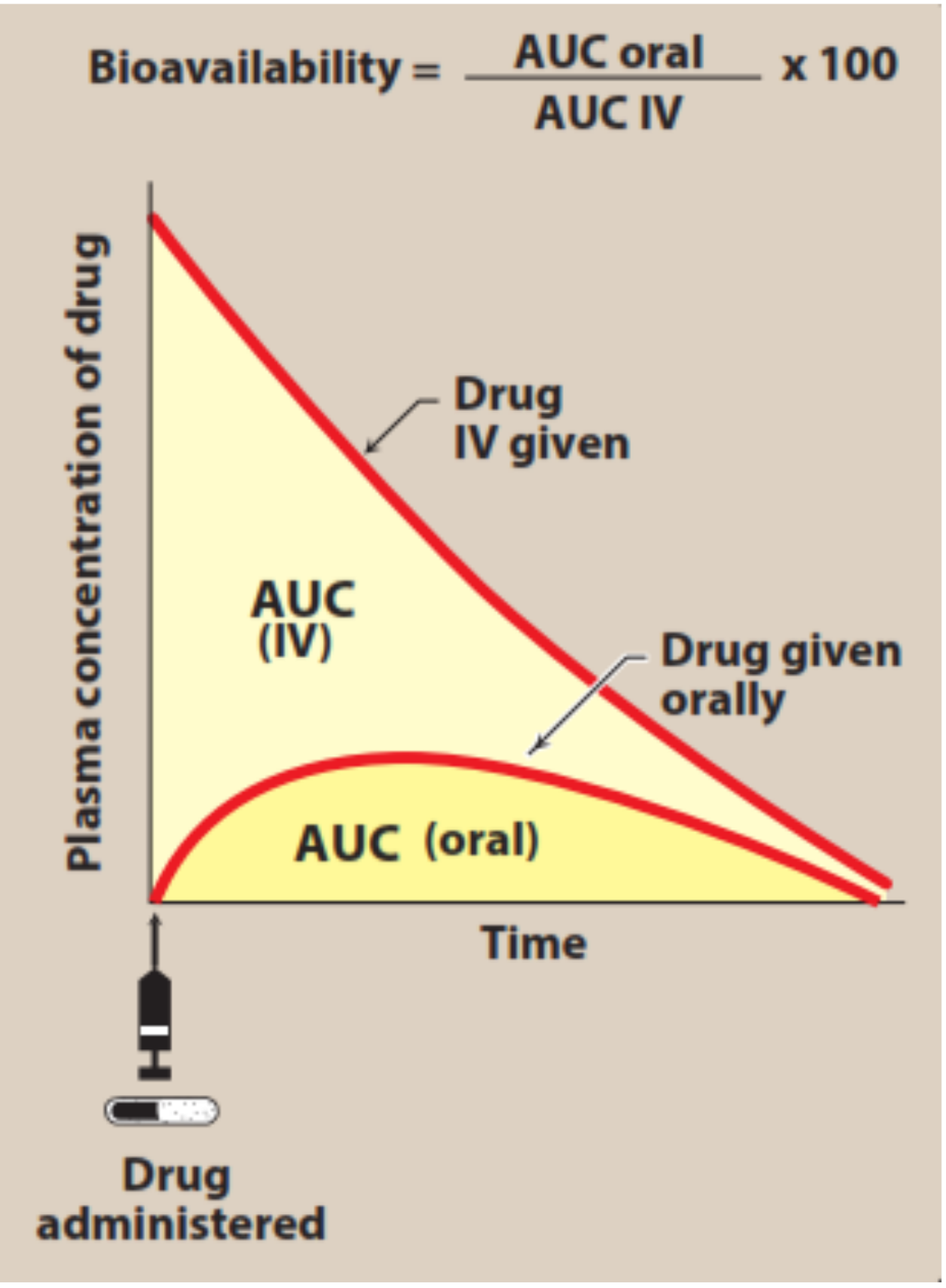
*4- Contact time (diarrhea, parasympathetic, sympathetic, anticholinergic)*

