MANCHESTER 1824

The University of Manchester

Basic Concepts in Pharmacokinetics

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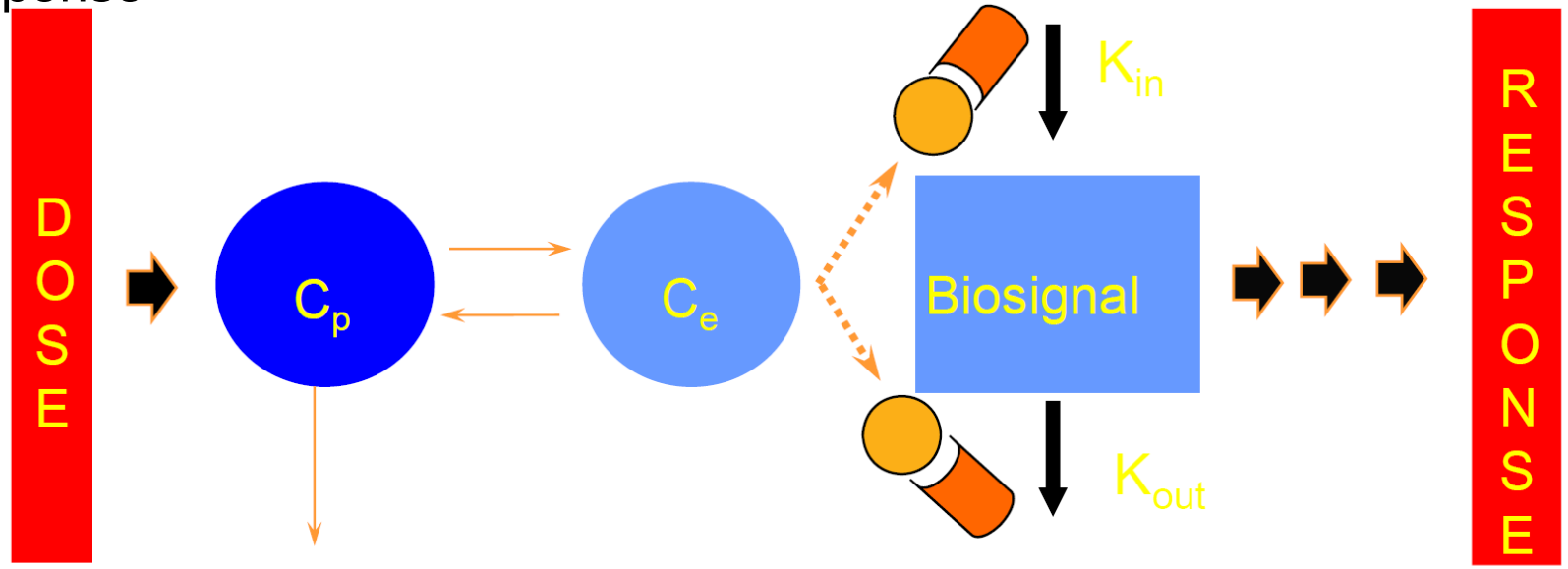
Objectives

1. **Define pharmacokinetics**
2. **Describe absorption**
3. **Describe distribution**
4. **Describe elimination**

Why do we study PK?

We administer drugs (dose) because we seek a certain effect (response), but a complex chain of events links the administered dose to the observed response



Jusko, Ko, Ebling 1995

Disposition kinetics | Biophase distribution — Pharmacokinetics

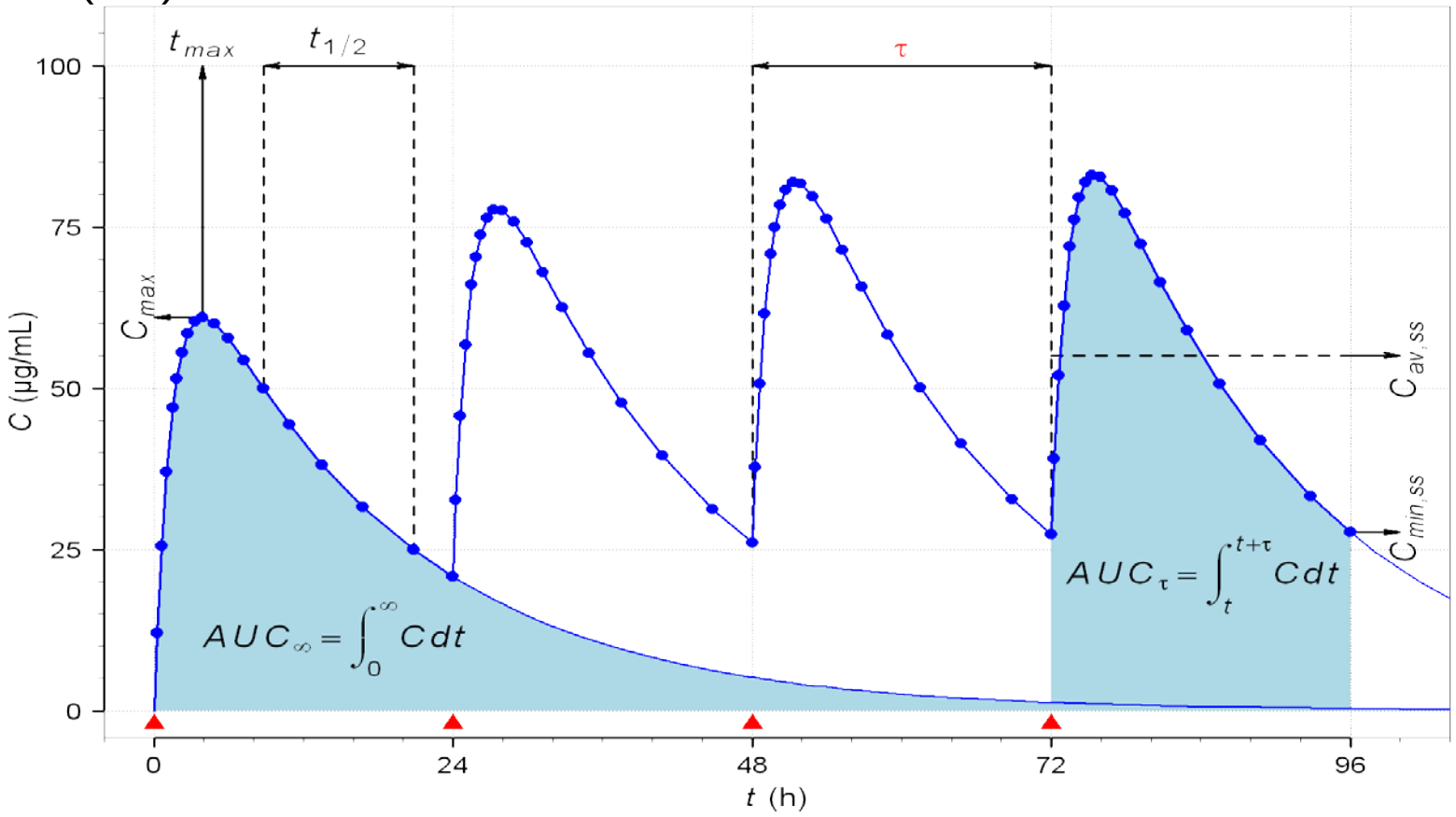
Biosensor process | Biosignal flux | Trans-duction — Pharmacodynamics

Drug concentration

PK is based on the analysis of drug concentrations.

After one or more doses (▲), the drug concentration in the desired matrix is measured (-●-).

Image from http://en.wikipedia.com



(L)ADME

The processes that characterize PK are summarized in the **(L)ADME** scheme.

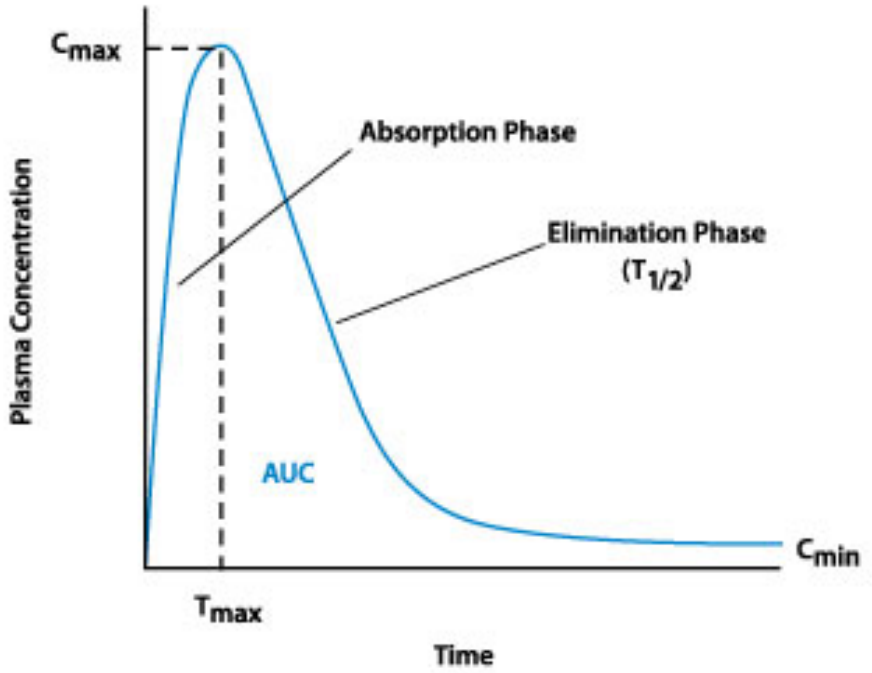


Image from http://saladax.com

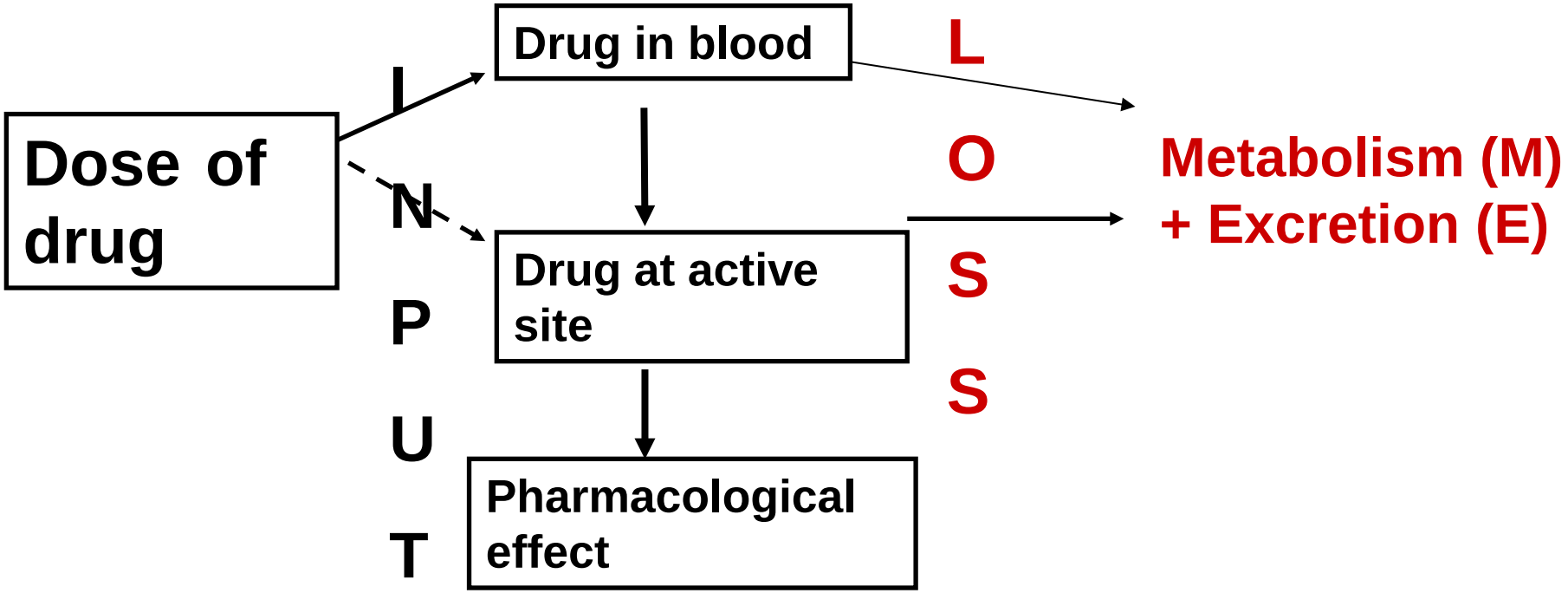
1. Liberation
2. Absorption
3. Distribution
4. Metabolism
5. Excretion

