Pharmacokinetics

What is pharmacokinetics?

- Study of the time course of a drug's movement through the body.
- Understanding of what the body does to (or with) the drug.
- Application of Therapeutic Drug Monitoring (TDM) and individualisation of drug therapy.

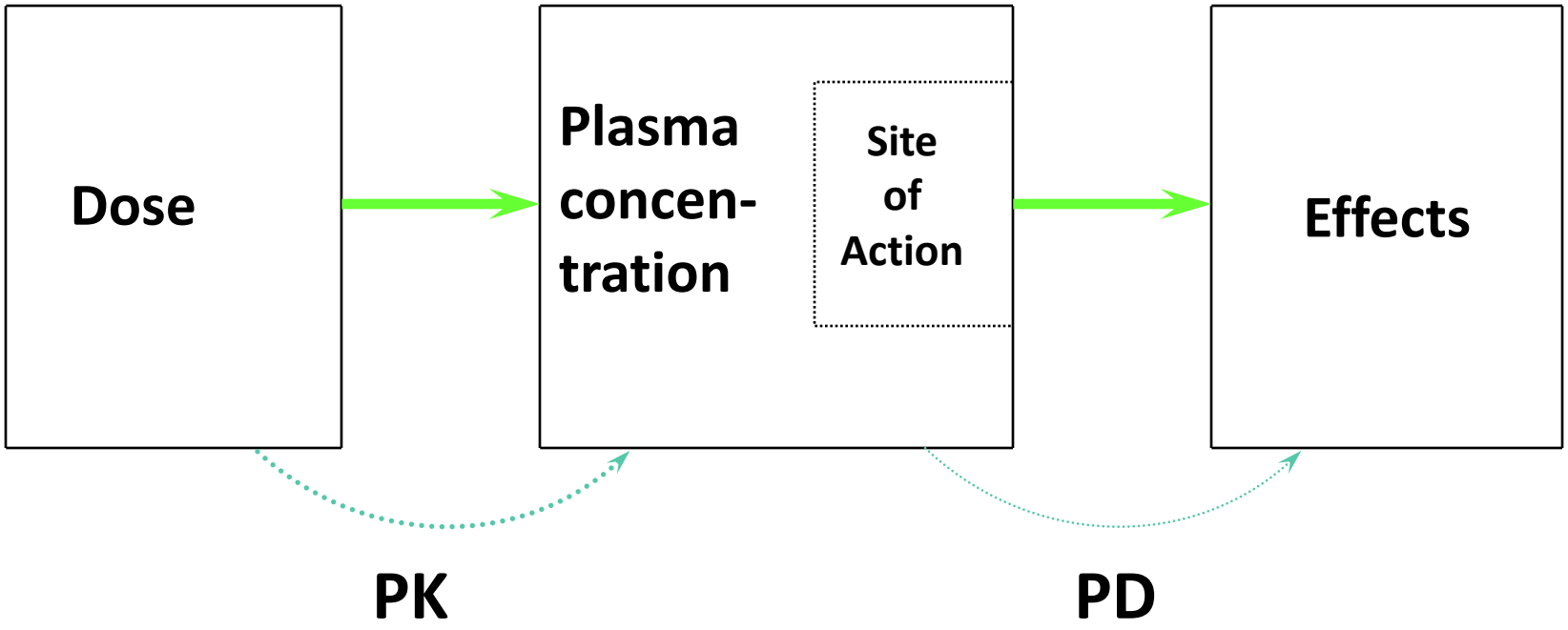
Outline

- Drug disposition stages
- Review of Concepts
  - Clearance, K, Half-Life, Volume of Distribution
- Pharmacokinetic Drug Interactions

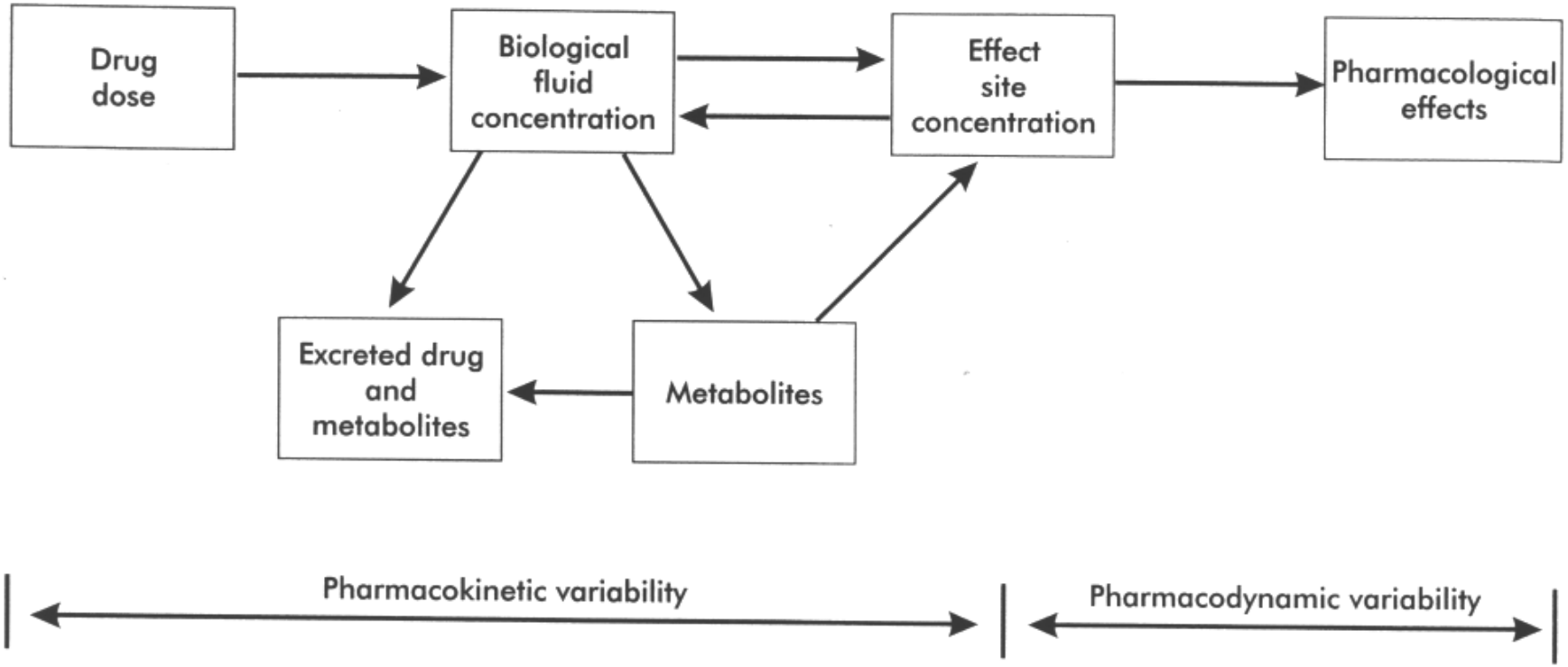
Pharmacokinetics (PK) & pharmacodynamics (PD)

- PK - What the body does to the drug?
  - Absorption; distribution, metabolism, excretion (ADME)
- PD - What the drug does to the body?
  - Drug concentration at the site of action or in the plasma is related to a magnitude of effect

Pharmacokinetics (PK) and pharmacodynamics (PD)



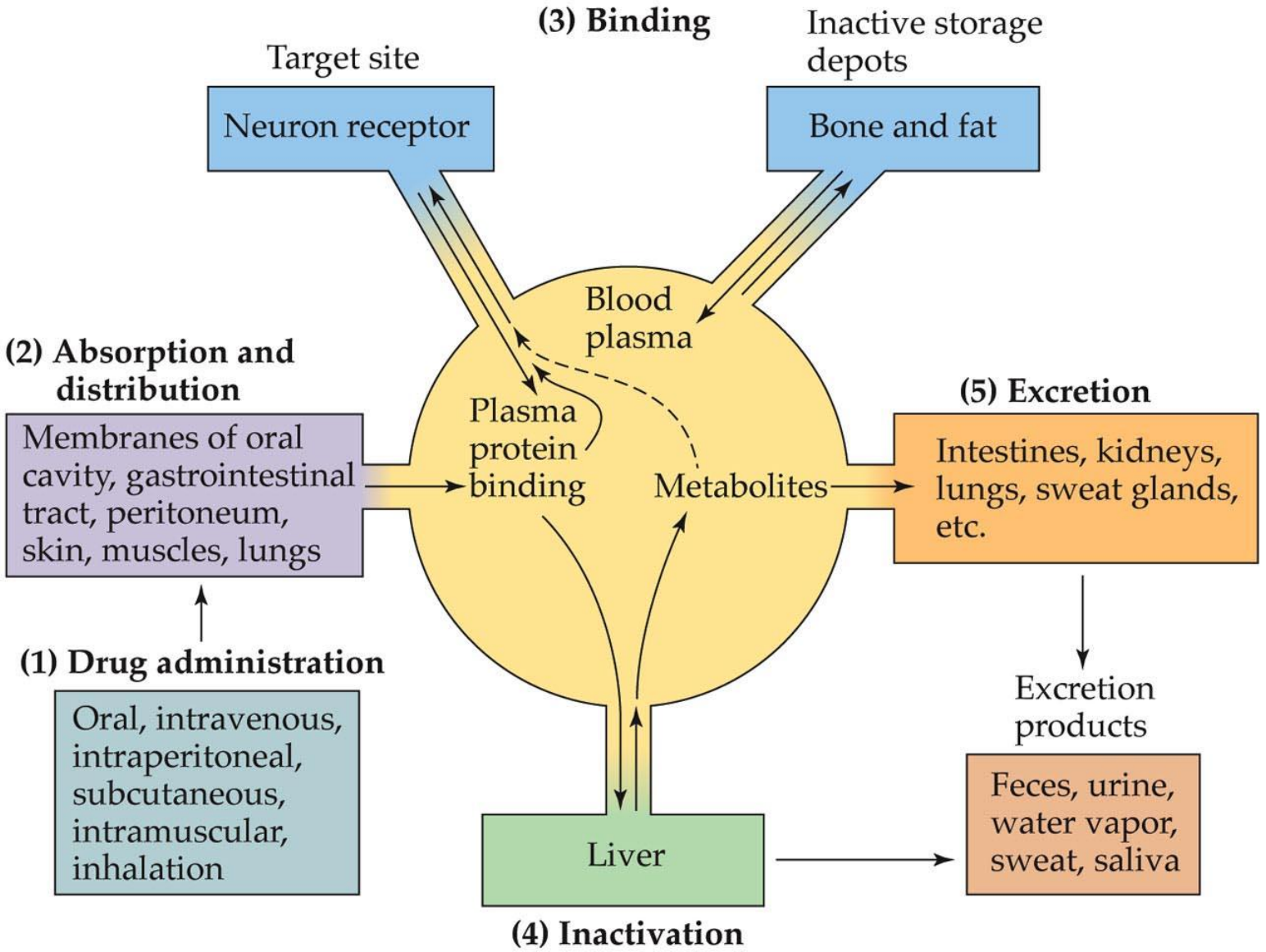
Overview


Drug dose
Biological fluid concentration
Effect site concentration
Pharmacological effects
Excreted drug and metabolites
Metabolites
Pharmacokinetic variability
Pharmacodynamic variability