*5- Expression of P-glycoprotein (expression, resistance)*



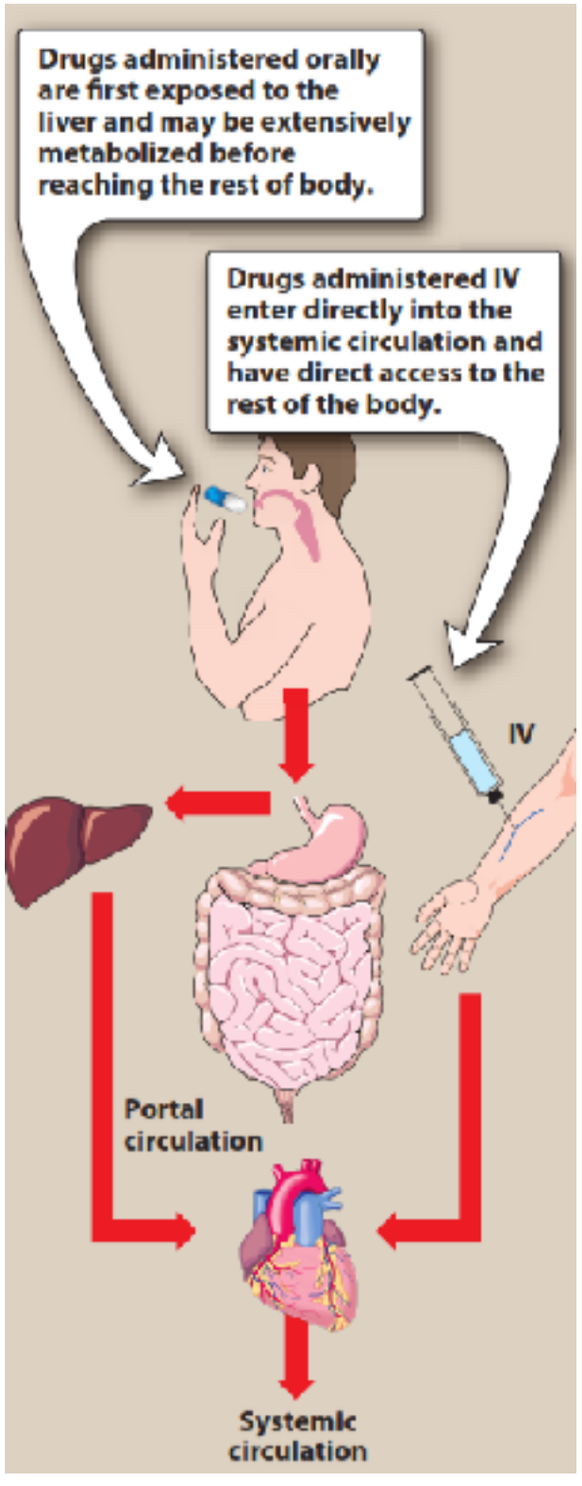

# *Expression of P-glycoprotein*

- *Multidrug transmembrane transporter ptn*
- *Expression*
- *Function*
- *Multidrug resistance*




# *Bioavailability*

*The fraction of the administered drug that reach the systemic circulation*




# *Factors Influencing Bioavailability:*

- *1st-pass effect*
- *Solubility of D*
- *Chemical instability*
- *Nature of D formulation*