Elimination

Disposition

Absorption

Absorption **Distribution** **Elimination**

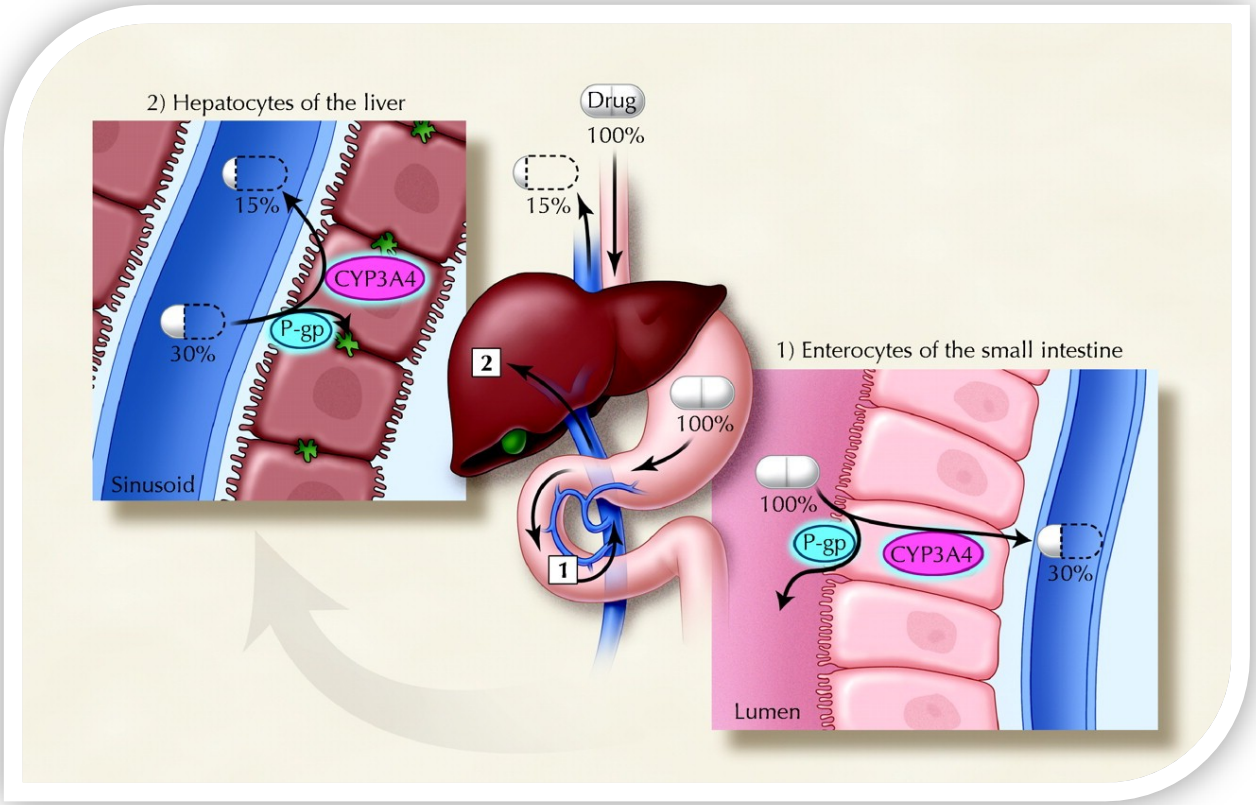


Need to maintain plasma concentration of a drug to achieve a therapeutic effect

Absorption

- **Absorption - Passage of compound from the site of administration into the bloodstream (or lymph), usually across a membrane**
- **Systemic routes of drug administration:**
  - **Intravascular** – placement of the drug directly into blood (intravenous (iv) or intra-arterial)
  - **Extravascular** – **oral**, sublingual, subcutaneous, intramuscular, rectal
- **Most drugs administered extravascularly act systemically. In such cases, systemic absorption is a prerequisite for efficacy**
- **Local effect - systemic absorption is a safety issue.**

Absorption after oral administration



Movement of unchanged drug from the site of administration to the site of measurement

Few potential sites of loss – contributes to decrease in systemic absorption

Bioavailability

- Bioavailability (F) refers to the extent of absorption of intact drug. Generally, refers to the fraction of an extravascularly administered dose that reaches the systemic circulation intact

- BA studies provide useful information on the dosage/dosage regimen

- BA studies provide information regarding the performance of a formulation

Bioavailability

Relative F – comparison of F between formulations of a drug given by the same or different routes of administration

Absolute F is usually assessed with reference to an intravenous dose

Relative F

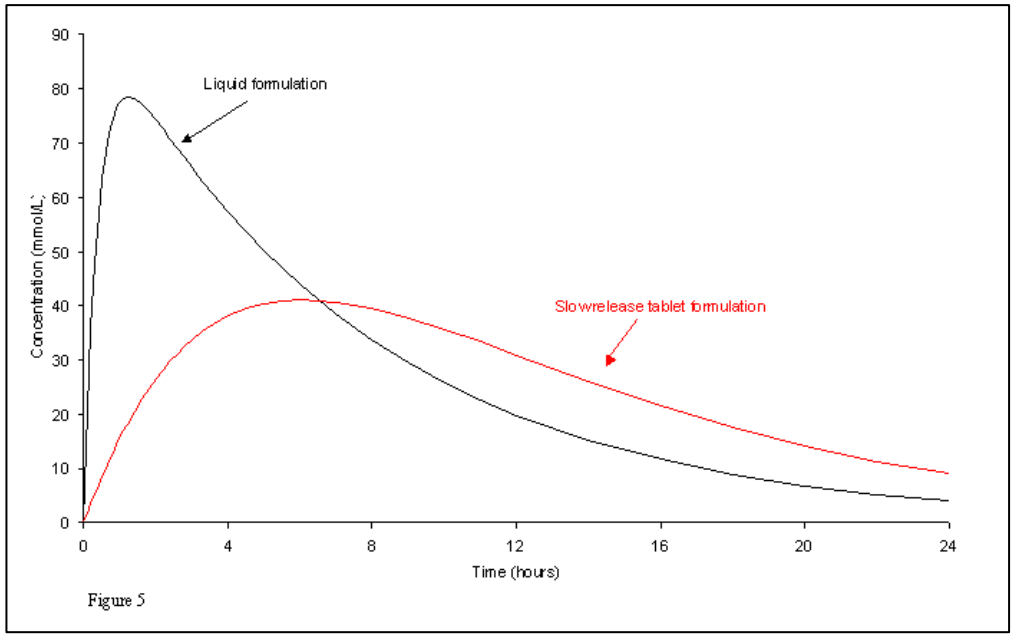
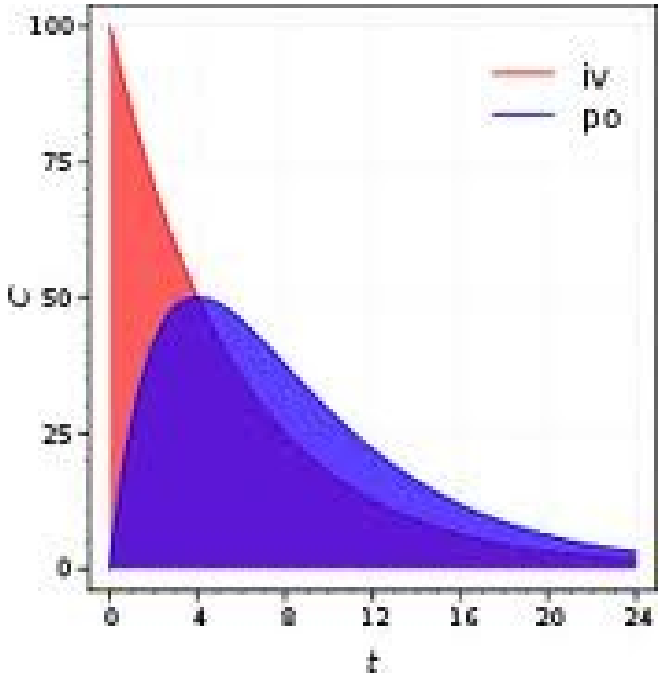


Figure 5

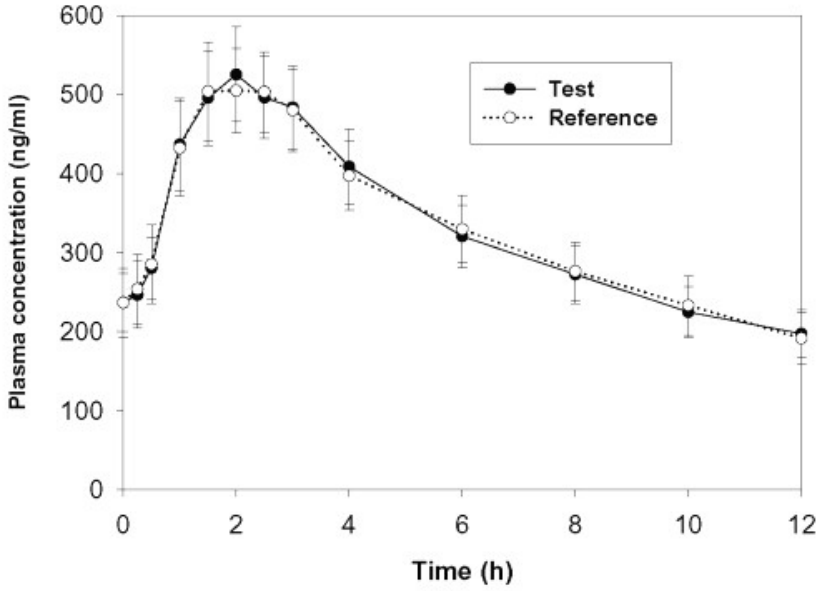
Absolute F

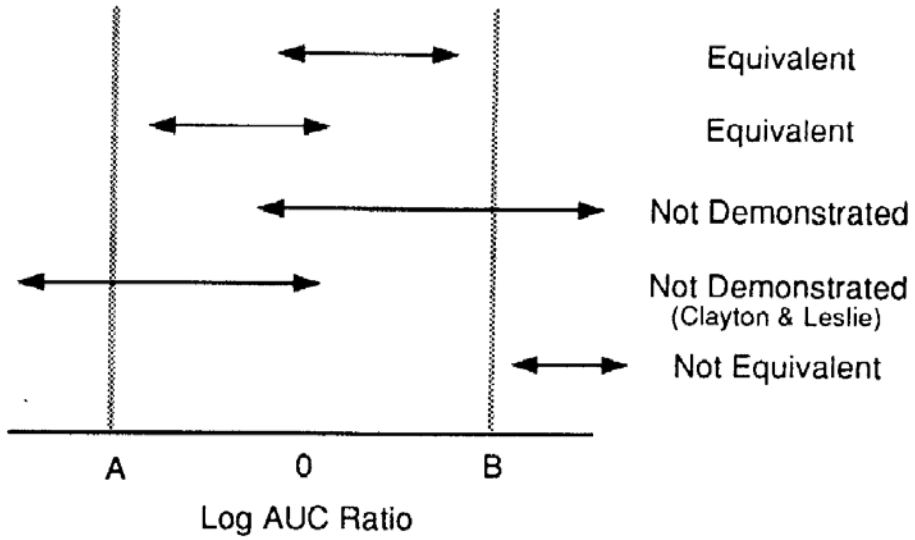


Bioequivalence (BE)

- Bioequivalence: Formulations containing the same dose of same chemical entity, generally in the same dosage form, intended to be interchangeable
- BE documentation may be useful to:
  - Link early and late phase clinical formulations
  - Compare clinical versus to-be-marketed formulation
  - Evaluate change of formulation (tablet vs. capsule)
  - Compare generic versus branded drug

Bioequivalence





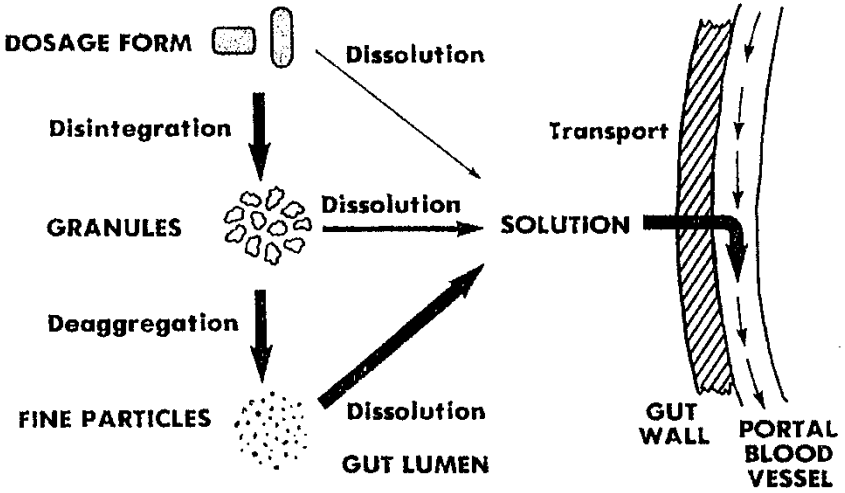
C-t profiles similar, NOT likely to cause clinically relevant differences in therapeutic and adverse effects!

A and B are the limits set (often ± 20%) around the reference product.