Pharmacokinetics

- Drug molecules interact with target sites to effect the nervous system
  - The drug must be absorbed into the bloodstream and then carried to the target site(s)
- Pharmacokinetics is the study of drug absorption, distribution within body, and drug elimination over time.
  - Absorption depends on the route of administration
  - Distribution depends on how soluble the drug molecule is in fat (to pass through membranes) and on the extent to which the drug binds to blood proteins (albumin)
  - Metabolism
  - Elimination is accomplished by excretion into urine and/or by inactivation by enzymes in the liver

Pharmacokinetics

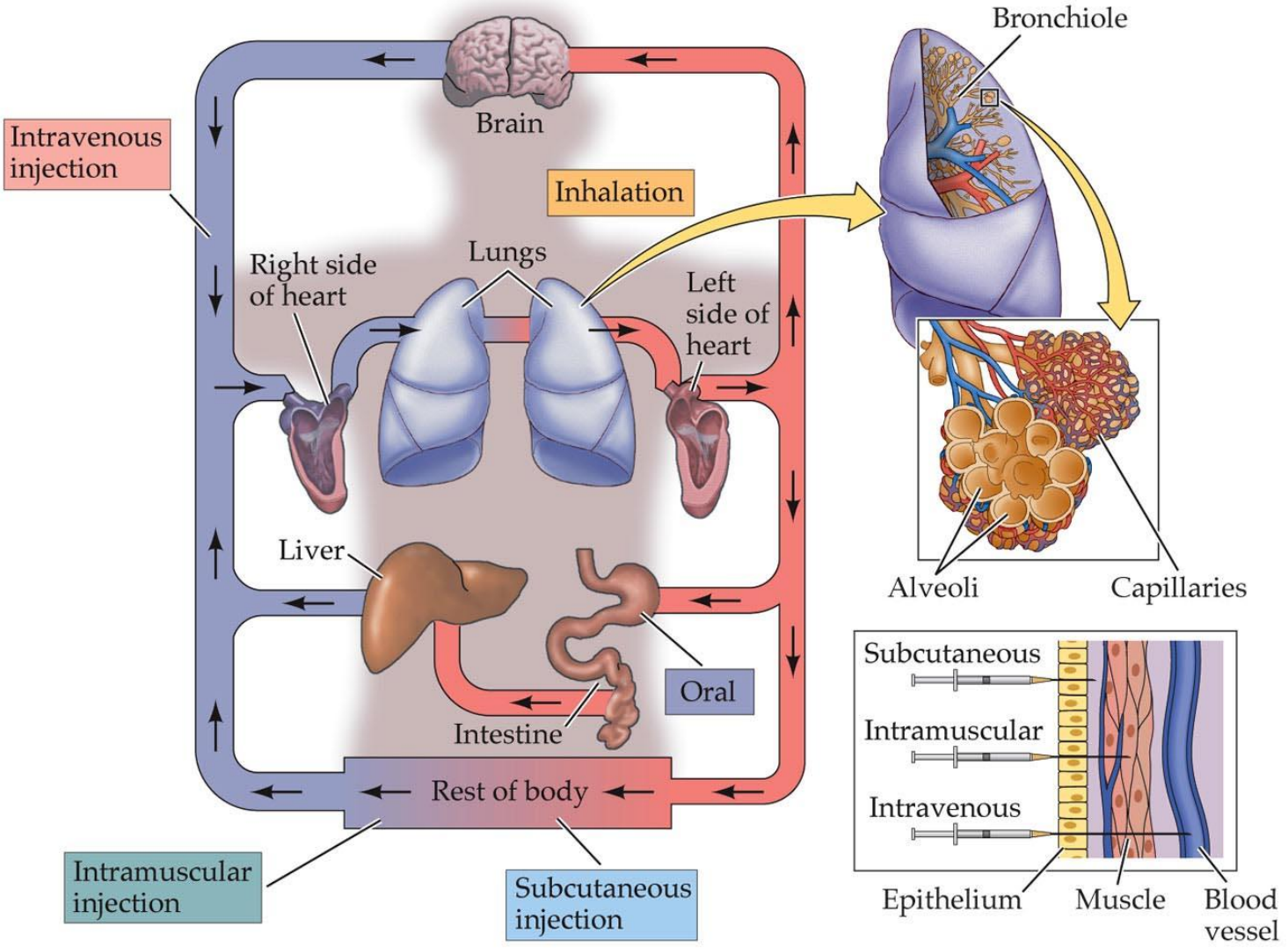


PSYCHOPHARMACOLOGY, Figure 1.1

Routes of Administration

- Routes of Administration:Orally:
- Rectally:
- Inhalation: Absorption through mucous membranes:
- Topical:
- Parenterally:
  - *Intravenous:*
  - *Intramuscular:*
  - *Subcutaneous:*

Routes of Administration



PSYCHOPHARMACOLOGY, Figure 1.2 © 2005 Sinauer Associates, Inc.

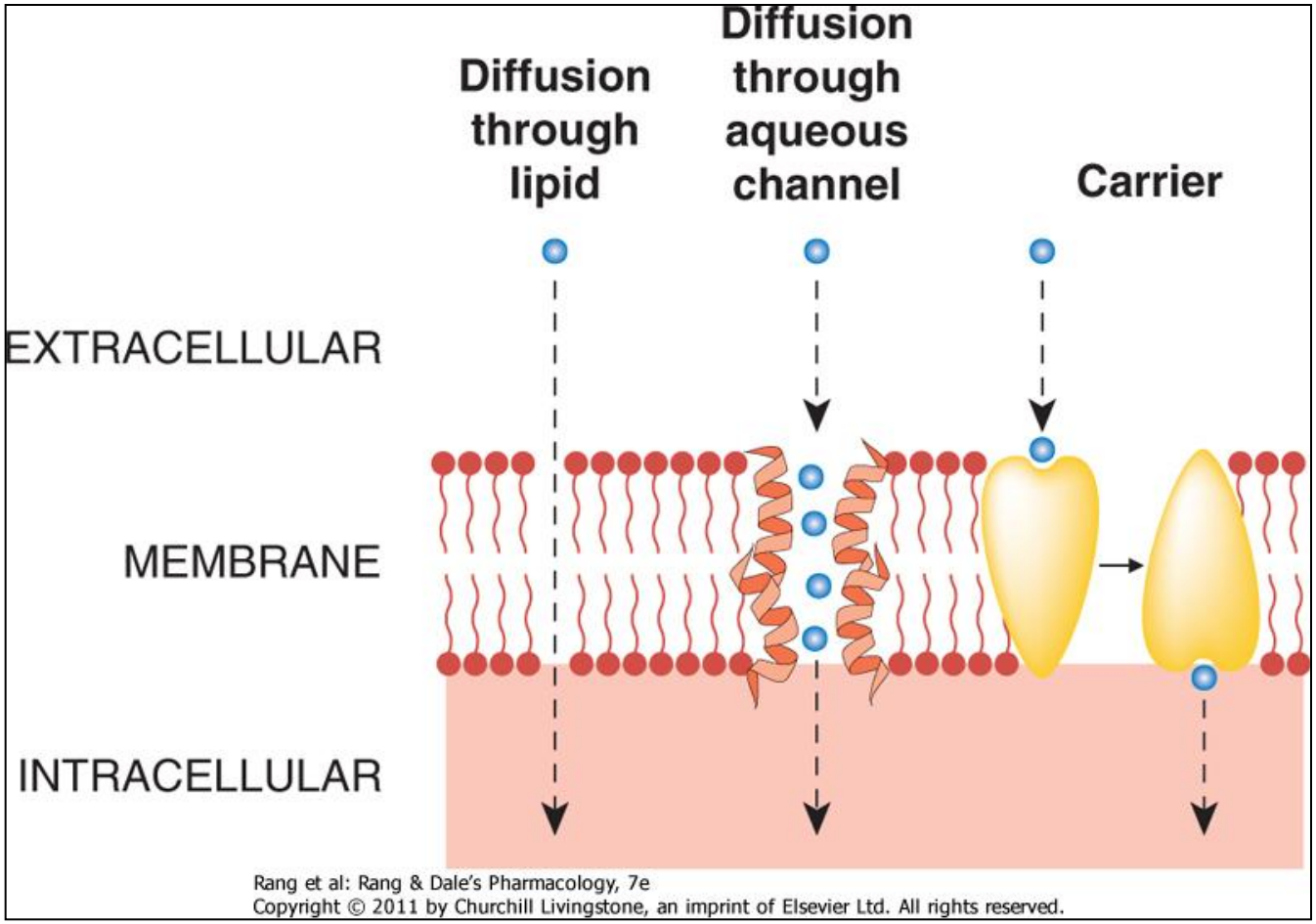
Membranes

- Types of Membranes:
- **Cell Membranes:** This barrier is permeable to many drug molecules but not to others, depending on their lipid solubility. Small pores, 8 angstroms, permit small molecules such as alcohol and water to pass through.
- **Walls of Capillaries:** Pores between the cells are larger than most drug molecules, allowing them to pass freely, without lipid solubility being a factor.
- **Blood/Brain Barrier:** This barrier provides a protective environment for the brain. Speed of transport across this barrier is limited by the lipid solubility of the psychoactive molecule.
- **Placental Barrier:** This barrier separates two distinct human beings but is very permeable to lipid soluble drugs.