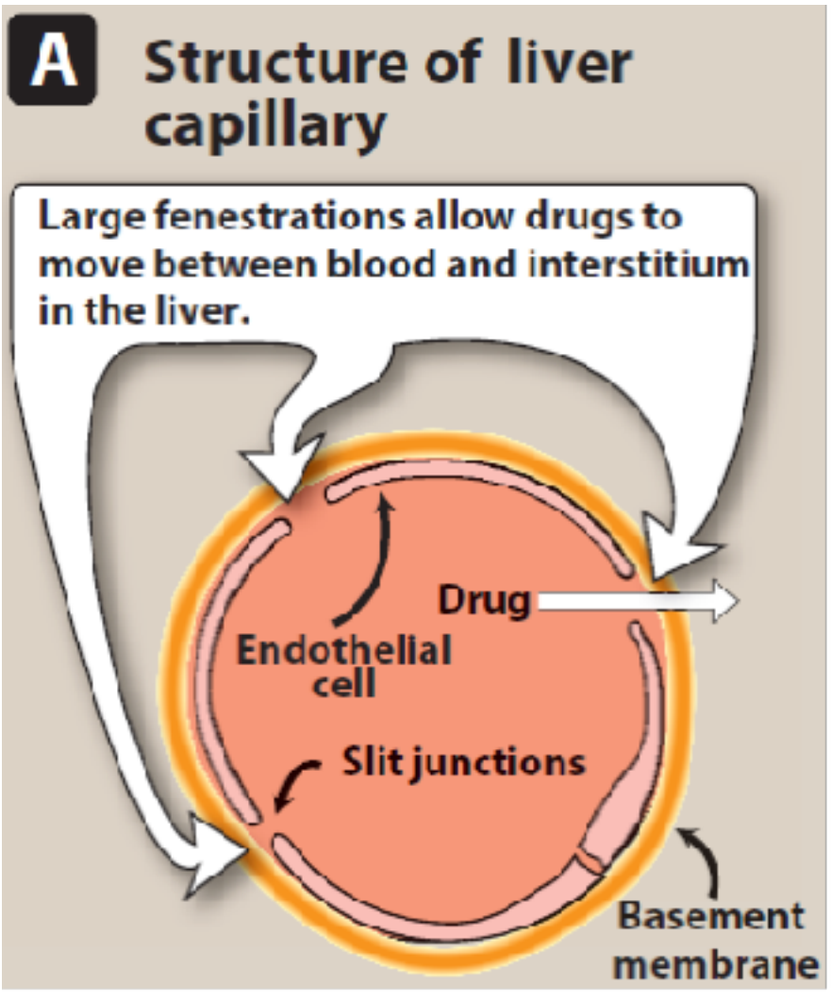
✓ *Bioequivalence*

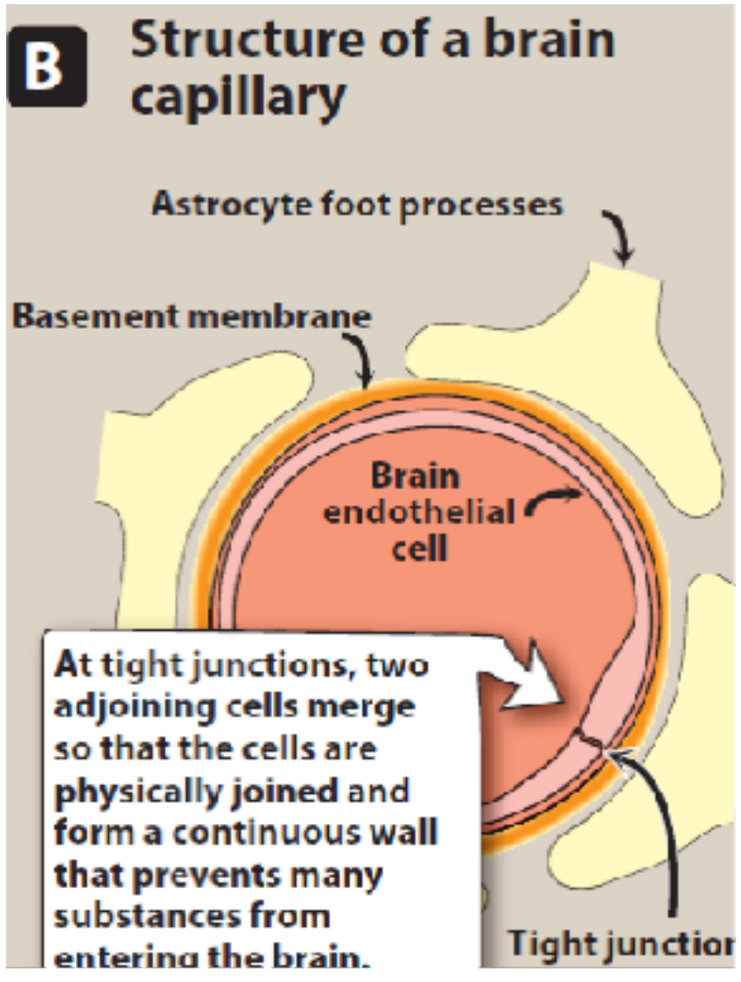
✓ *Therapeutic equivalence*

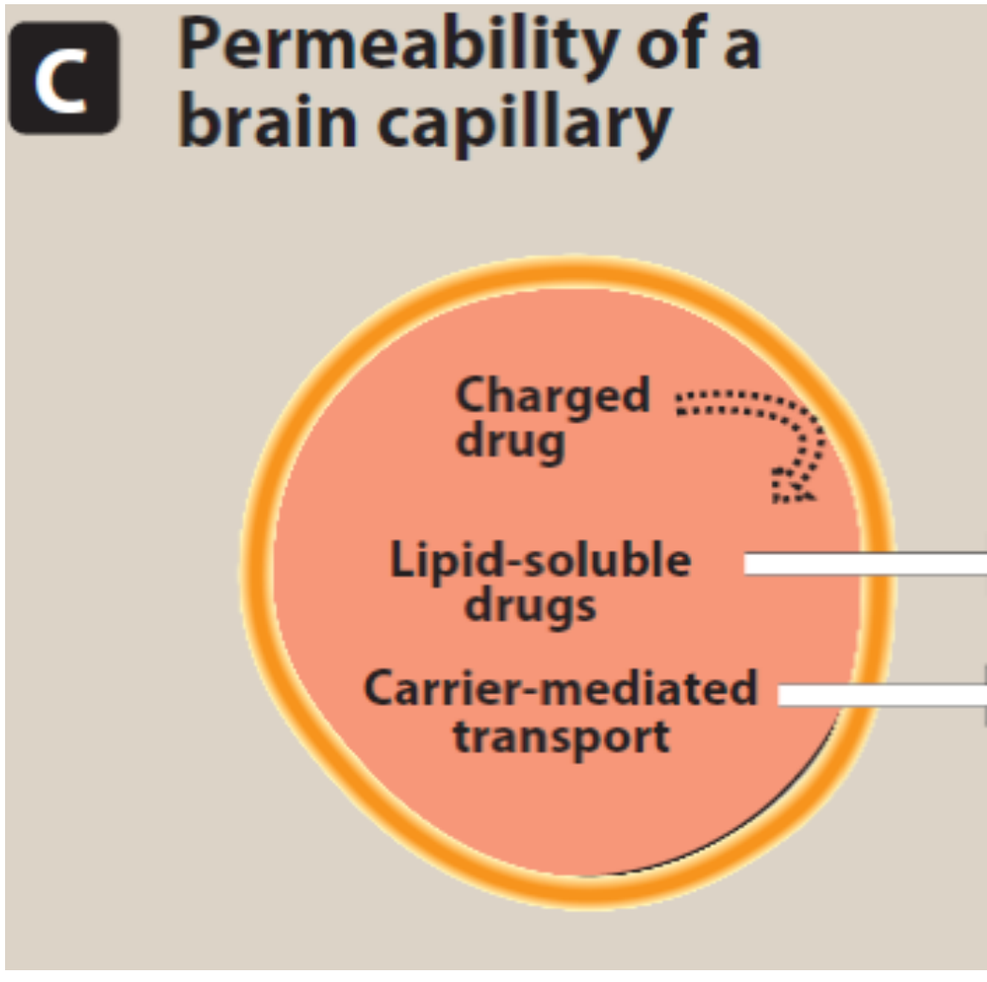
# *Drug Distribution*

- *The process by which a drug reversibly leaves the blood stream and enters interstitium (ECF) and tissues*
- *capillary permeability, T vol., pl ptns binding, & relative lipophilicity*
- *Blood Flow (CO & local BF)*
- *Capillary permeability (capillary structure, chemical nature)e.g. levodopa*
- *Binding to pl ptns & tissues (acrolein metabolite of cyclophosphamide)*
- *lipophilicity*