Bioequivalent preparations generally considered to be therapeutically equivalent

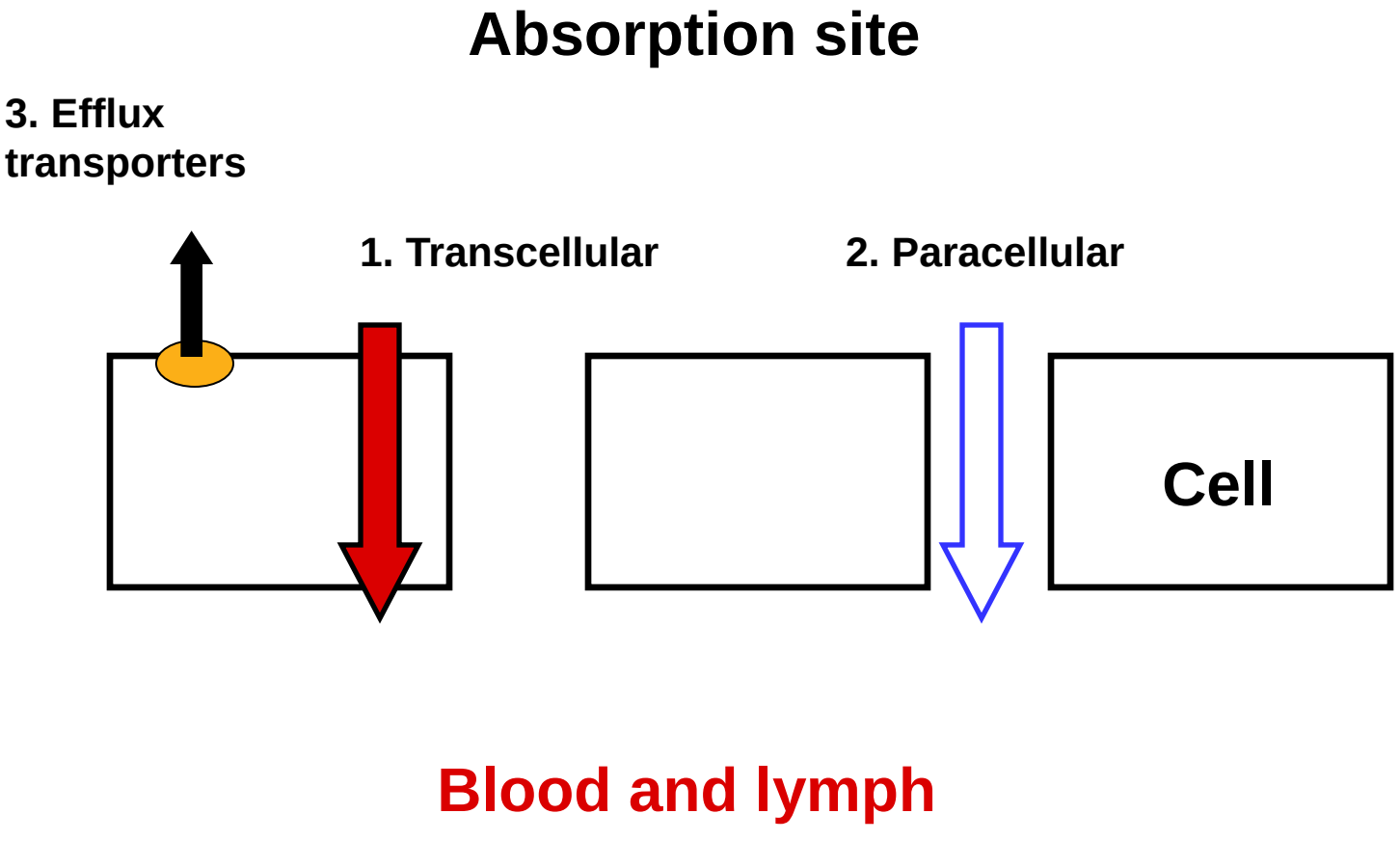
Rate limiting steps for oral absorption

1. **Disintegration time and dissolution rate**
2. **Movement through membranes**
   a) perfusion or
   b) permeability limitations
3. **Gastric emptying and intestinal transit**
4. **First-pass metabolism in the gut/liver**

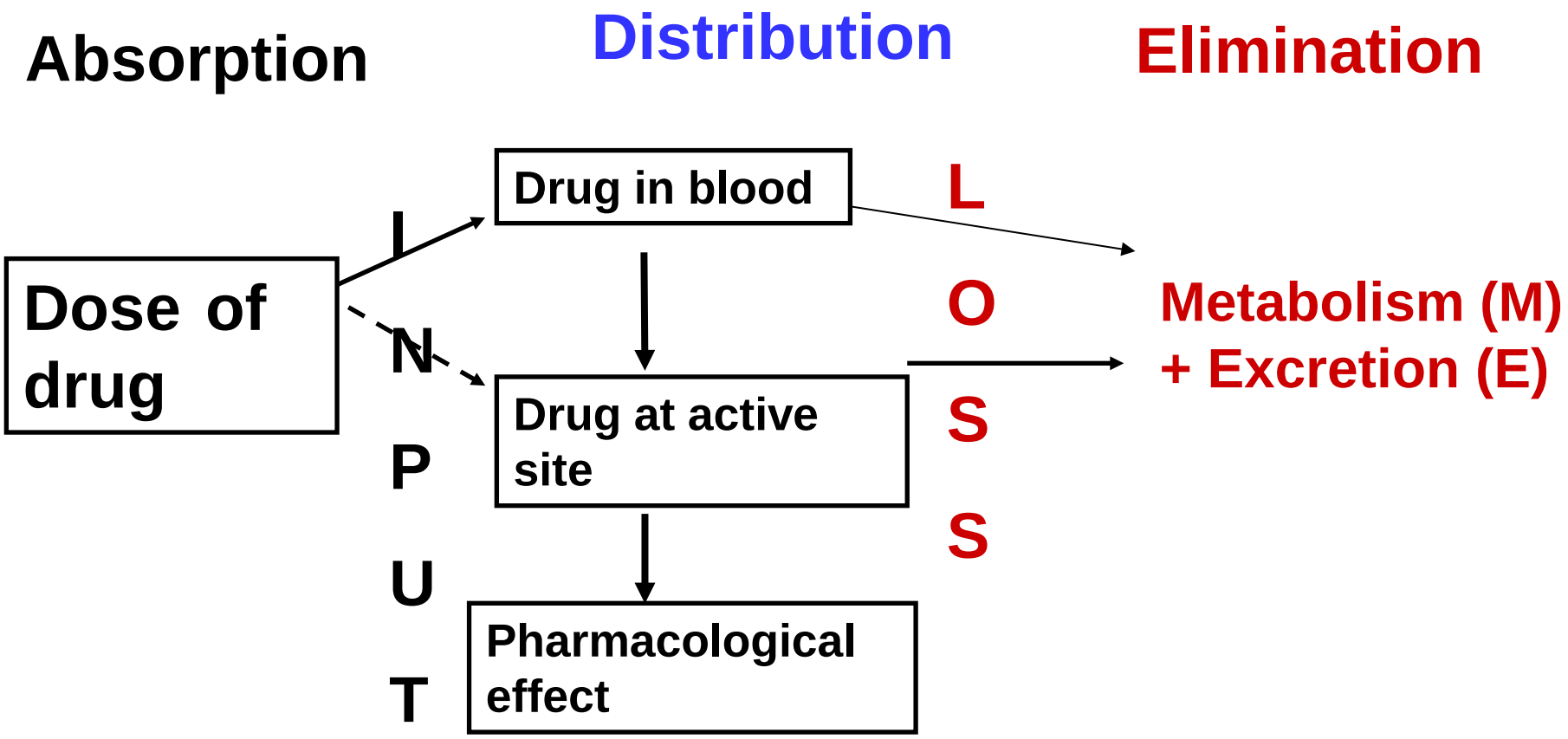


Can cause delay or loss of drug – alteration of drug concentration!

Absorption from solution: Movement through membrane

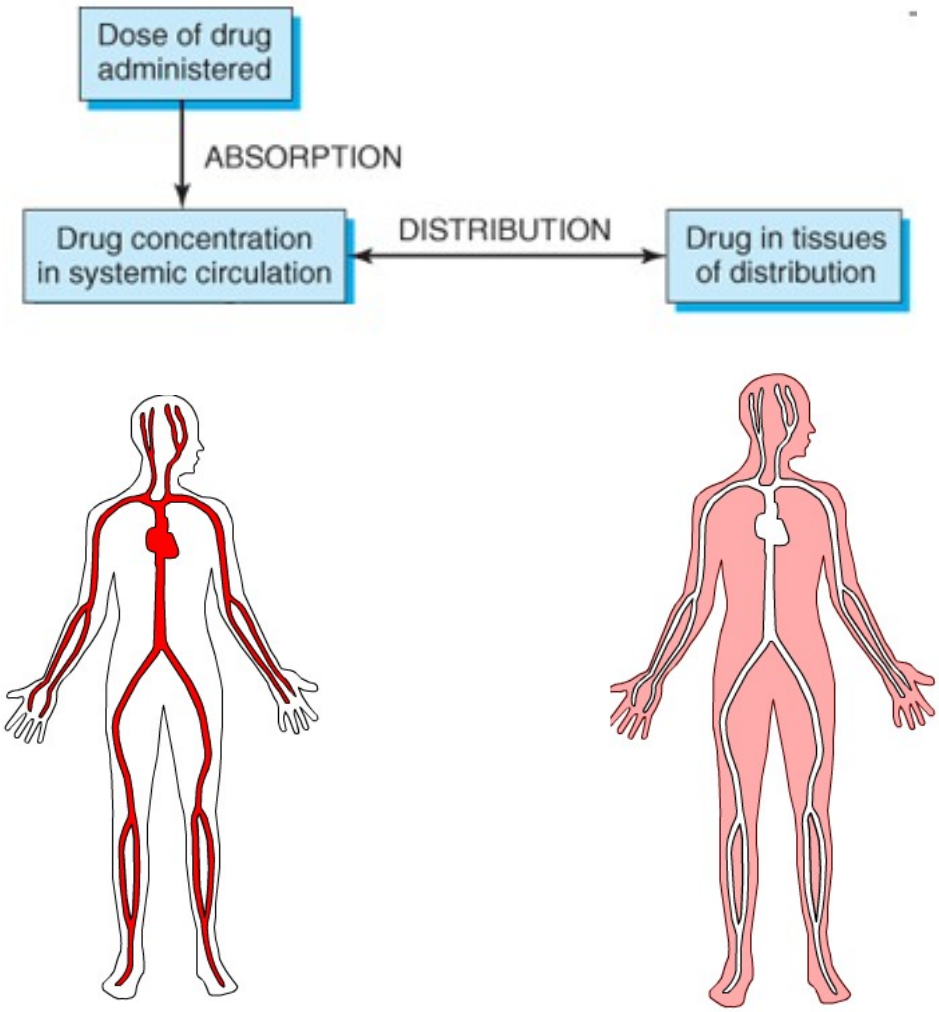


Distribution



Need to maintain plasma concentration of a drug to achieve a therapeutic effect

Distribution



Distribution

- Volume of Distribution (V_d) = Apparent and hypothetical volume in which the drug is dispersed
- An equilibrium concept
- Relates measured plasma (or blood) drug concentration (C) to the amount of drug in the body (A)
- Important for drug dosage regimen to determine the loading dose

$$V = \frac{A}{C}$$

Distribution

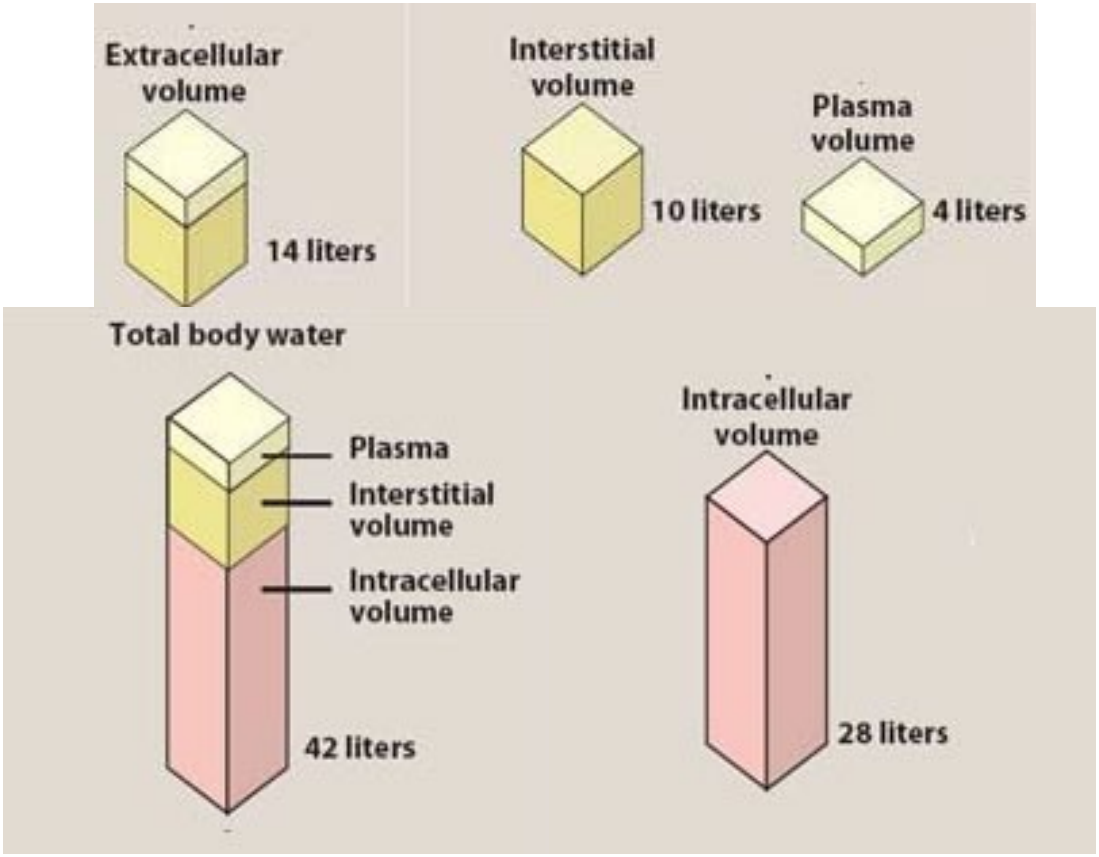
- Value depends on reference fluid measured (plasma, blood, unbound drug)
- Cb, C and Cu can differ as a consequence of binding to cells and plasma proteins