Absorption

- Movement of drug from site of administration into circulation
- Different ways of crossing the membrane for small molecules:
  - Diffusing through lipid membrane
  - Diffusing through aqueous pores (aquaporins)
  - Solute carriers or other transporters
  - Pinocytosis

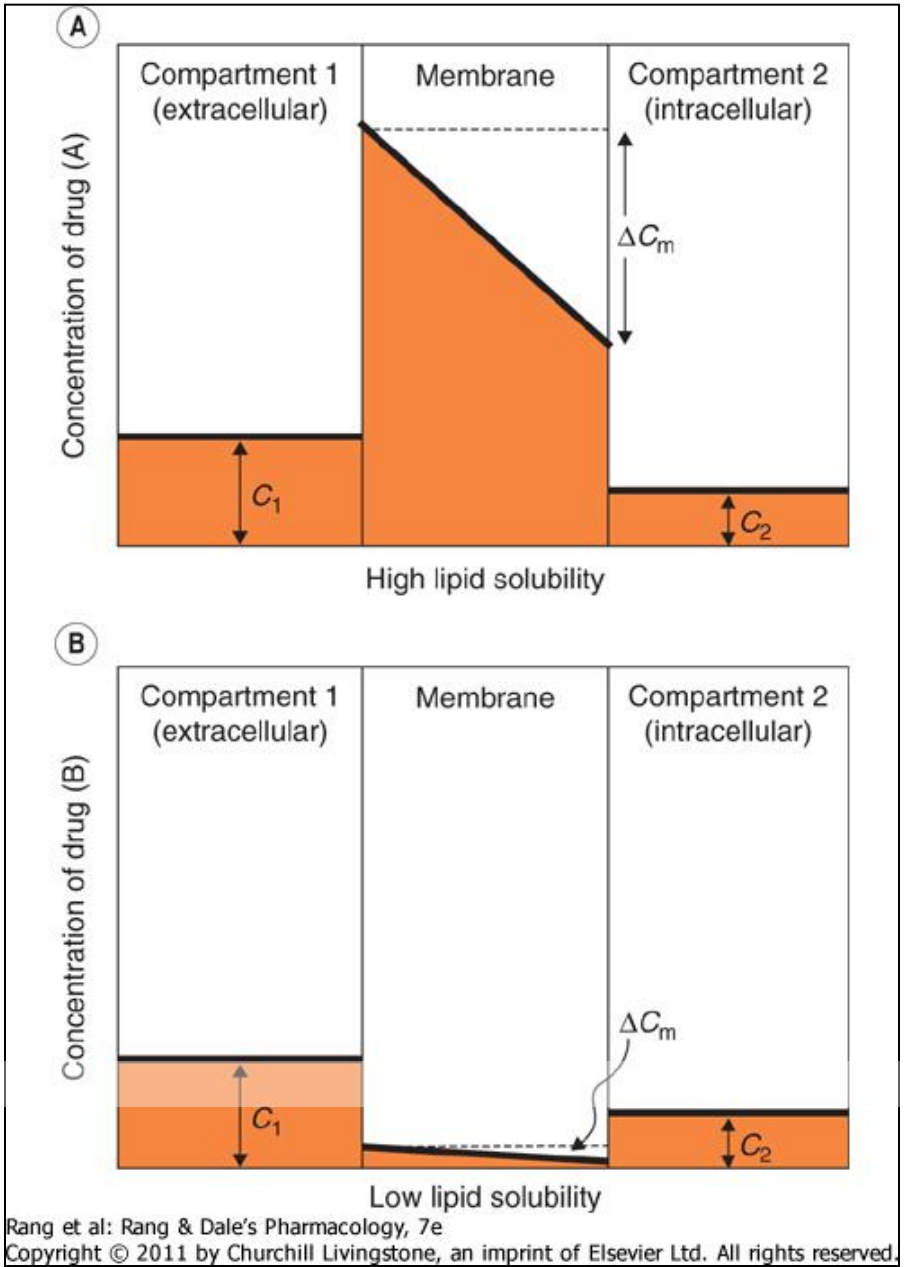
Routes by which solutes can traverse cell membranes



Passive transport mechanisms

- No need of energy
- Size of particles
- Lipid solubility
- Level of ionisation

Importance of lipid solubility in membrane



Passive transport mechanisms

- No need of energy
- Size of particles
- Lipid solubility
- Level of ionisation

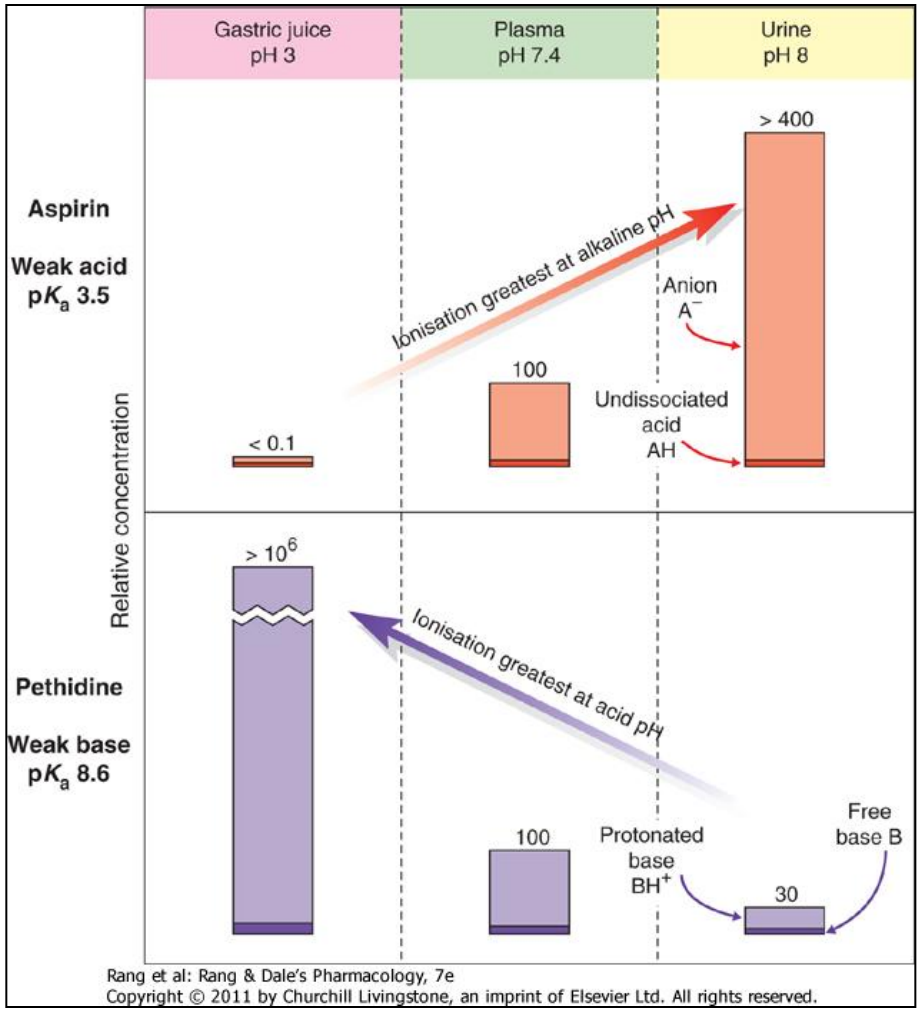
$$BH^+ \underset{}{\overset{K_a}{\rightleftharpoons}} B + H^+$$

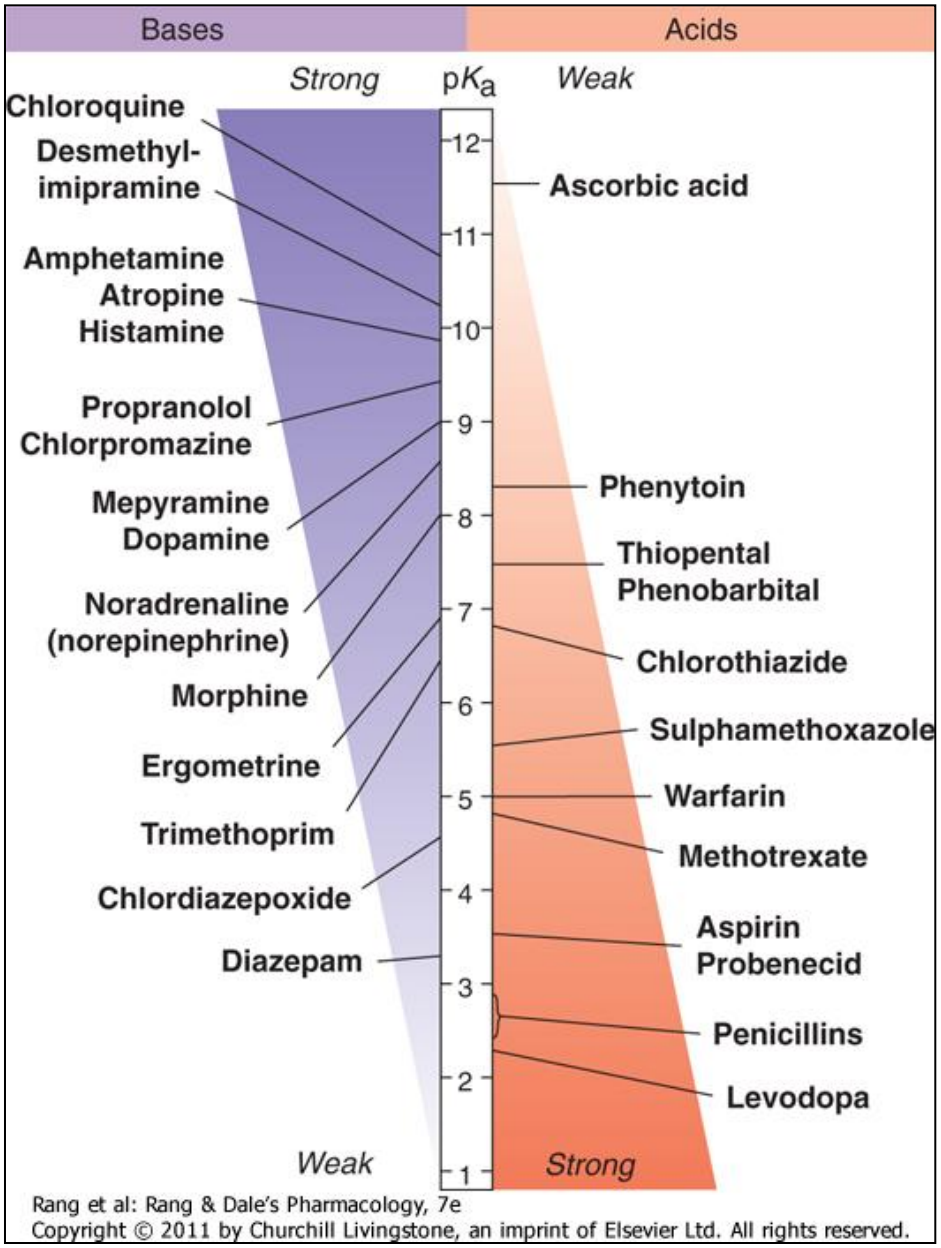
$$pK_a = pH + \log_{10}\frac{[BH^+]}{[B]}$$