# *Liver and Brain Capillaries*



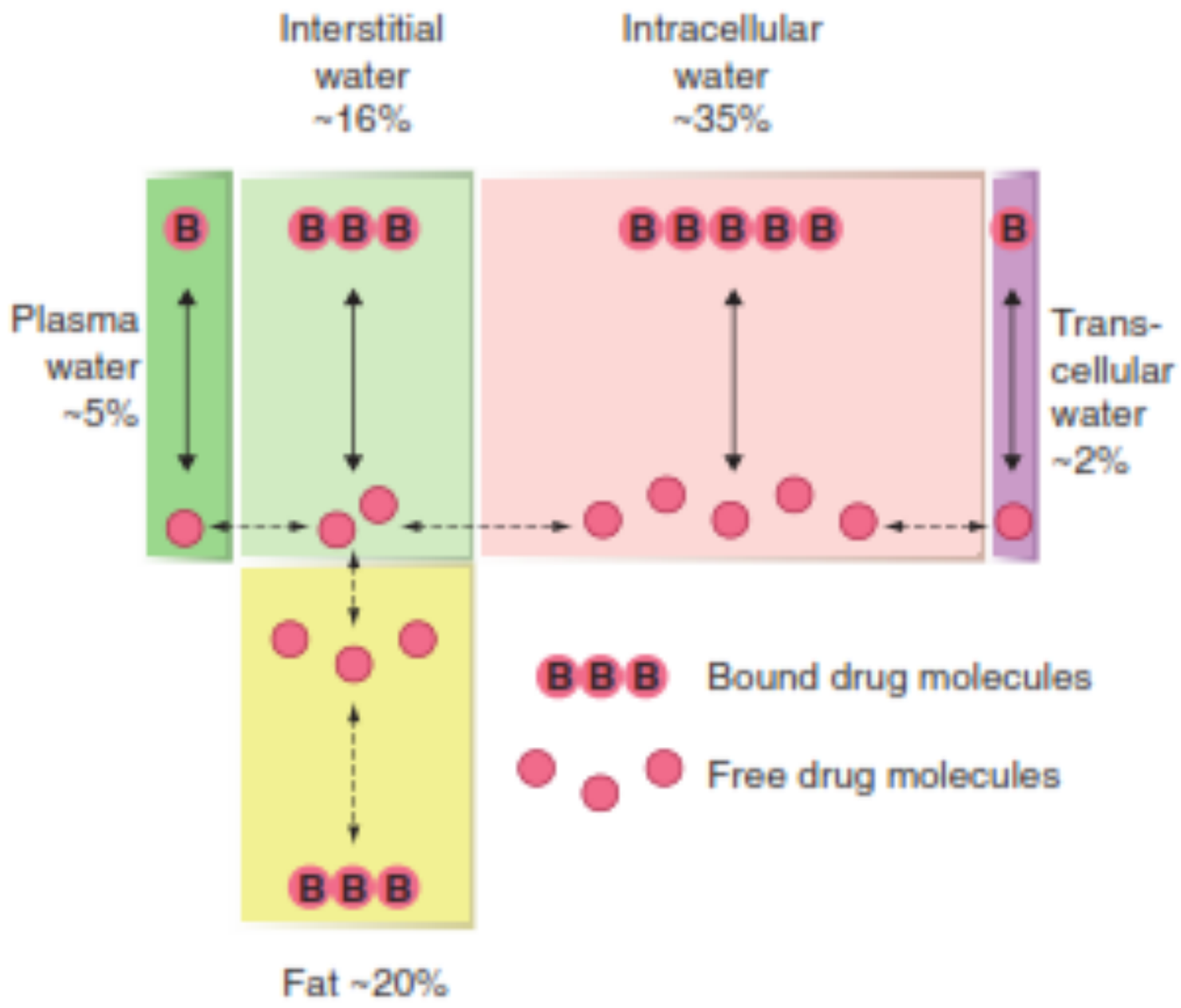
# *Volume of Distribution*

*Apparent volume of distribution: the fluid volume required to contain the entire drug in the body at the same concentration measured in the plasma*