However, at equilibrium:

$$A = V \cdot C = V_b \cdot C_b = V_u \cdot C_u$$

amount **plasma** **blood** **plasma water**

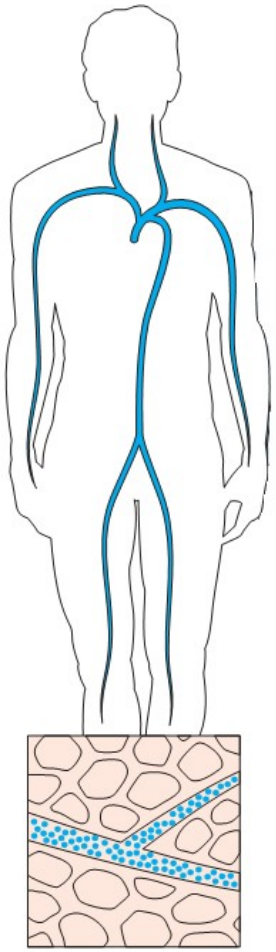
Distribution

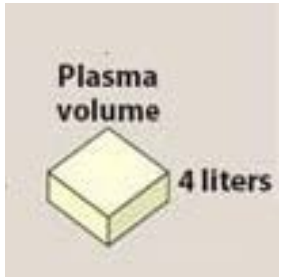


Relative size of various distribution volumes within a 70-kg individual

- Plasma: 4 liters.
- Interstitial volume: 10 liters.
- Intracellular volume: 28 liters

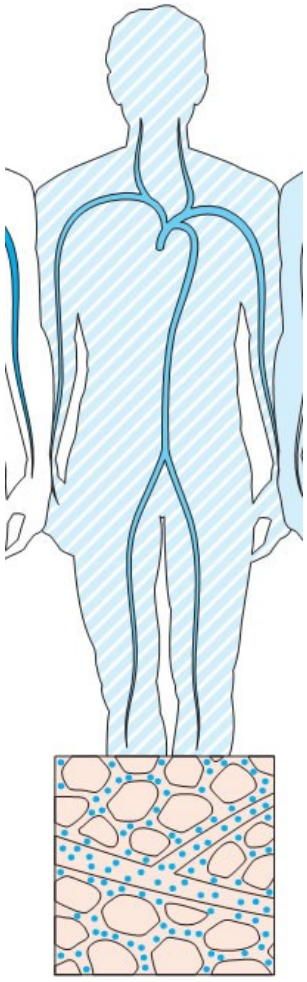
Distribution

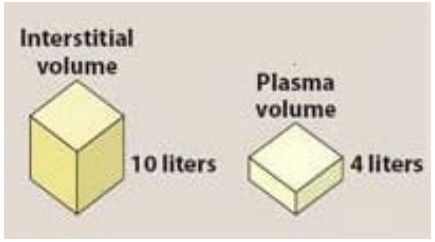




- Vd: around 5 L.
- Very high molecular weight drugs, or drugs that bind to plasma proteins excessively
- Example: heparin 4L (3-5)

Distribution





Vd: between 4 and 14 L.

- Drugs that have a low molecular weight but are hydrophilic.

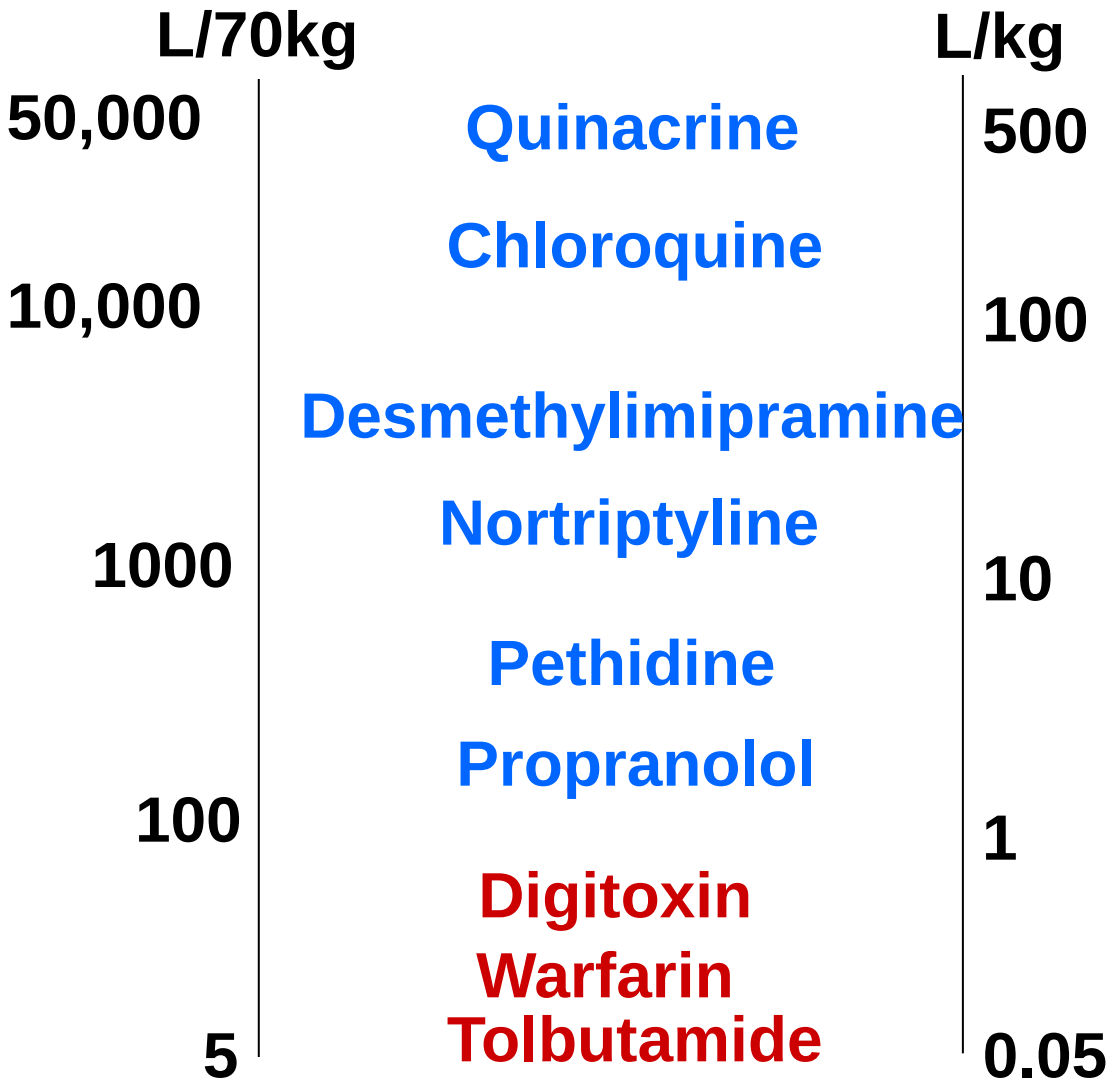
Example:

Atracuronium 11 L (8-15)

Distribution

- Diffusion to intracellular fluid . Vd equal to total body water.
  - Ethanol 38 L (34-41)
  - Alfentanyl 56 L (35-77)
- Drug that binds strongly to tissues. Vd higher than total body water.
  - Fentanyl: 280 L
  - Propofol: 560 L
  - Digoxin:385 L

Volume of Distribution



Cautious interpretation of V that are in the range of physiological values

Drug can bind to plasma proteins, blood cells and tissue components

Plasma Protein Binding

1. **Generally reversible, very rapid**

2. **Extent of binding**

fu = fraction of drug unbound in plasma (Cu/C)

1 – fu = fraction of drug bound

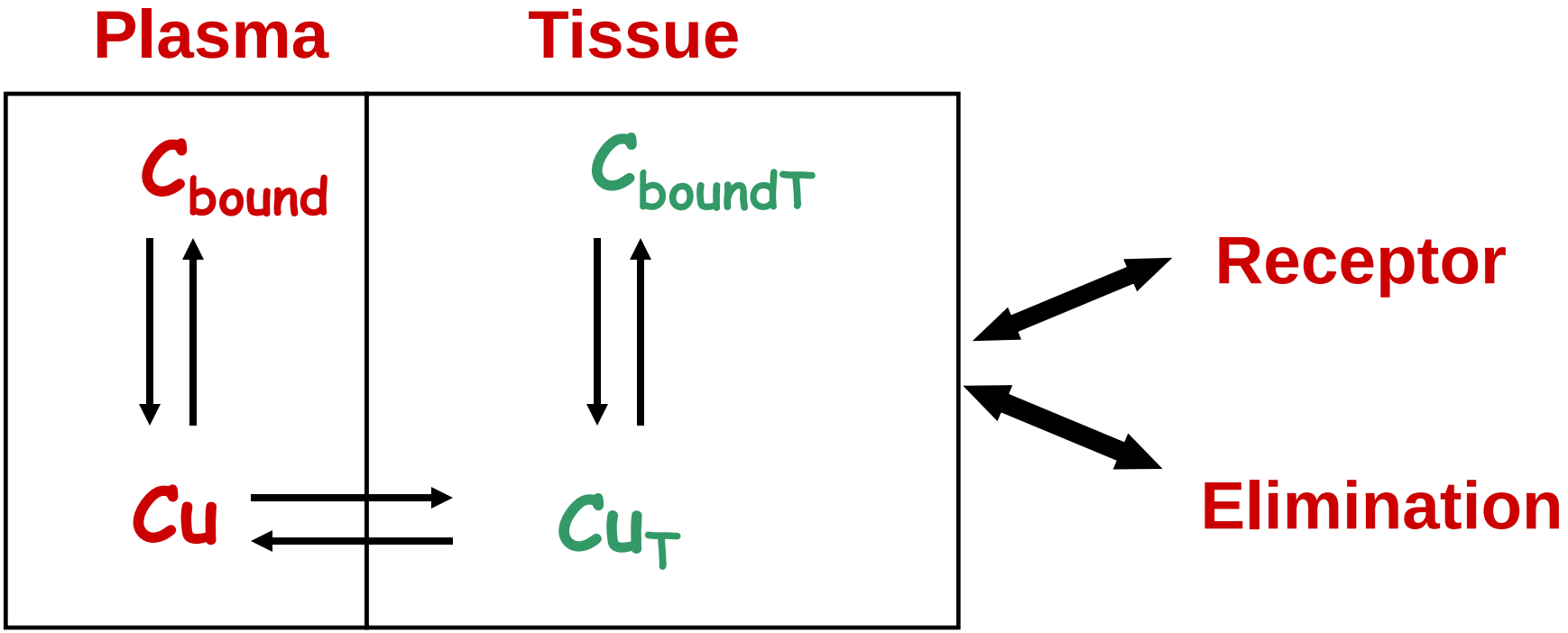
3. fu varies widely among the drugs

Total plasma concentration (C) usually measured rather than the more important unbound concentration (Cu)

Distribution

WHY IS UNBOUND CONCENTRATION IMPORTANT?