$$AH \underset{}{\overset{K_a}{\rightleftharpoons}} A^- + H^+$$

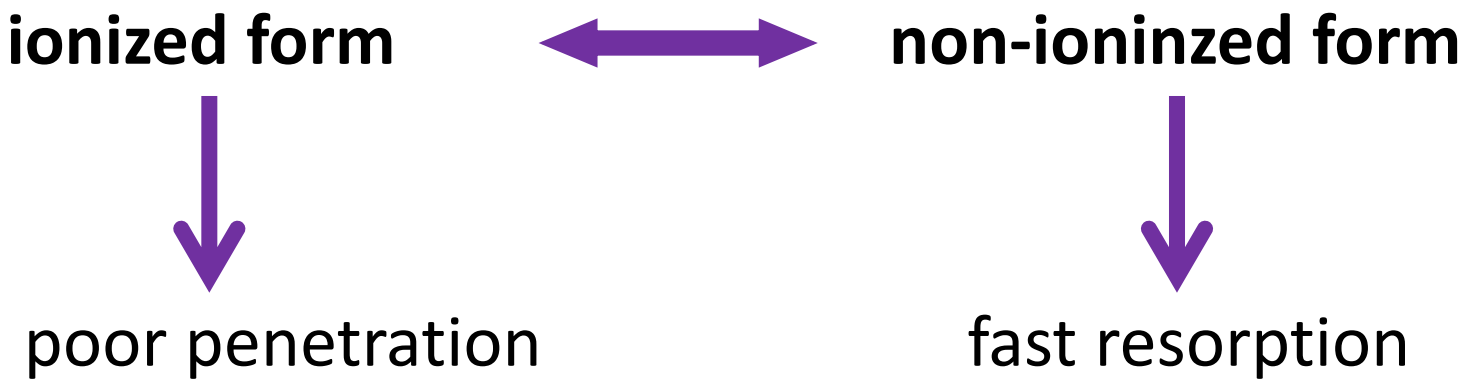
$$pK_a = pH + \log_{10}\frac{[AH]}{[A^-]}$$

pH partition





Steady state in the body



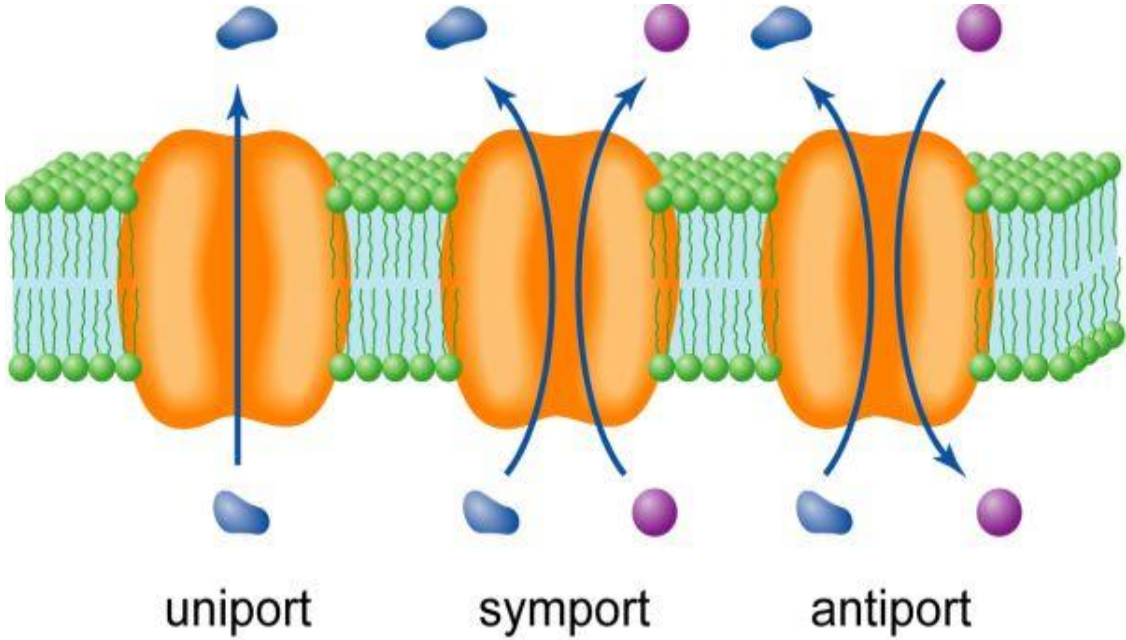
Changes of pH and absorption

↓ pH	- ↓ acids dissociation	- ↑ resorption
	- ↑ base dissociation	- ↓ resorption
↑ pH	- ↓ base dissociation	- ↑ resorption
	- ↑ acids dissociation	- ↓ resorption

- ! interactions
- practical use – pH of urine
- Acidic agents are absorbed better from acidic environment
- Basic agents are better absorbed from basic environment

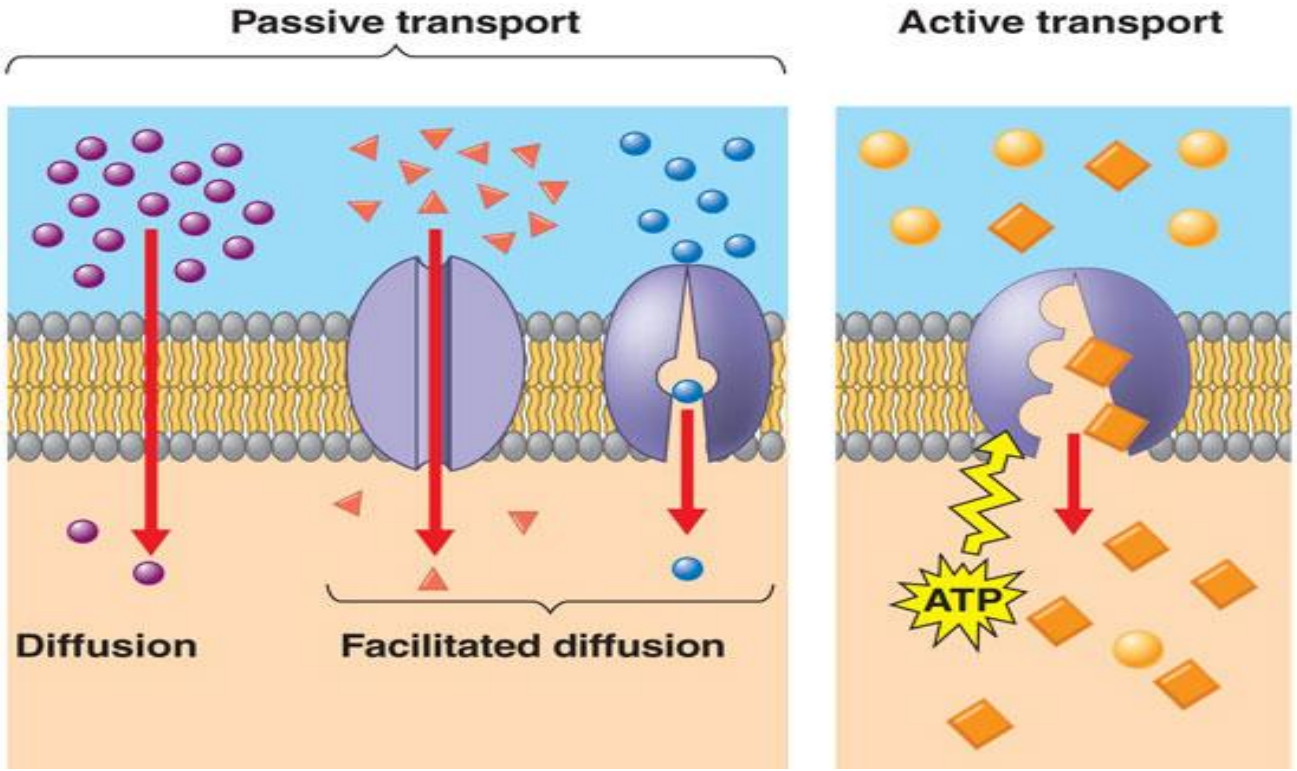
Facilitated transport mechanisms

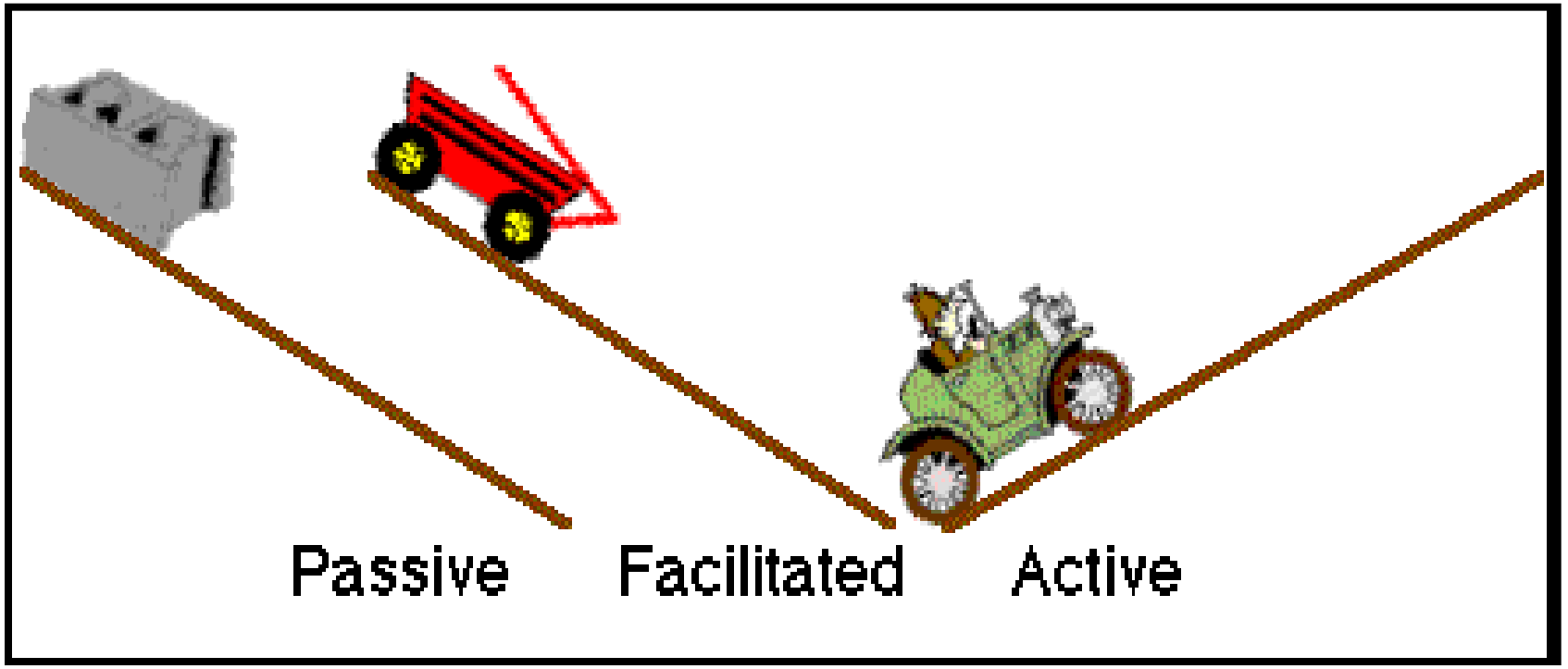
- Not against concentration gradient
- Specific transporters (membrane proteins)
  - Transporters
  - Ion channels