$$V_d = \frac{\text{Amount of drug in the body}}{C_0}$$

- ✓ *Plasma compartment*
- ✓ *ECF*
- ✓ *Total body water*

# *The Main Body Fluid Compartments*



# *Volume of Distribution (cont.)*

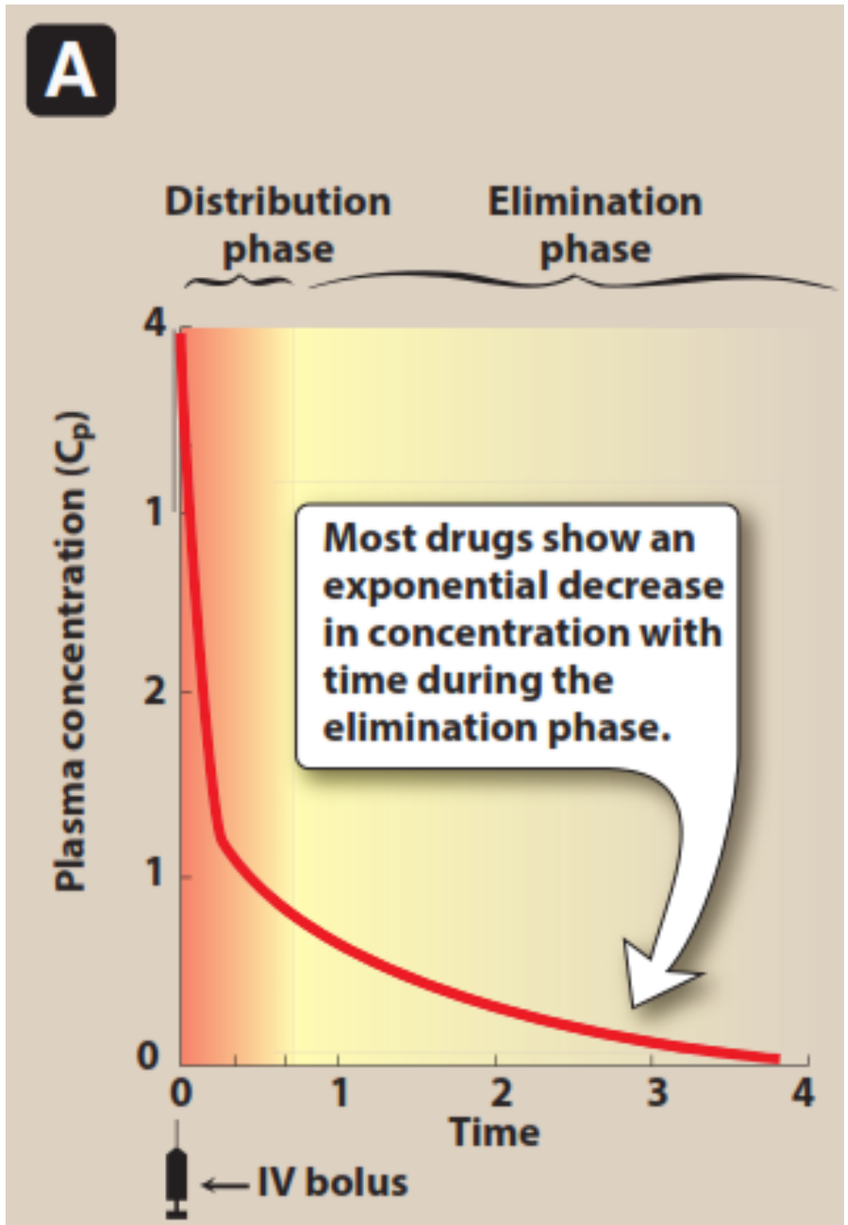
- Apparent volume of distribution ($V_d$)
- Determination of volume of distribution