Assumption – only <u>unbound</u> drug diffuses into tissues, have pharmacological/toxicological effect and can be eliminated

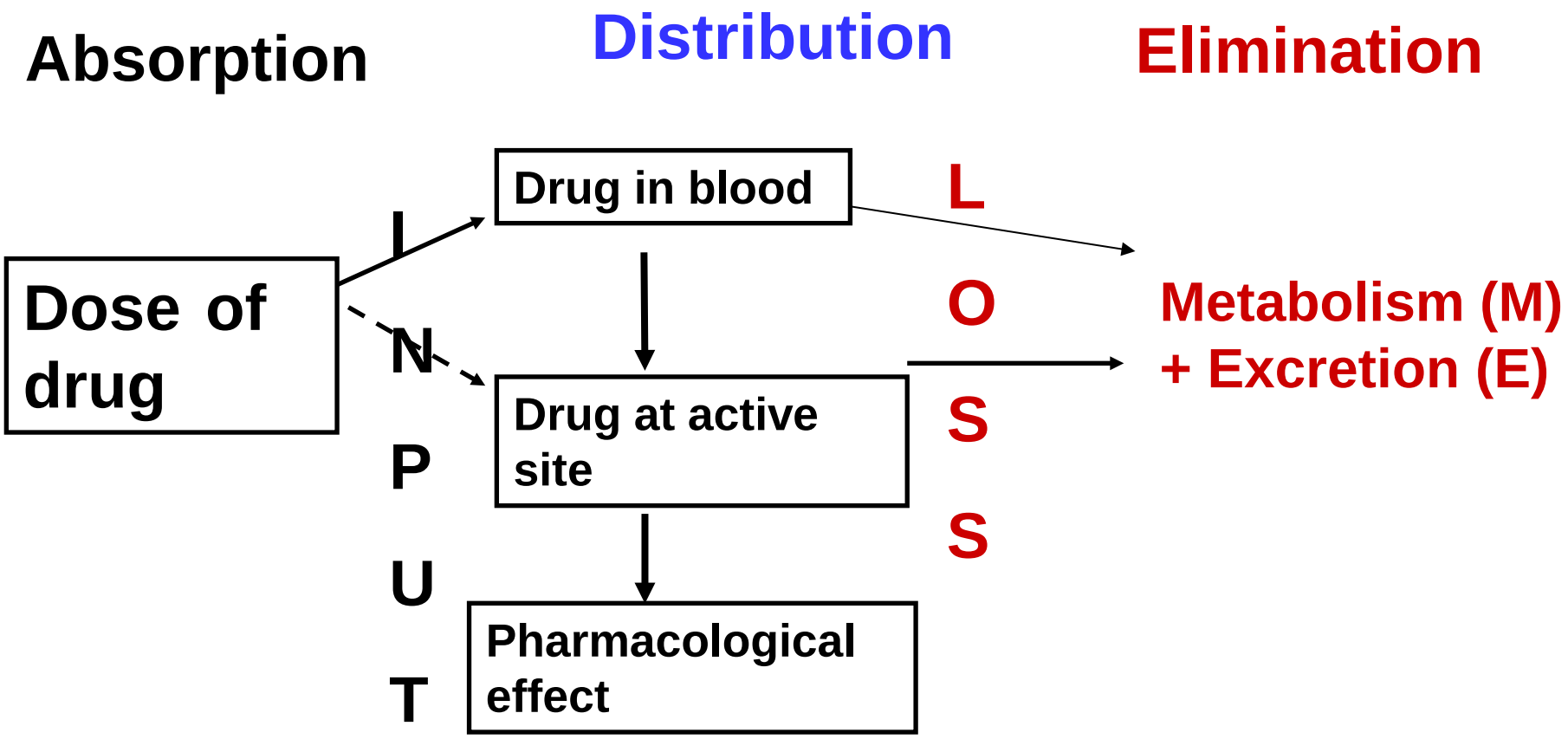


Distribution

$$V = V_P + V_T \cdot fu/fu_T$$

V↑	fu ↑
V↓	fu_T ↑

Elimination



Need to maintain plasma concentration of a drug to achieve a therapeutic effect

Elimination

Elimination = irreversible removal of the drug from the body

Metabolism – liver and intestine as major sites

– main mechanism of drug elimination

– metabolites more polar than the parent drug and renally excreted

Excretion – kidneys - renal

– liver – biliary excretion of drugs (hepatic)

– lungs - pulmonary (volatiles)

Concept of Clearance

PROPORTIONALITY CONSTANT

CLEARANCE is the parameter that relates rate of elimination to concentration:

CL = Rate of Elimination / C plasma

Units of flow

(mg/h)/(mg/L) =

L/h

If CL= 1L/hr and C=0.5 mg/L Rate of elimination =0.5 mg/hr - A steady-state concept

Concept of Clearance

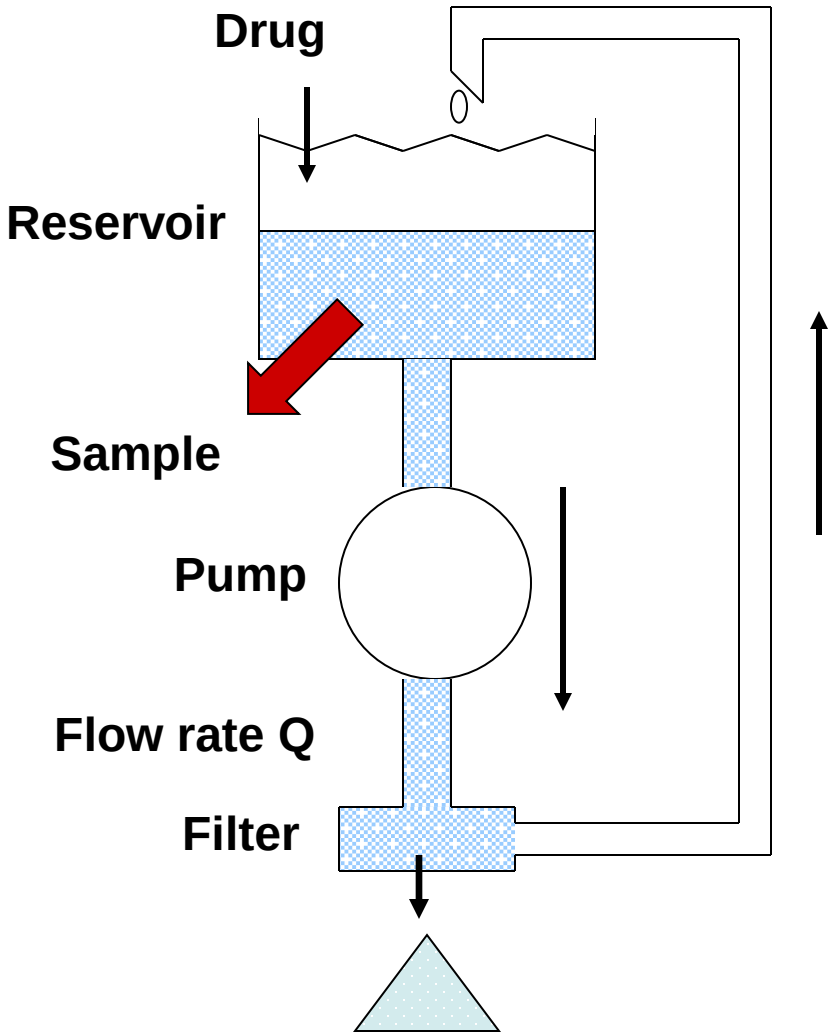
CL is the apparent volume of plasma (or blood or plasma water) completely cleared of drug per unit of time.

Rate of elimination = $CL \cdot C = CL_b \cdot C_b = CL_u \cdot C_u$

plasma blood plasma water

Value of clearance depends upon site of measurement

Dependence of elimination on both V and CL



- **Volume** of reservoir (V)= 1000mL
- Dose = 10 mg
- Initial concentration = 10 mg/L
- Perfect filter (organ), removes all drug: Flow rate 100 mL/min
- **Clearance** (Volume of blood completely cleared of drug per unit of time = Flow Rate, Q = 100 ml/min)
- **CL** = 100 mL/min
- **Fractional rate of removal**,

k = 100 mL/min/1000 mL = 0.1 or 10% /min

Dependence of elimination on both V and CL

Amount in body (A) $A = V \cdot C$

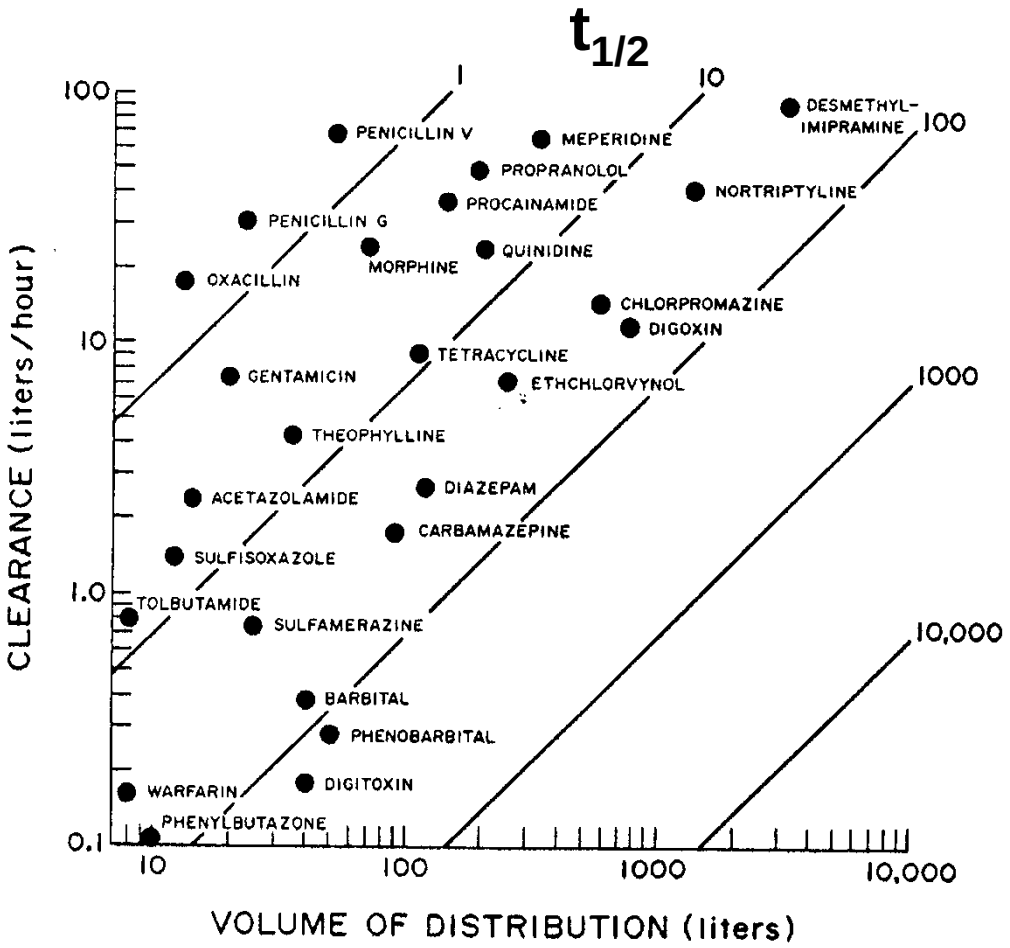
Fractional elimination rate constant, k, defined as:

$$k = \frac{\text{Rate of elimination}}{\text{Amount}} = \frac{CL \cdot C}{V \cdot C} = \frac{CL}{V}$$

$$CL = k \cdot V$$

Dependence of elimination on both distribution and CL

CL



V

$$t_{1/2} = \frac{0.693\ V}{CL}$$

Relationship of PK parameters

The elimination half-life is defined as the time for the drug concentration to reach half of its value. Clinically interesting because intuitive, used to calculate when steady state is reached. It is a secondary parameter, which can be derived from CL and V

$$t_{1/2} = \frac{\ln(2) \cdot V}{CL}$$

Rate of elimination = CL*C

Remember that $AUC = \int_0^\infty C(t)dt$

If CL is constant with time

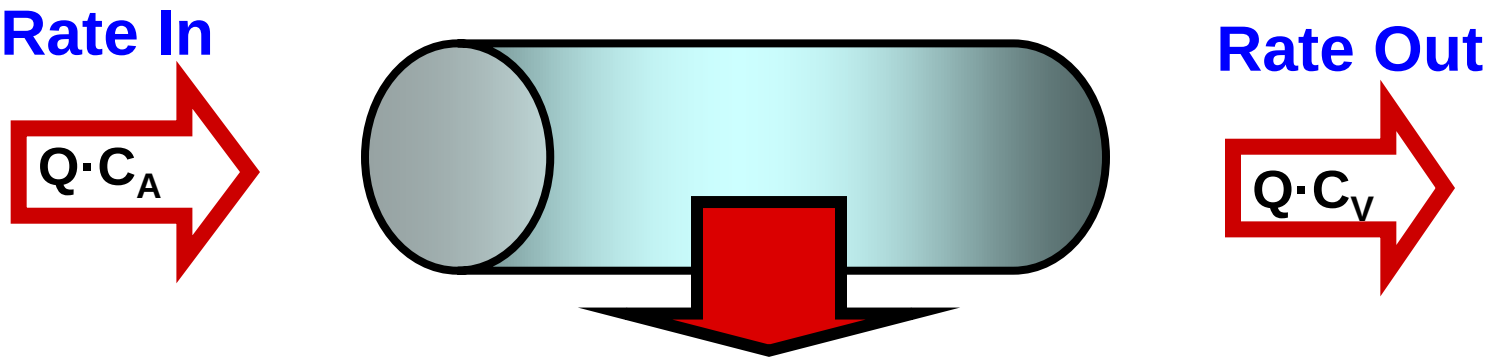
Amount eliminated = $\int_0^\infty CL.C(t)dt = CL\int_0^\infty C(t)dt = CL.AUC$