Active transport mechanisms

- Against gradient
- Need of energy (ATP-dependent)
- Carrier mediated transport




Passive
Facilitated
Active

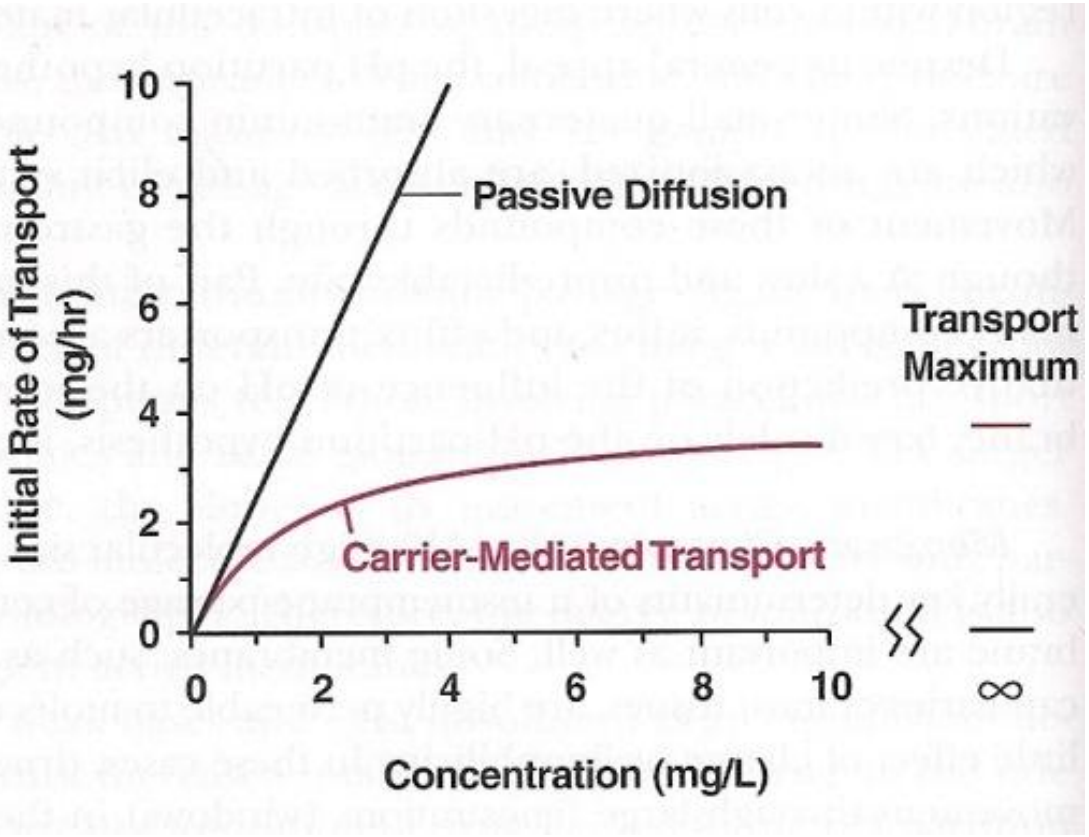
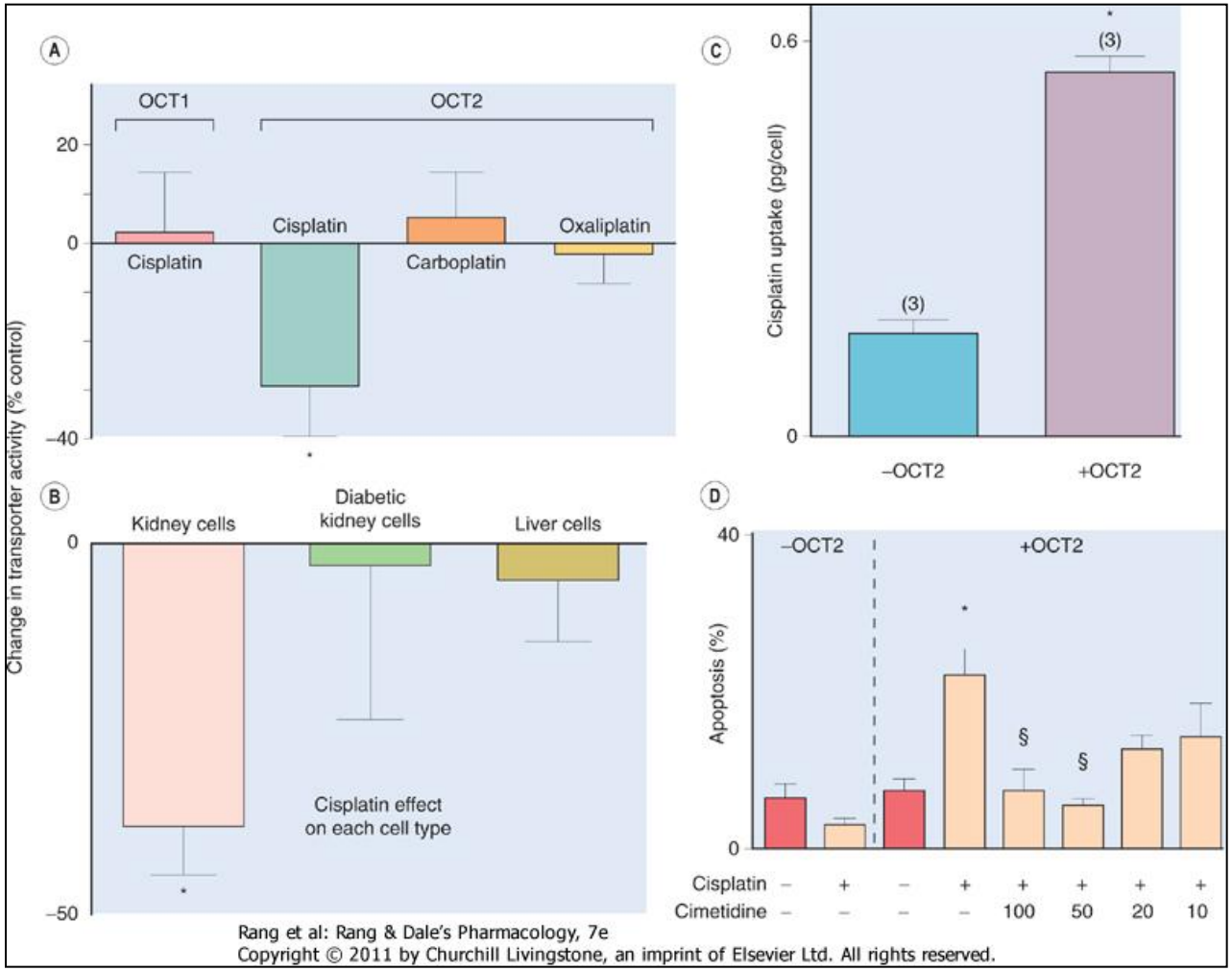


FIGURE 4-6. Initial rate of drug transport is plotted against the concentration of drug placed on one side of a membrane. With passive diffusion, the rate of transport increases linearly with concentration. With carrier-mediated transport, the rate of transport approaches a limiting value at high concentrations, the transport maximum.

Rowland and Tozer, Clinical Pharmacokinetics and Pharmacodynamics, LWW, 2011

Carrier-mediated transport

- SLC – solute carrier (SLC) transporters
  - Passive
  - OCT, OAT
    - Important in BBB, GIT, renal tubule, biliary tract, placenta
  - Facilitated diffusion
- ATP-binding cassette (ABC) transporters
  - Active, influx or efflux transporters
  - P-glycoprotein (P-gp) transporters
  - Responsible for multidrug resistance in cancer cells
    - Important in renal tubule, bile canaliculi, astrocyte foot processes in brain microvessels, GIT



A – cultured cell line
B – cisplatin effect
C – cisplatin accumulation
D – apoptosis prevention by cimetidine

- Human organic cation transporter 2 (OCT2) mediates cisplatin toxicity
  - OCT2 – kidneys, OCT1 - liver

Key	Process	Example Transporter
A	Intestinal Uptake	OATPs
B	Intestinal Efflux	MDR1*, BCRP
C	Hepatic Uptake	OATPs
D	Hepatic Efflux	MRP3
E	Biliary Secretion	MDR1, MRP2
F	Renal Uptake	OAT3
G	Renal Secretion	MDR1, MRP2
H	Renal Reabsorption	SVCT1
I	Brain Uptake	LAT1
J	Brain Efflux	MDR1, BCRP