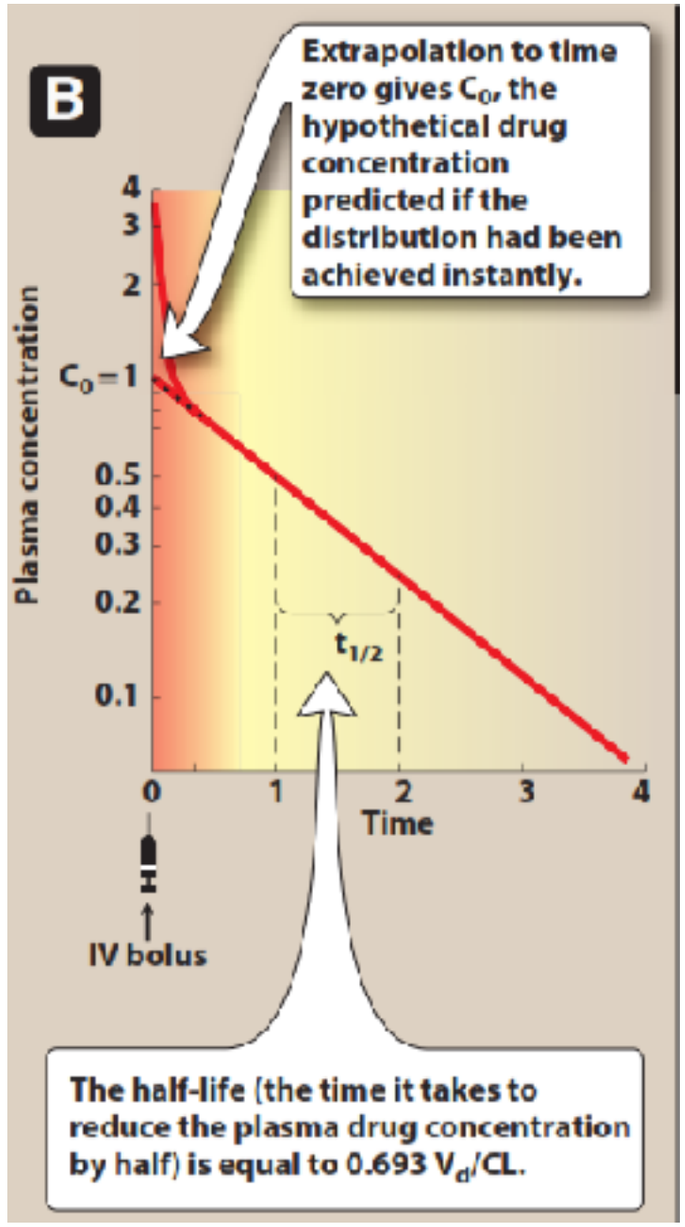
$$V_d = \frac{\text{Dose}}{C_0}$$

- Plasma half life ($t_{1/2}$)

- Effect of $V_d$ on $t_{1/2}$

# *Plasma Drug Concentration after Single Injection*



# *Drug Clearance through Metabolism*

*Drugs are eliminated from the body by:*

- ✓ *Hepatic metabolism*
- ✓ *Elimination in bile*
- ✓ *Elimination in urine*

*Clearance (CL): amount of drug removed from bod per unit time*

$$CL = 0.693 \times V_d / t_{1/2}$$

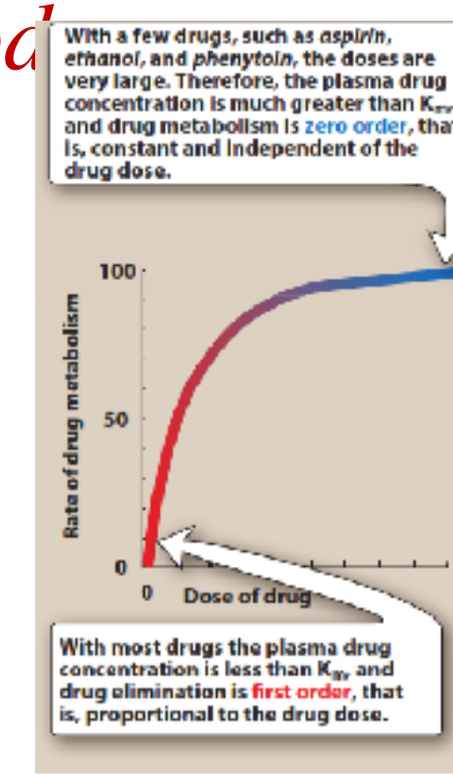
*1st order kinetics*

$$v = \text{Rate of drug metabolism} = \frac{V_{max}[C]}{K_m + [C]}$$

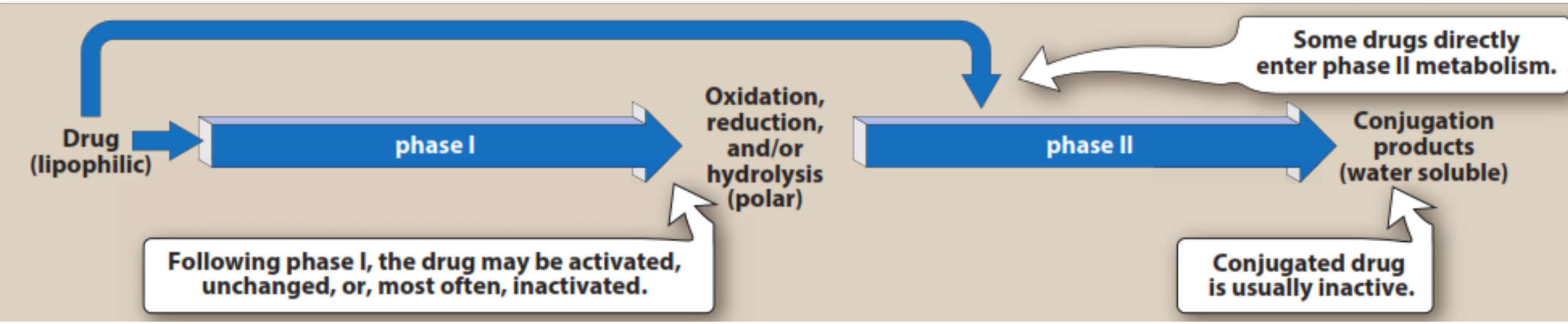
$$v = \text{Rate of drug metabolism} = \frac{V_{max}[C]}{}$$