Amount eliminated = Dose*F = CL*AUC

$$CL = \frac{Dose \cdot F}{AUC}$$

1. Loss Across Organ of Elimination

Mass balance

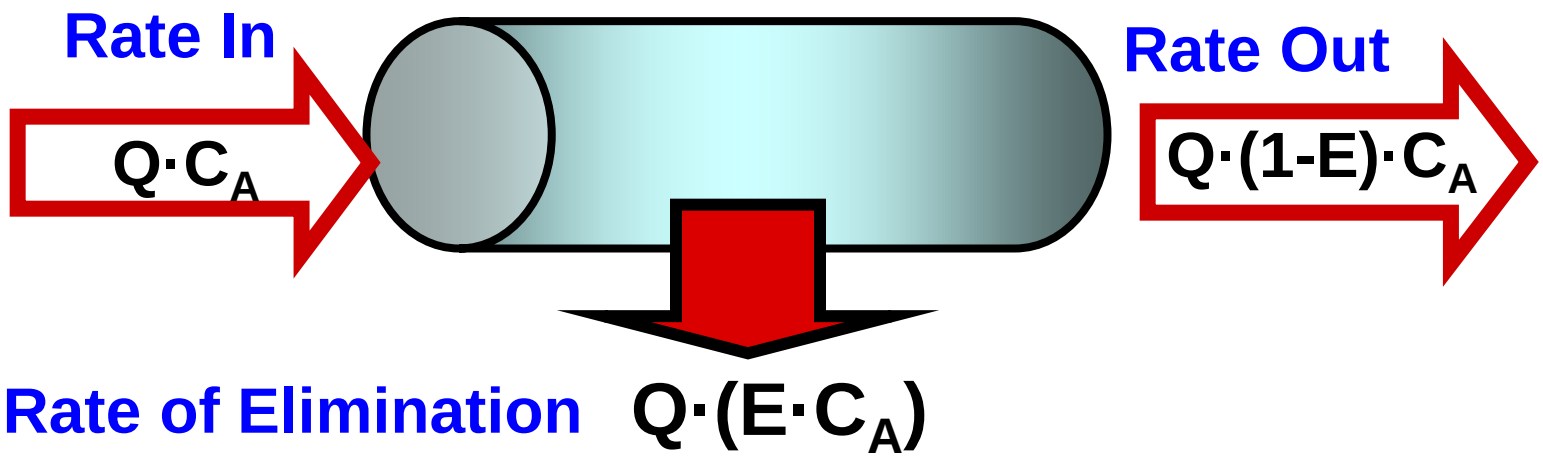


Rate of Elimination $Q \cdot C_A - Q \cdot C_V$

Rate of Elimination = Rate In – Rate Out

$$\text{Extraction ratio (E)} = \frac{\text{Rate of Elim.}}{\text{Rate In}} = \frac{Q \cdot (C_A - CV)}{Q \cdot C_A} = \frac{(C_A - CV)}{C_A}$$

1. Loss Across Organ of Elimination



$$CL = \frac{\text{Rate of Elimination}}{\text{Entering concentration}} = \frac{Q\,(C_A - C_V)}{C_A} = Q \cdot E$$

Extraction ratio

$$E = \frac{Q\,(C_A - C_V)}{C_A}$$

E 0 → 1

E = 0 No elimination

E = 1 Complete elimination

Typical blood flow values

Liver	1300-1500 mL/min
Kidney	1100 mL/min
Cardiac output	6000 mL/min

2. Additivity of Clearance

Liver and kidney are major organs of elimination

Rate of Elimination = Rate of Excretion + Rate of Hepatic Metabolism

$$CL \cdot C = CL_R \cdot C + CL_H \cdot C$$

Dividing by C:

$$CL = CL_R + CL_H$$

Hepatic Elimination

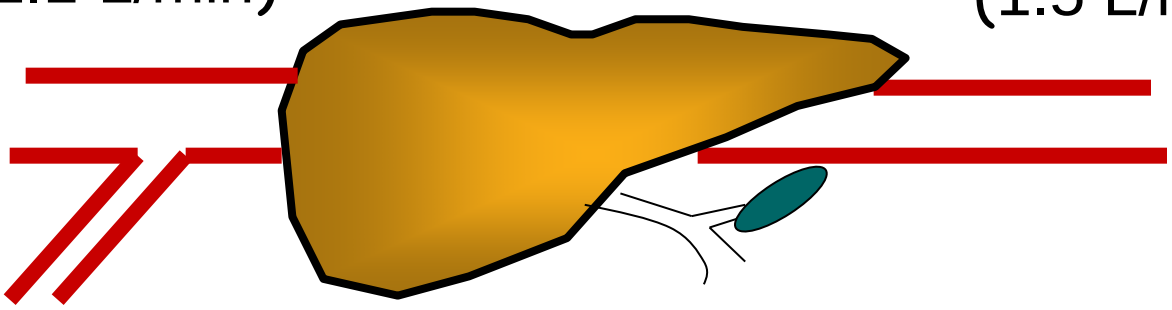
MAJOR ROUTES:

1. Metabolism
2. Biliary Excretion

Two blood supplies:

Hepatic Portal Vein (1.1 L/min)

Hepatic vein (1.5 L/min)



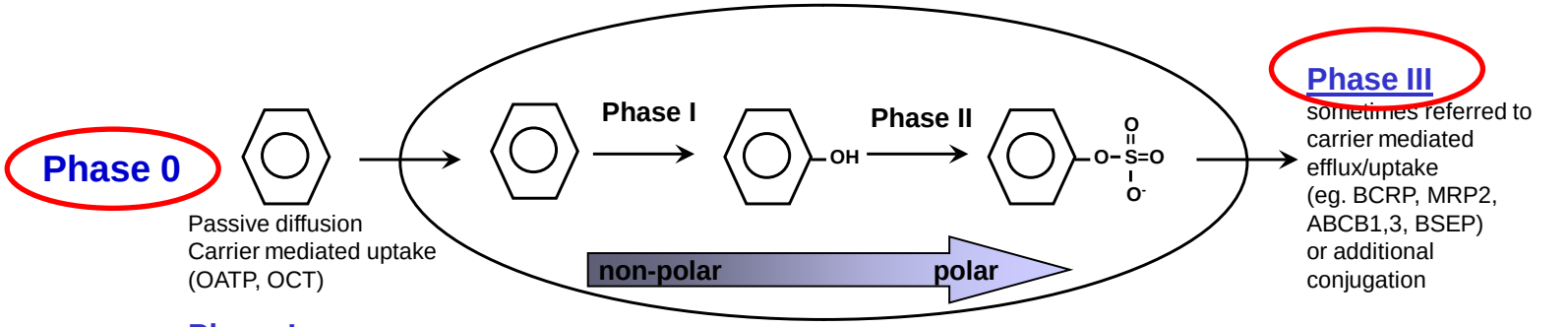
Hepatic Artery (0.4 L/min)

Metabolism

- The drug is “changed” so it can be eliminated
- Generates more polar (water soluble), inactive metabolites
- Metabolites may still have potent biological activity (or may have toxic properties)

Metabolism

Metabolic enzymes and reactions



Phase I

In most cases, generation or exposing of functional groups (eg. -OH, -NH_2, -SH, -COOH)

Reactions:
- oxidation
- reduction
- hydrolysis
- dealkylations
- deamination

Enzymes:

Hydrolysis
- esterase
- peptidase
- epoxide hydrolase

Reduction
- azo and nitro reductase
- carbonyl reductase
- quinone reductase

Oxidation
- cytochrome P450s (P450s or CYP)
- flavin-containing monooxygenases (FMO)
- monoamine oxidase (MAO)
- alcohol dehydrogenase
- aldehyde dehydrogenase and oxidase

Phase II

Conjugation with endogenous substrates, large increase in drug polarity

Reactions:
- glucuronide conjugation
- sulfate conjugation
- glutathione conjugation
- amino acid conjugation
- methylation
- acetylation
- hydration

Enzymes:
- UDP-glucuronosyltransferases (UGT)
- sulfotransferase (ST)
- glutathione *S*-transferase (GST)
- amino acid conjugating enzymes
- methyl transferase
- *N*-acethyltransferase

Metabolism

Phase I

- Converts the parent drug to a more polar metabolite by introducing or unmasking a functional group (-OH, -NH2, -SH) – via oxidation, reduction, and hydrolysis
- Usually results in loss of pharmacological activity
- Sometimes may be equally or more active than parent
- Occurs primarily in the liver

Metabolism

Phase II (conjugation reactions)

- Subsequent reaction in which a covalent linkage is formed between the parent compound or Phase I metabolite and an endogenous substrate such as glucuronic acid, sulfate, acetate, or an amino acid
- Highly polar – rapidly excreted in urine and feces
- Usually inactive - notable exception is morphine 6-glucuronide
- Usually occurs in liver and kidney (other organs sometimes involved)

Metabolism

Most oxidative metabolism occurs via CYP450 system

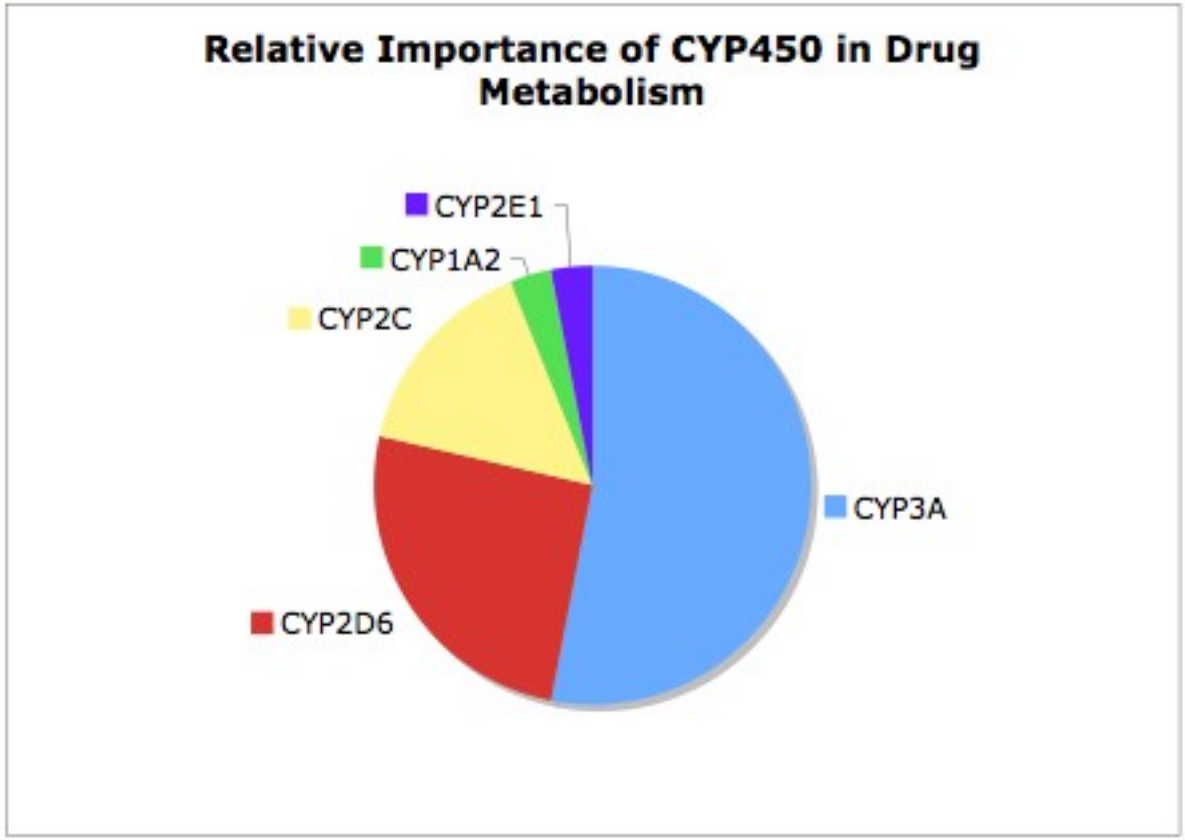
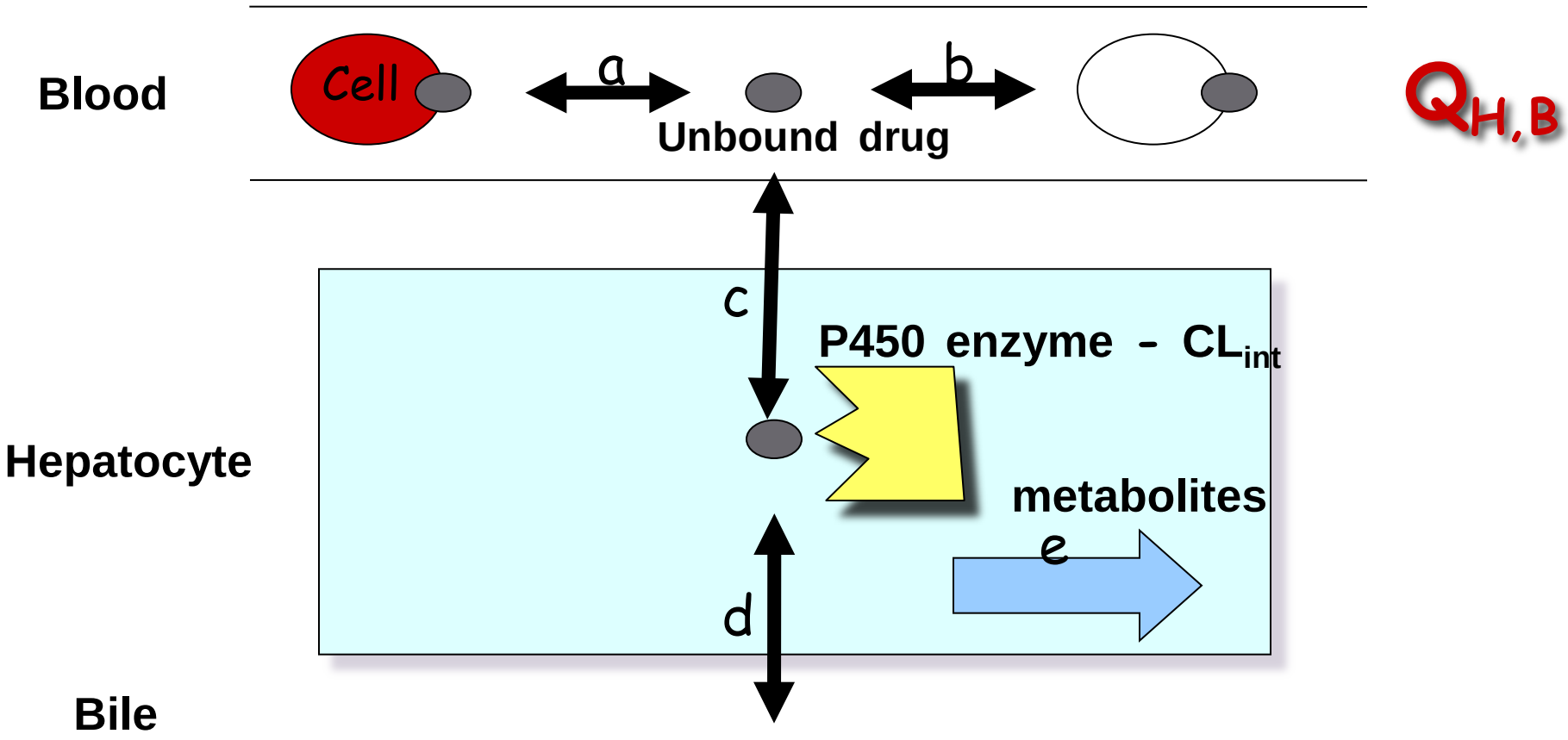