*Commonly called P-glycoprotein

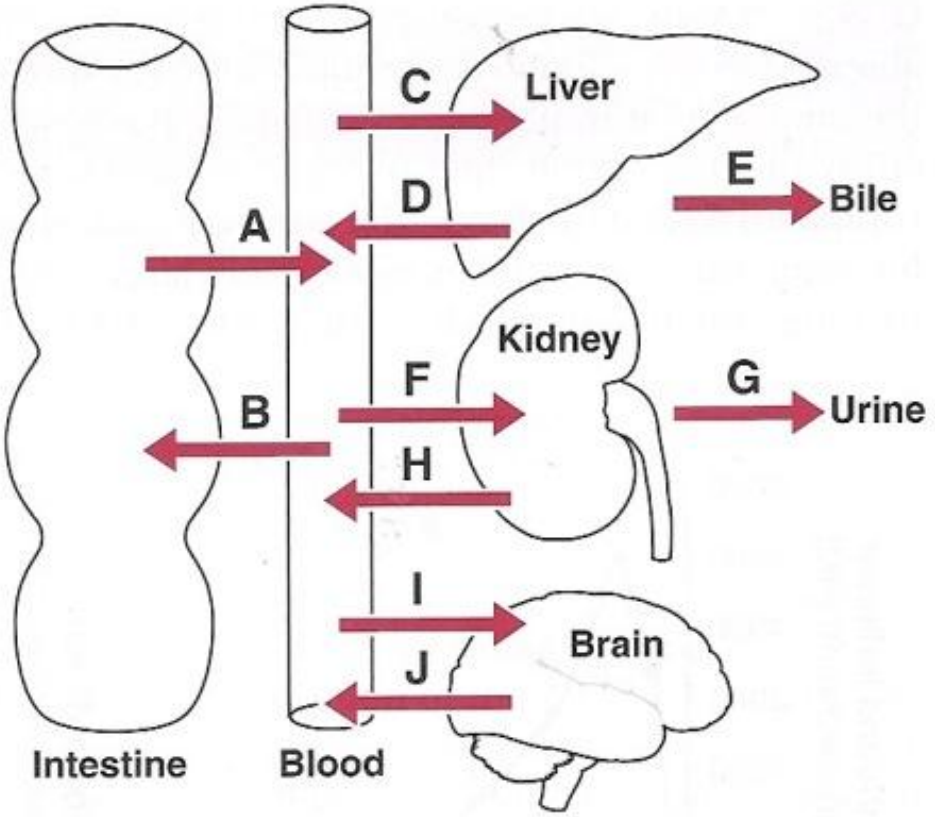


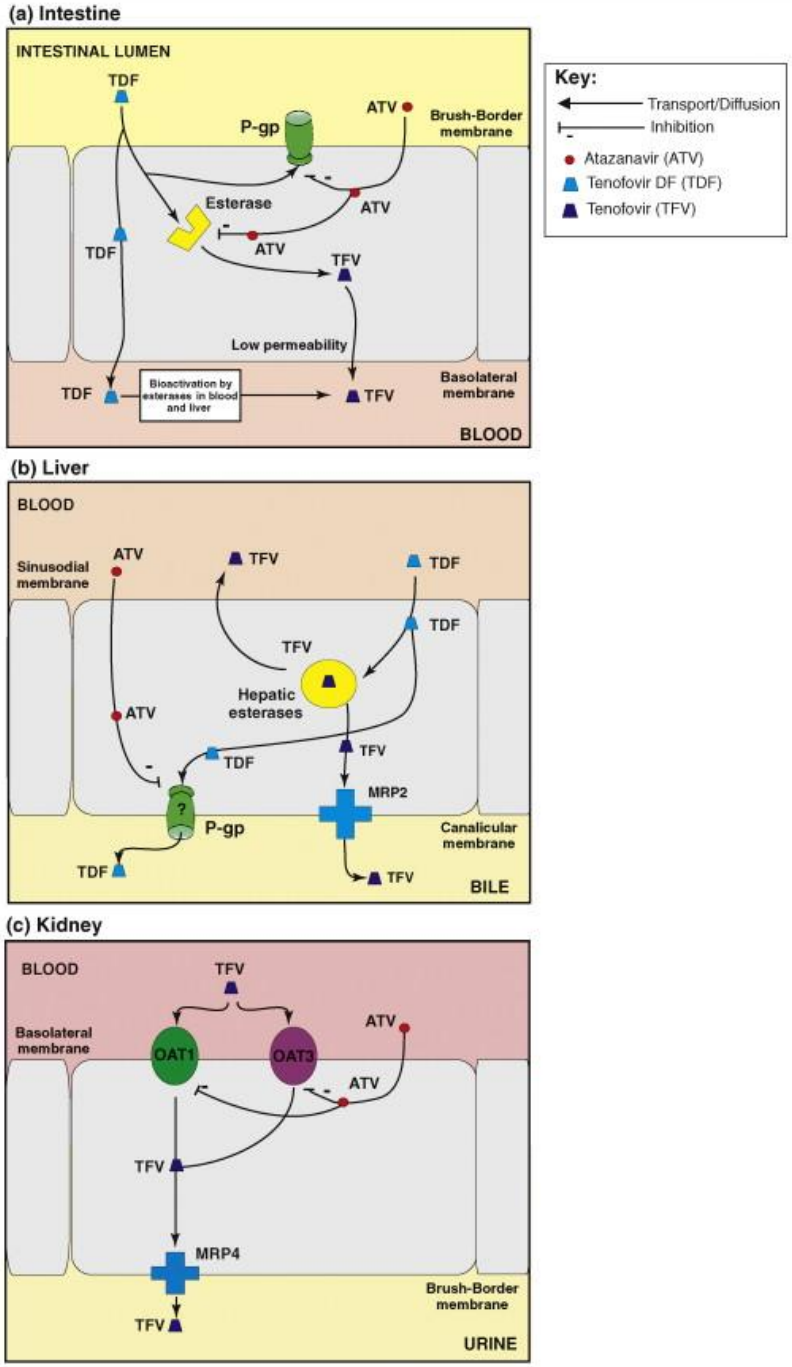
FIGURE 4-8. Selected transporters involved in intestinal absorption and in disposition of drugs within the liver, kidney, and brain. The names of these transporters and their general transport function within each of these tissues are identified.

Rowland and Tozer, Clinical Pharmacokinetics and Pharmacodynamics, LWW, 2011

TABLE 4-2 Human Liver and Kidney Transporters Important in Drug Disposition

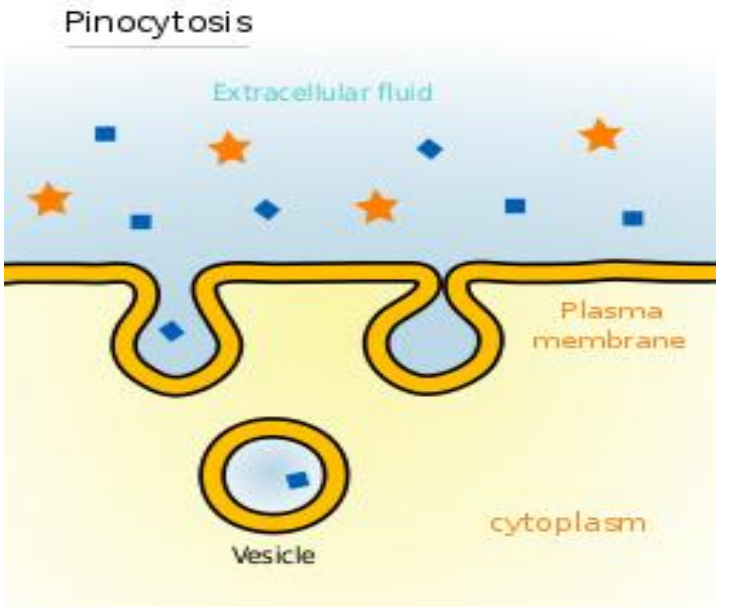
Gene Symbol	Protein Name	Full Protein Name	Representative Substrates
Influx transporters			
SLC22A1	OCT1	Organic cation transporter 1	Metformin, oxaliplatin
SLC22A2	OCT2	Organic cation transporter 2	Metformin, amantadine
SLC22A4	OCTN1	Novel organic cation transporter 1	Gabapentin
SLC22A5	OCTN2	Novel organic cation transporter 2	Carnitine
SLC22A6	OAT1	Organic anion transporter 1	Adefovir, tenofovir
SLC22A7	OAT2	Organic anion transporter 2	Ganciclovir, allopurinol
SLC22A8	OAT3	Organic anion transporter 3	Cimetidine, cefotaxime
SLC22A11	OAT4	Organic anion transporter 4	Bumetanide, ketoprofen
SLC22A12	URAT1	Urate anion exchanger 1	Uric acid, oxypurinol
SLCO1A2	OATP1A2	Organic anion transporting polypeptide A	Methotrexate, fexofenadine
SLCO1B1	OATP1B1	Organic anion transporting polypeptide C	Pravastatin, repaglinide
SLCO1B3	OATP1B3	Organic anion transporting polypeptide B	Digoxin, paclitaxel
SLCO2B1	OATOP2B1	Organic anion transporting polypeptide B	Atorvastatin benzylpenicillin
SLC47A1	MATE1	Multidrug and toxin extrusion 1	Cimetidine, metformin
SLC47A2	MATE2-K	Multidrug and toxin extrusion 2	Cimetidine, metformin
Efflux transporters			
ABCB1	P-gp	P-glycoprotein	Etoposide, imatinib
ABCB11	BSEP	Bile salt export pump	Paclitaxel
ABCC1	MRP1	Multidrug resistance-associated protein 1	Methotrexate
ABCC2	MRP2	Multidrug resistance-associated protein 2	Doxorubicin, cisplatin
ABCC3	MRP3	Multidrug resistance-associated protein 3	Etoposide, methotrexate
ABCC4	MRP4	Multidrug resistance-associated protein 4	Methotrexate
ABCC6	MRP6	Multidrug resistance-associated protein 6	Anthracyclines
ABCG2	BCRP	Breast cancer resistance protein	Mitoxantrone, doxorubicin

From: Cropp CD, Yee SW, Giacomini KM. Genetic variation in drug transporters in ethnic populations. Clin Pharmacol Ther 2008;84:412–416.


(a) Intestine
INTESTINAL LUMEN
TDF
ATV
Brush-Border membrane
P-gp
Esterase
ATV
ATV
TDF
TFV
Low permeability
TDF
Bioactivation by esterases in blood and liver
TFV
Basolateral membrane
BLOOD
Key:
Transport/Diffusion
Inhibition
Atazanavir (ATV)
Tenofovir DF (TDF)
Tenofovir (TFV)
(b) Liver
BLOOD
Sinusodial membrane
ATV
TFV
TDF
TDF
TFV
Hepatic esterases
ATV
TFV
TDF
MRP2
P-gp
Canalicular membrane
TDF
TFV
BILE
(c) Kidney
BLOOD
TFV
Basolateral membrane
OAT1
OAT3
ATV
ATV
TFV
MRP4
Brush-Border membrane
TFV
URINE

Pinocytosis

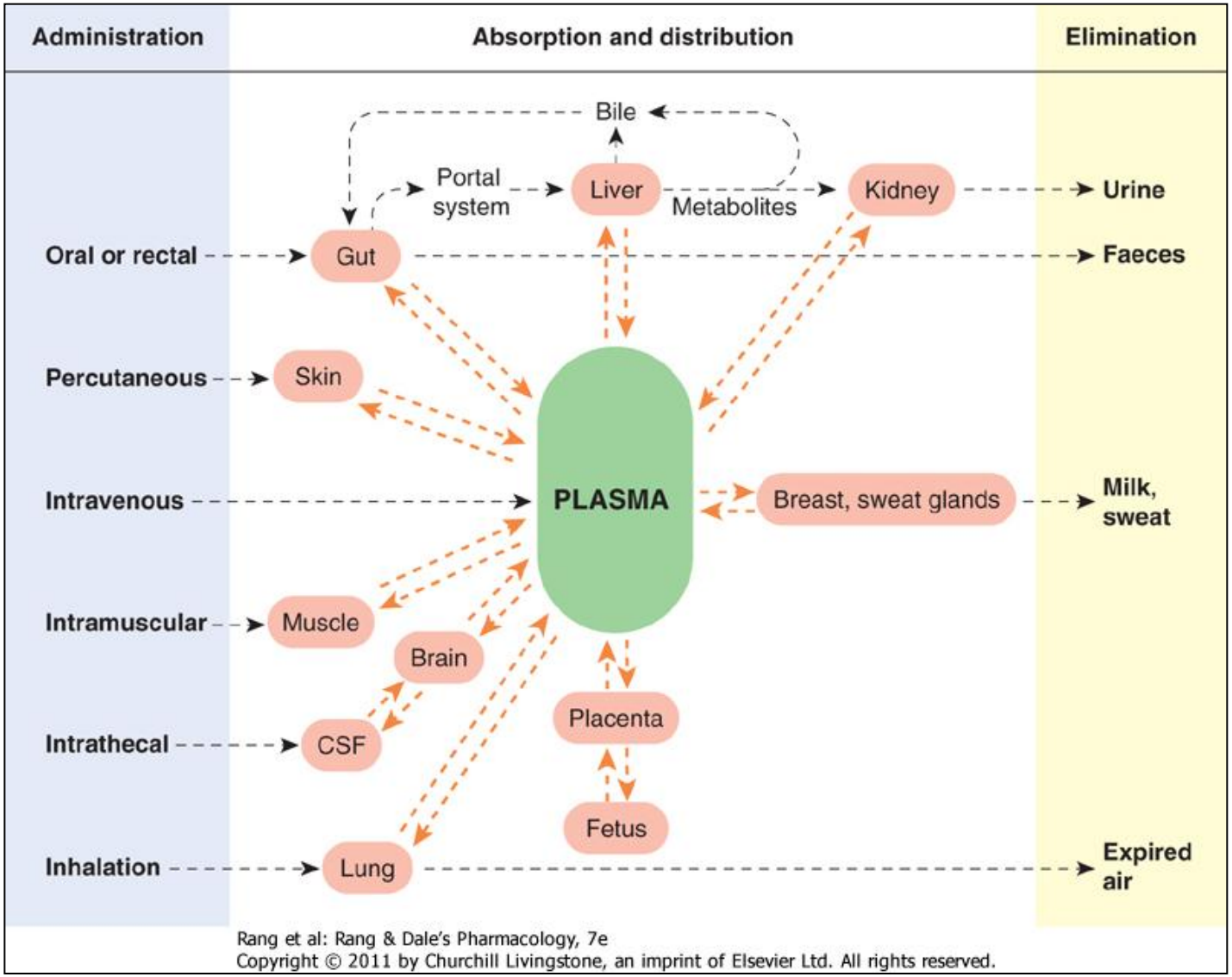
- Invagination of part of cell membrane with trapping the extracellular constituents
- Released intracellulary or transcellular extrusion on other site
- E.g. insulin transport through BBB