*Zero order kinetics*

$$v = \text{Rate of drug metabolism} = \frac{V_{max}[C]}{[C]} = V_{max}$$



# *Drug Metabolism*



# *Reactions of Drug Metabolism*

➢*Phase I*

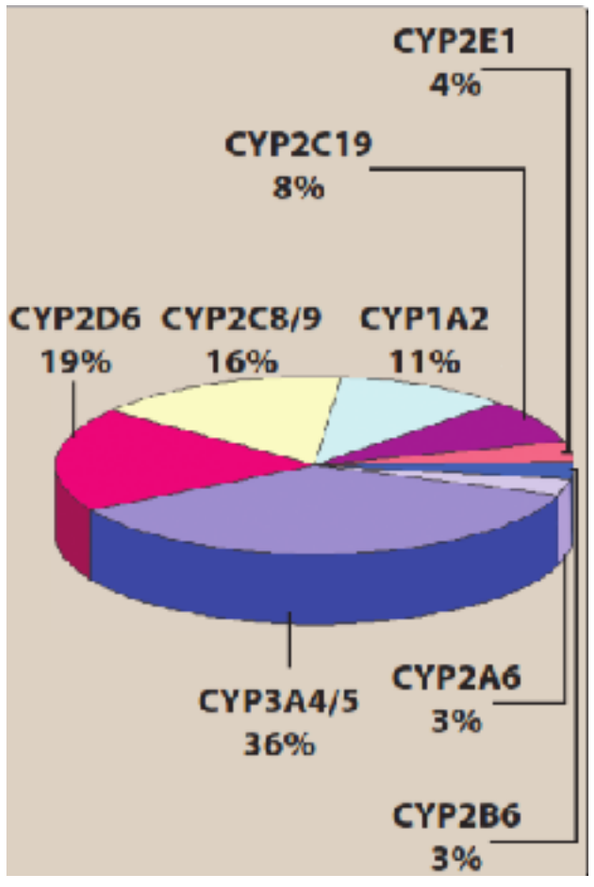
✓ *Phase I through P450*

*Specificity*

*Genetic variability*

*Inducers*

*Inhibitors (omeprazole, grapefruit)*




✓ *Phase I not involving P450*

➢ *Phase II*

## Isozyme: CYP2C9/10

| COMMON SUBSTRATES | INDUCERS |
|---|---|
| *Warfarin*<br>*Phenytoin*<br>*Ibuprofen*<br>*Tolbutamide* | *Phenobarbital*<br>*Rifampin* |

## Isozyme: CYP2D6

| COMMON SUBSTRATES | INDUCERS |
|---|---|
| *Desipramine*<br>*Imipramine*<br>*Haloperidol*<br>*Propranolol* | None* |

## Isozyme: CYP3A4/5

| COMMON SUBSTRATES | INDUCERS |
|---|---|
| *Carbamazepine*<br>*Cyclosporine*<br>*Erythromycin*<br>*Nifedipine*<br>*Verapamil* | *Carbamazepine*<br>*Dexamethasone*<br>*Phenobarbital*<br>*Phenytoin*<br>*Rifampin* |

1. *1- decrease pl D conc*
2. *decrease D activity*
3. *Decrease therapeutic effect*
4. *Decrease therapeutic D effect*

# *Drug Clearance by the Kidney*

*1.Glomerular filtration*

*2.Proximal tubular secretion*

*3.Distal tubular reabsorption*