Image from: Guzman, Cambridge MedChem Consulting

3. Hepatic extraction and clearance



a – binding to blood cells

b – binding to plasma proteins

c – transport into (and out of) hepatocytes

d – biliary excretion

e - metabolism

Saturable kinetics

Saturable kinetics can be approximated

- as 1st order for lower concentrations,
- and 0 order for higher concentrations, as the system saturates.

Described by the Michaelis-Menten equation:

$$\frac{dC}{dt} = V_{max} \cdot \frac{C}{K_m + C}$$

Maximum rate

Michaelis constant

Concentration at which $V_{max}/2$ is reached

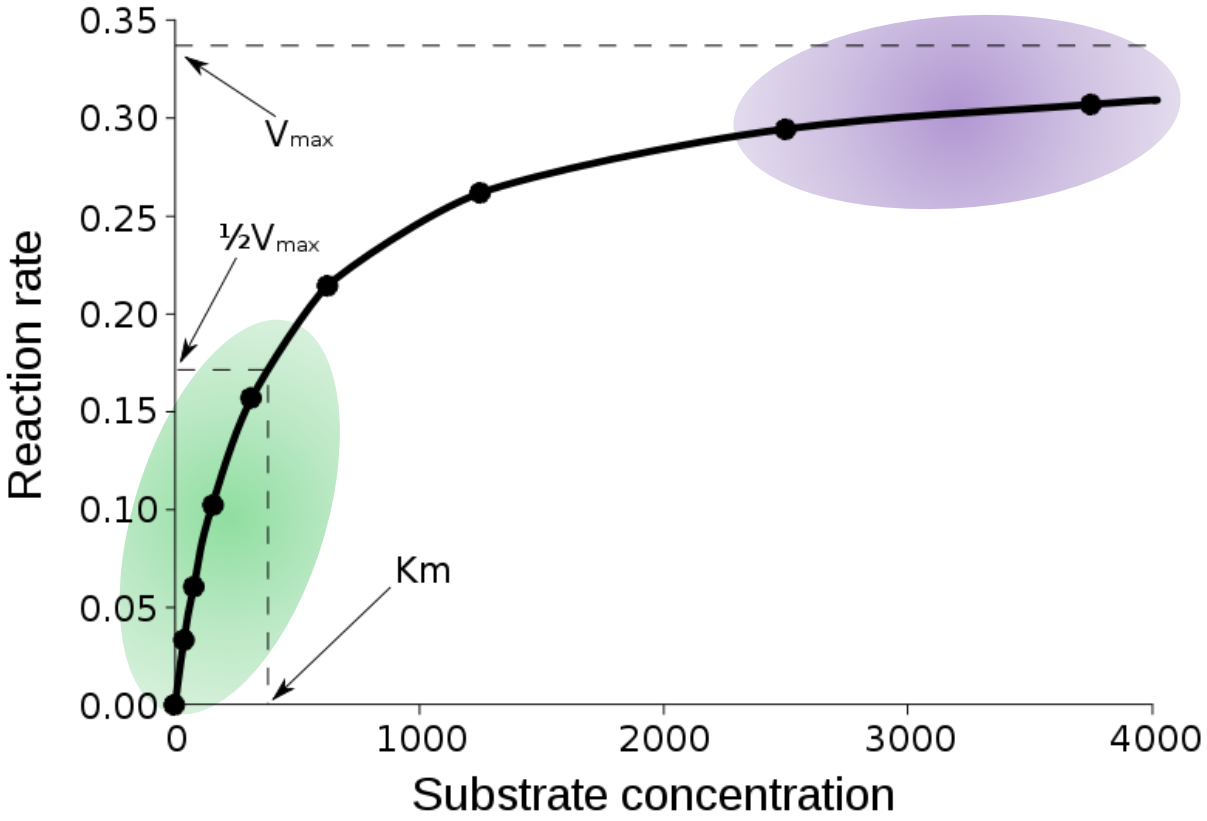


Image from http://en.wikipedia.com

RENAL EXCRETION

Rate of excretion = $CL_R \cdot C$

RENAL

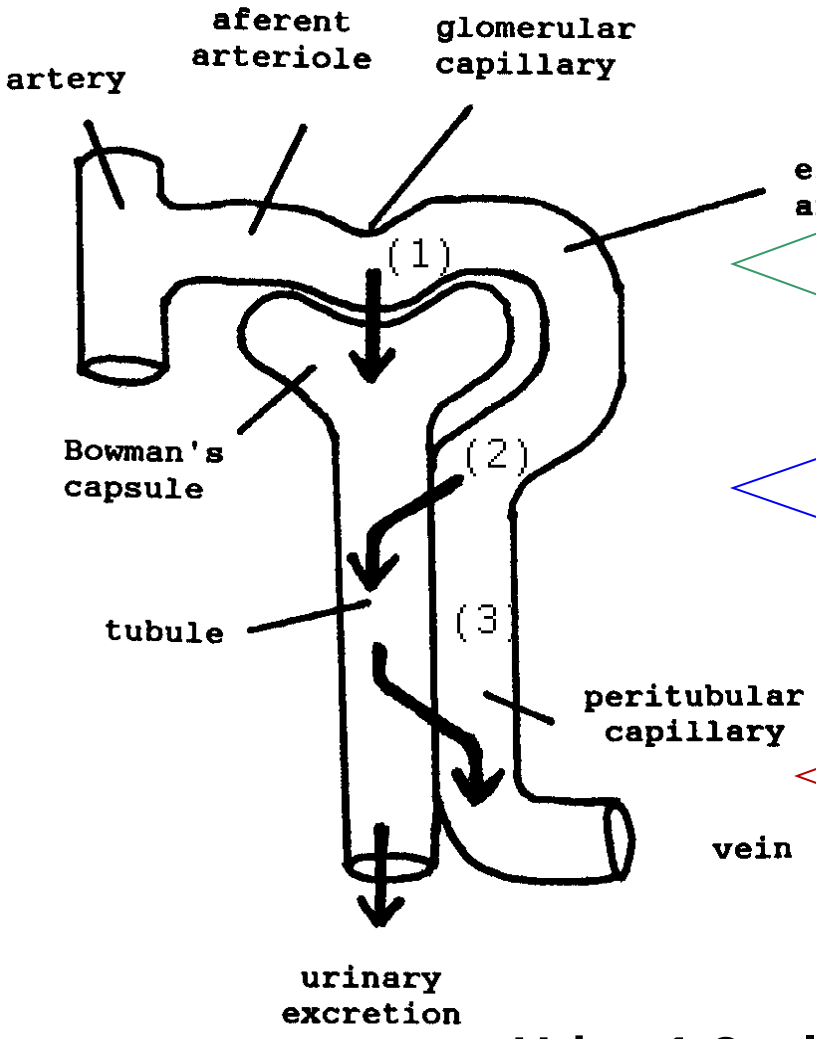
CL_R = Rate of Urinary Excretion /C plasma

= $V_{urine} . C_{urine} / C_{midpoint}$

Units of flow = **L/h**

Renal Excretion

A net effect



1. Glomerular filtration

GFR= 120 ml/min

2. Secretion – proximal tubule

3. Reabsorption –distal tubule

Urine 1-2 ml/min; pH = 5 –7.8

Components of Renal Clearance

$$\text{Rate of Excretion} = \left[\text{Rate of Filtration} + \text{Rate of Secretion}\right] \times \left[1 - \text{Fraction reabsorbed}\right]$$

$$/C_{plasma}$$

$$CL_R = (CL_{RF} + CL_{RS})(1 - F_R)$$

CL_{RF} – renal filtration clearance

CL_{RS} – renal secretion clearance

F_R - fraction of filtered and secreted drug reabsorbed

Glomerular Filtration

Passive process, only plasma water containing unbound drug (Cu) is filtered

GFR - Glomerular Filtration Rate

- **usually constant and relatively independent of renal blood flow**

$$CL_{RF} = \frac{\text{Filtration Rate (Cu} \bullet \text{GFR)}}{\text{Plasma Concentration (C)}} = fu \bullet GFR$$

GFR

- Determined using inulin or creatinine

(fu=1 and not secreted or reabsorbed)

Renal clearance, $CL_R = fu \cdot GFR$

- GFR depends on body size, gender and age

Men (20 yr) – 120 ml/min per 1.73 m2

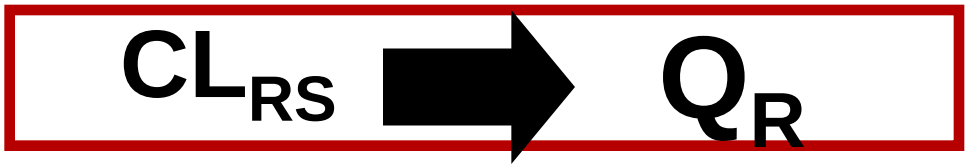
Women (20 yr) – 110 ml/min per 1.73 m2

- GFR decreases by 1% per year after age 20

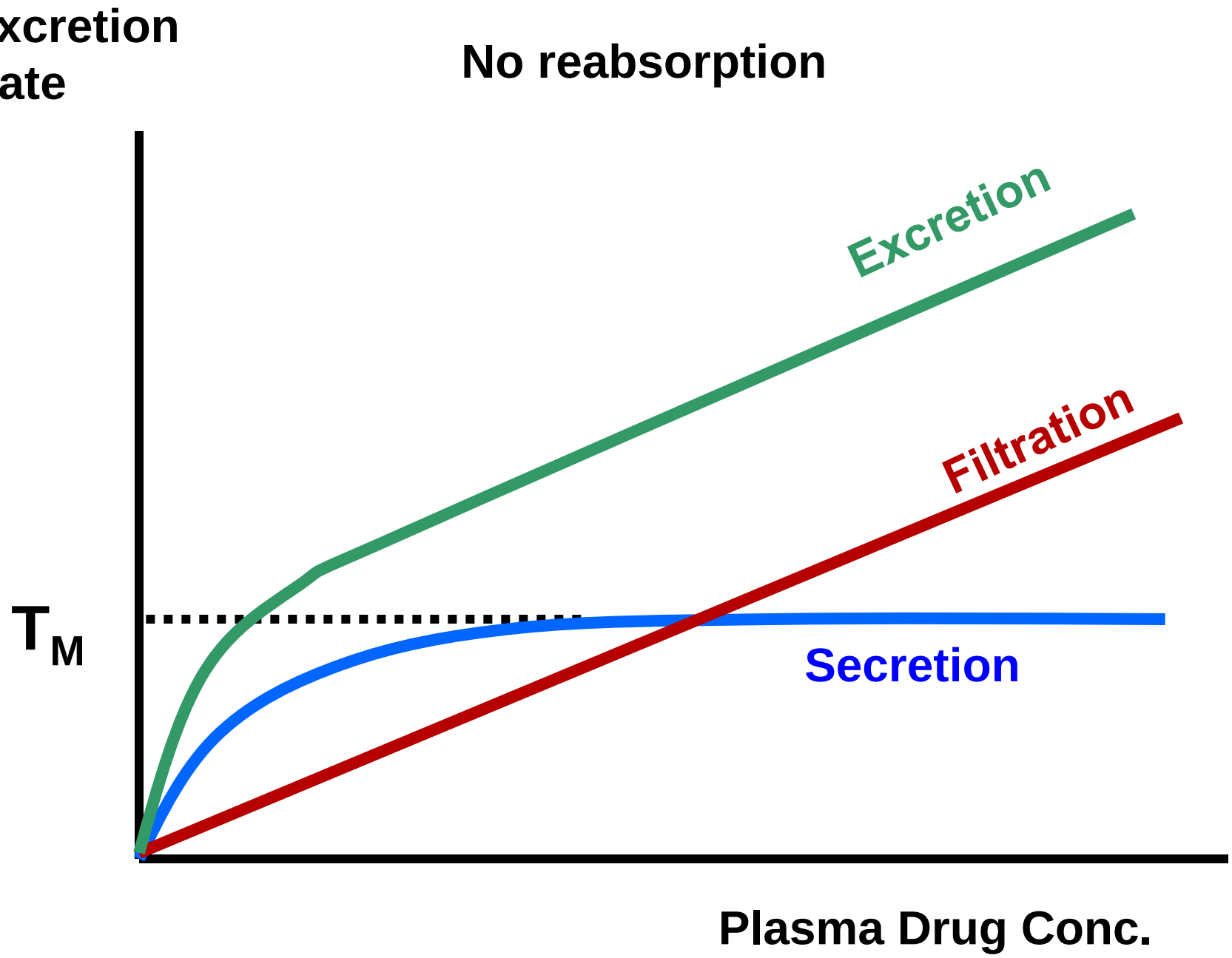
ACTIVE SECRETION

- **Facilitates excretion**
- **Transporters exist for basic and acidic drugs**

- **Dissociation of plasma drug-protein complex as unbound drug is transported**
- **If no reabsorption occurs, all drug presented to the kidney may be excreted in the urine**