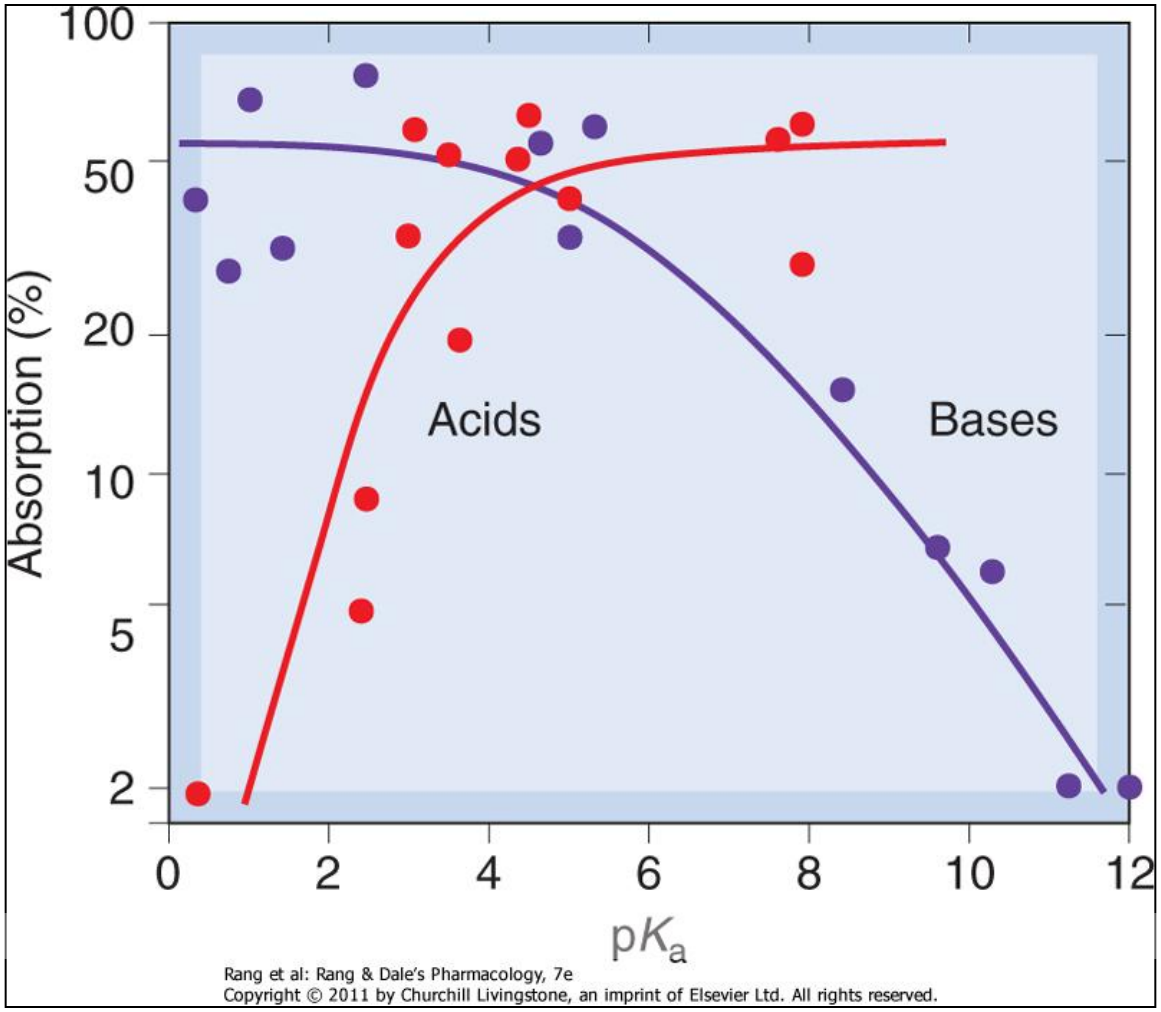
Penetration through intercellular pores

- Tissue barriers
  - Hematoencephalic – blood-brain-barrier
  - Placenta
- Tight junctions

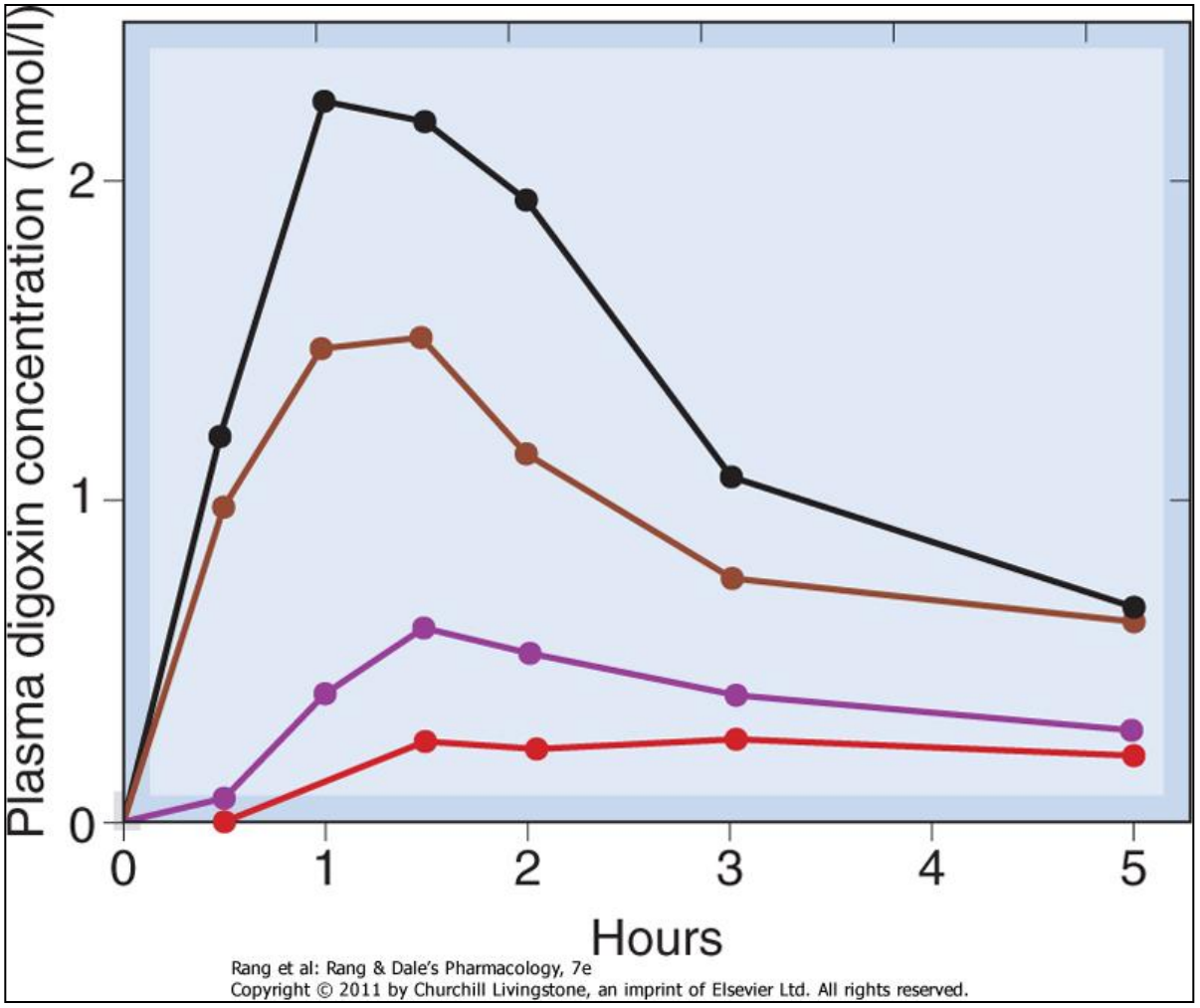
Drug absorption and routes of administration



Absorption of drugs from intestine, as a function of pKa, for acids and bases

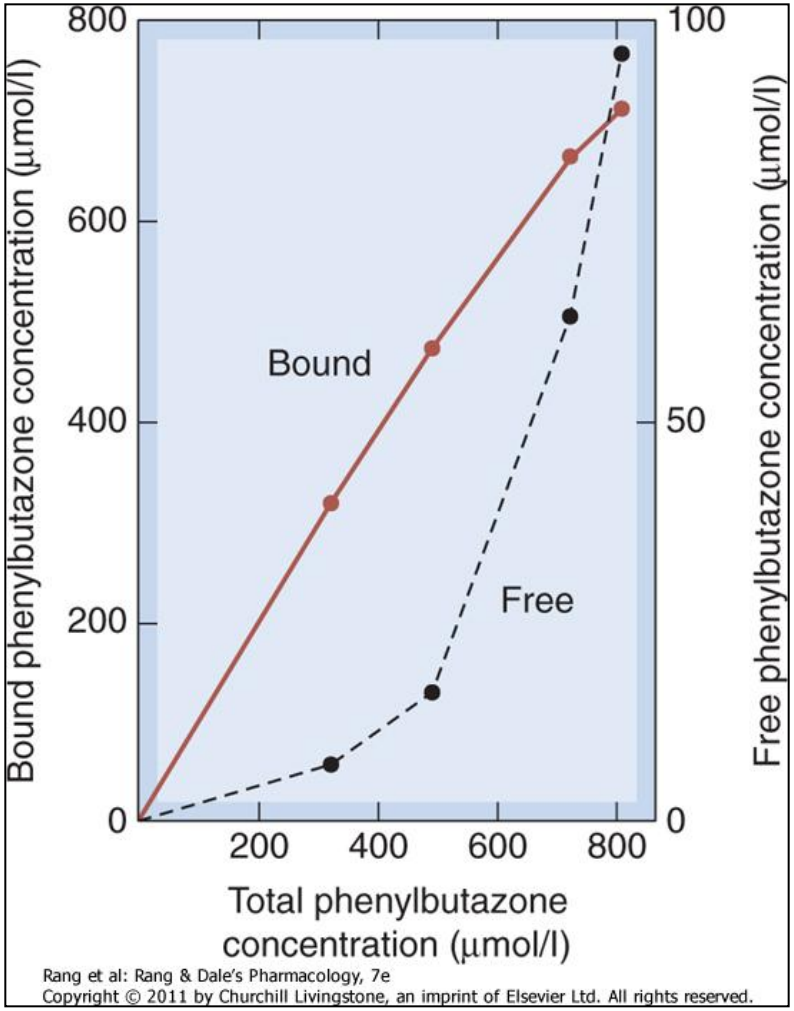


Variation in oral absorption among different formulations of digoxin



Binding to plasma proteins

Binding of phenylbutazone to plasma albumin



D	+	S	⇌	DS
free drug		binding site		complex

- Acidic drugs (anions) – albumin (warfarin, NSAIDs, sulfonamids)
- Basic drugs (cations) and neutral molecules – albumin (TCA, chlorpromazine), lipoproteins, alpha-glycoprotein, beta-globulin (quinine)