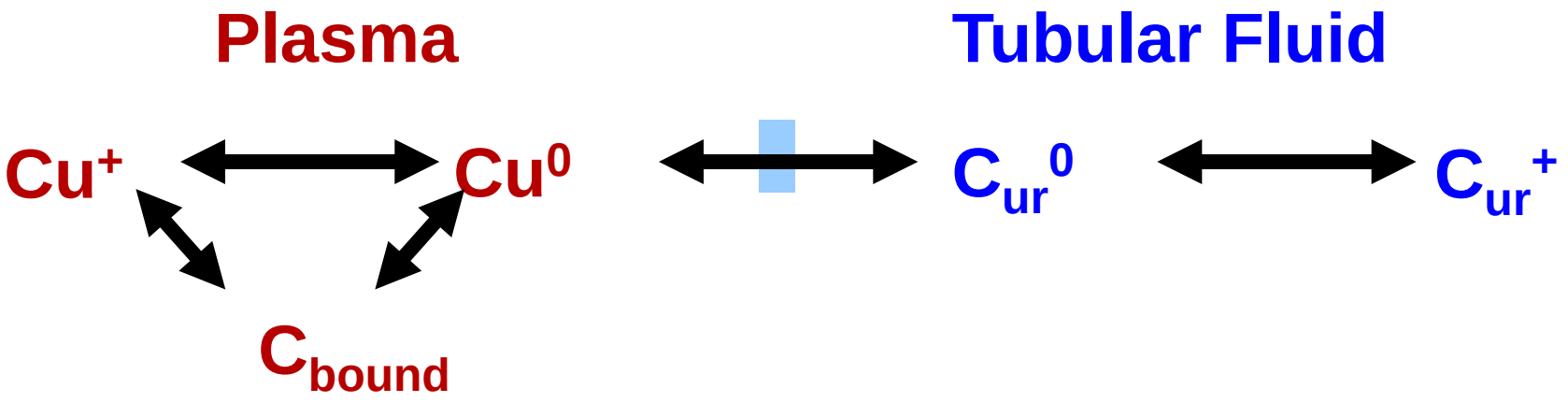


(1.1 L/min; e.g PAH)


Excretion Rate
No reabsorption
Excretion
Filtration
Secretion
T_M
Plasma Drug Conc.

PASSIVE REABSORPTION

Lipophilicity and degree of ionization affect rate and extent of reabsorption



Equilibrium not always achieved, especially for polar strong acids and bases

<u>Rate</u> of reabsoption is important

Passive reabsorption – effect of pH

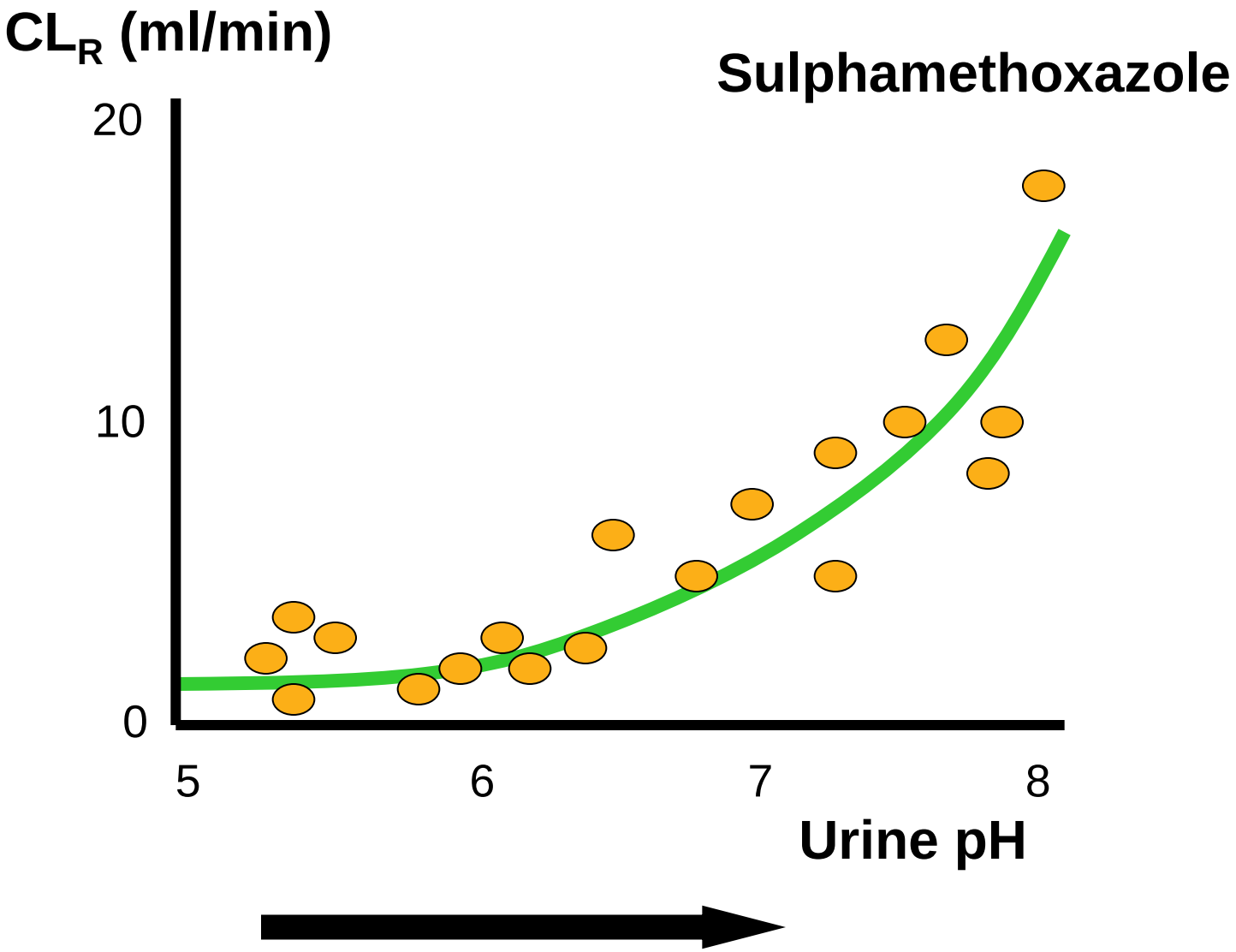
Urine pH varies: 4.5 – 7.6

Weak acids - CL_R is pH-sensitive if:

pKa = 3 – 7.5
and
lipophilic in un-ionised form

pKa < 3 strong acids, mostly ionised - little reabsorbed

pKa > 7.5 very weak acids, mostly un-ionised over urine pH range


CL_R (ml/min)
Sulphamethoxazole
20
10
0
5
6
7
8
Urine pH

Passive reabsorption – effect of pH

Urine pH varies: 4.5 – 7.6

Weak bases - CL_R is pH-sensitive if:

pKa = 6 – 12
and
lipophilic in un-ionised form

pKa < 6 - mostly un-ionised over urine pH range

pKa > 12 - mostly ionised; little reabsorbed

Effect of pH on urinary excretion

e.g. Amphetamine

Urine pH	Urinary recovery unchanged 24h
Normal (pH ≈ 6.3)	*40%*
Acidic (pH = 5.3)	*70%*
Alkaline (pH = 7.3)	*3%*

Passive reabsorption – effect of urine flow

- **Flow-dependent CL_R occurs when drug is reabsorbed**

- **If equilibrium is achieved – a higher urine volume means a higher amount of drug in urine and higher CL_R**

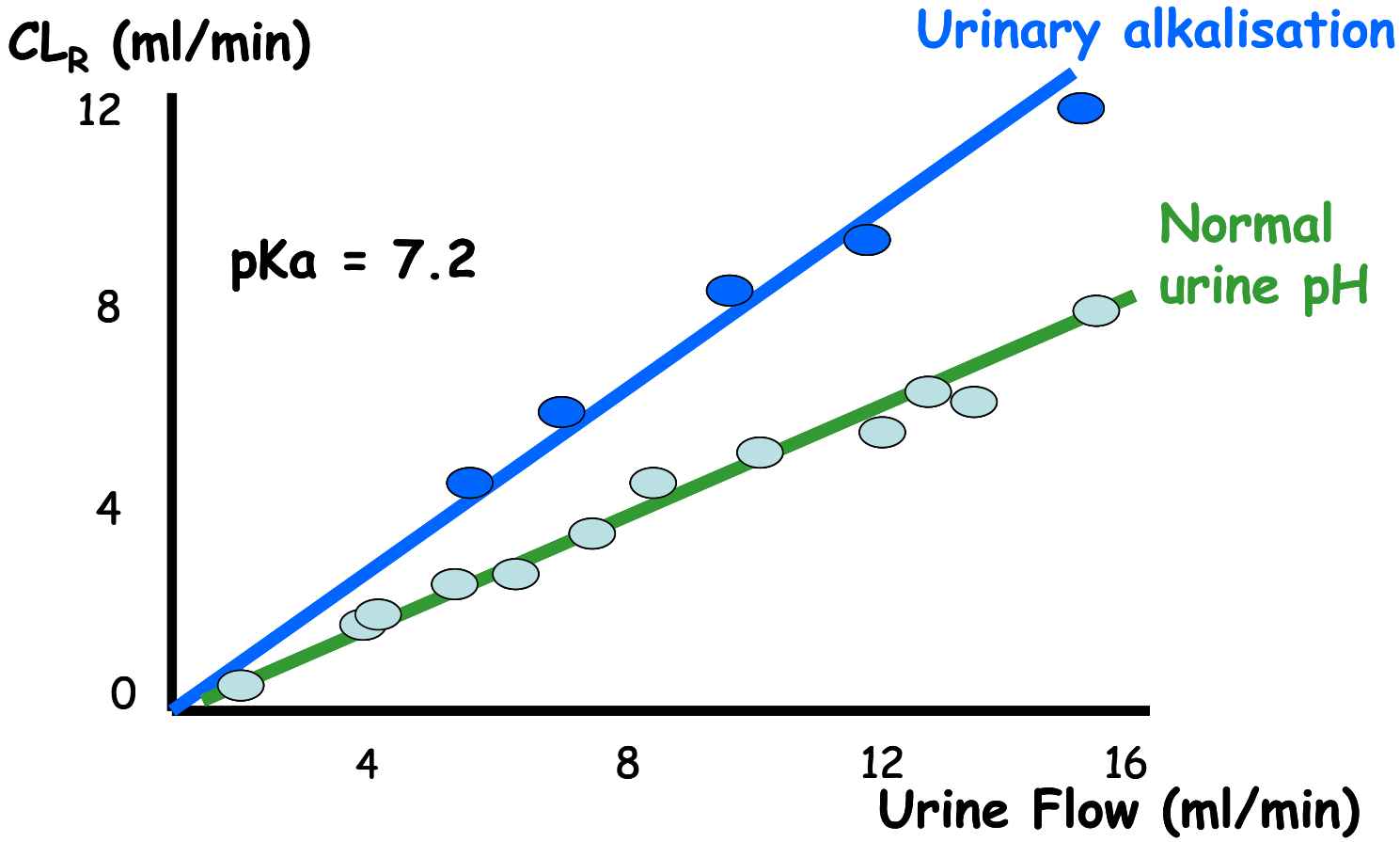
CL_R = Rate of excretion /C_{plasma}

= Urine Flow x Urine conc /C_{plasma}

At equilibrium: Cu = Urine Conc

CL_R = fu x Urine Flow

FORCED ALKALINE DIURESIS - Phenobarbitone



- **Drug overdose- forced diuresis and altered pH may be used to increase elimination of the drug**