Plasma Proteins that Bind Drugs

- **albumin**: binds many acidic drugs and a few basic drugs

- **β-globulin** and an α_1**acid glycoprotein** have also been found to bind certain basic drugs

A bound drug has no effect!

- **Amount bound depends on**:
- 1) free drug concentration
- 2) the protein concentration
- 3) affinity for binding sites

$$\% \text{ bound: } \frac{[\text{bound drug}]}{[\text{bound drug}] + [\text{free drug}]} \times 100$$

% Bound

- Renal failure, inflammation, fasting, malnutrition can have effect on plasma protein binding.
- Competition from other drugs can also affect % bound.

An Example

- Warfarin (anticoagulant) protein bound ~98%
- Therefore, for a 5 mg dose, only 0.1 mg of drug is free in the body to work!
- If patient takes normal dose of aspirin at same time (normally occupies 50% of binding sites), the aspirin displaces warfarin so that 96% of the warfarin dose is protein-bound; thus, 0.2 mg warfarin free; thus, doubles the injested dose

Distribution

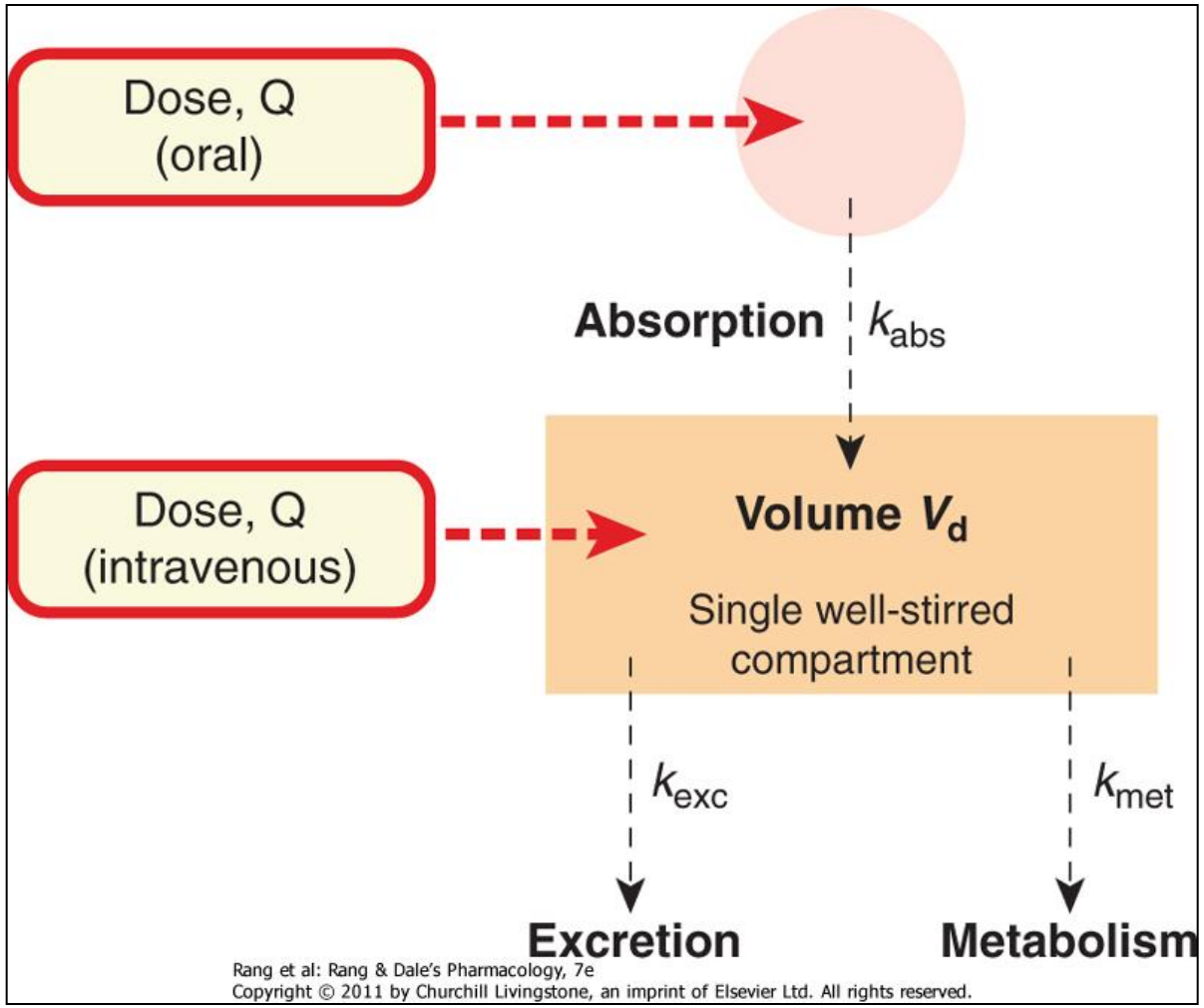
- Rate & Extent depend upon
  - Chemical structure of drug
  - Rate of blood flow
  - Ease of transport through membrane
  - Binding of drug to proteins in blood
  - Elimination processes

- Partition Coefficients: ratio of solubility of a drug in water or in an aqueous buffer to its solubility in a lipophilic, non-polar solvent
- pH and ionization: Ion Trapping

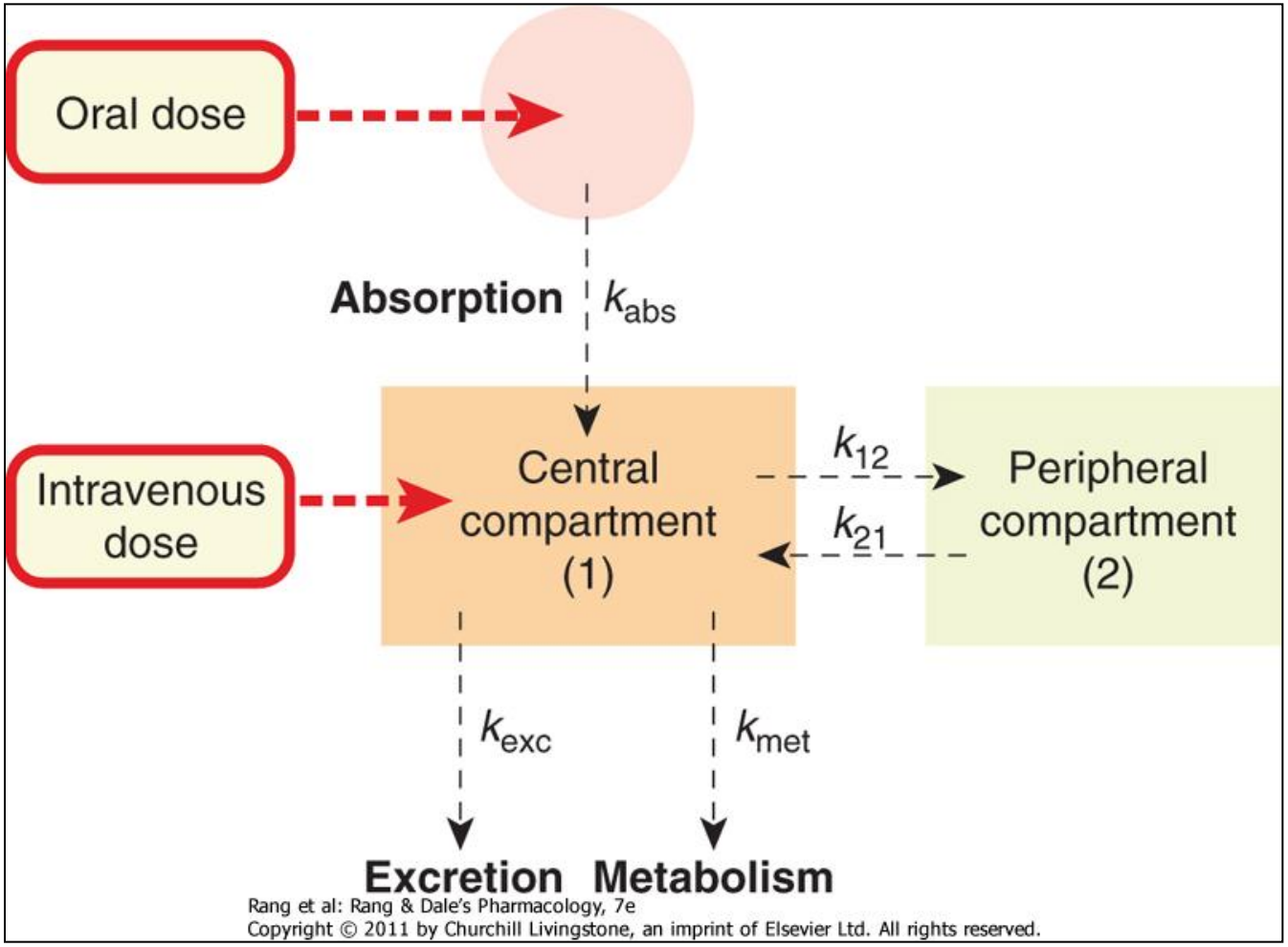
The Compartment Model

- We can generally think of the body as a series of interconnected well-stirred compartments within which the [drug] remains fairly constant.
- BUT movement BETWEEN compartments important in determining when and for how long a drug will be present in body.

Single-compartment pharmacokinetic model



Two-compartment pharmacokinetic model

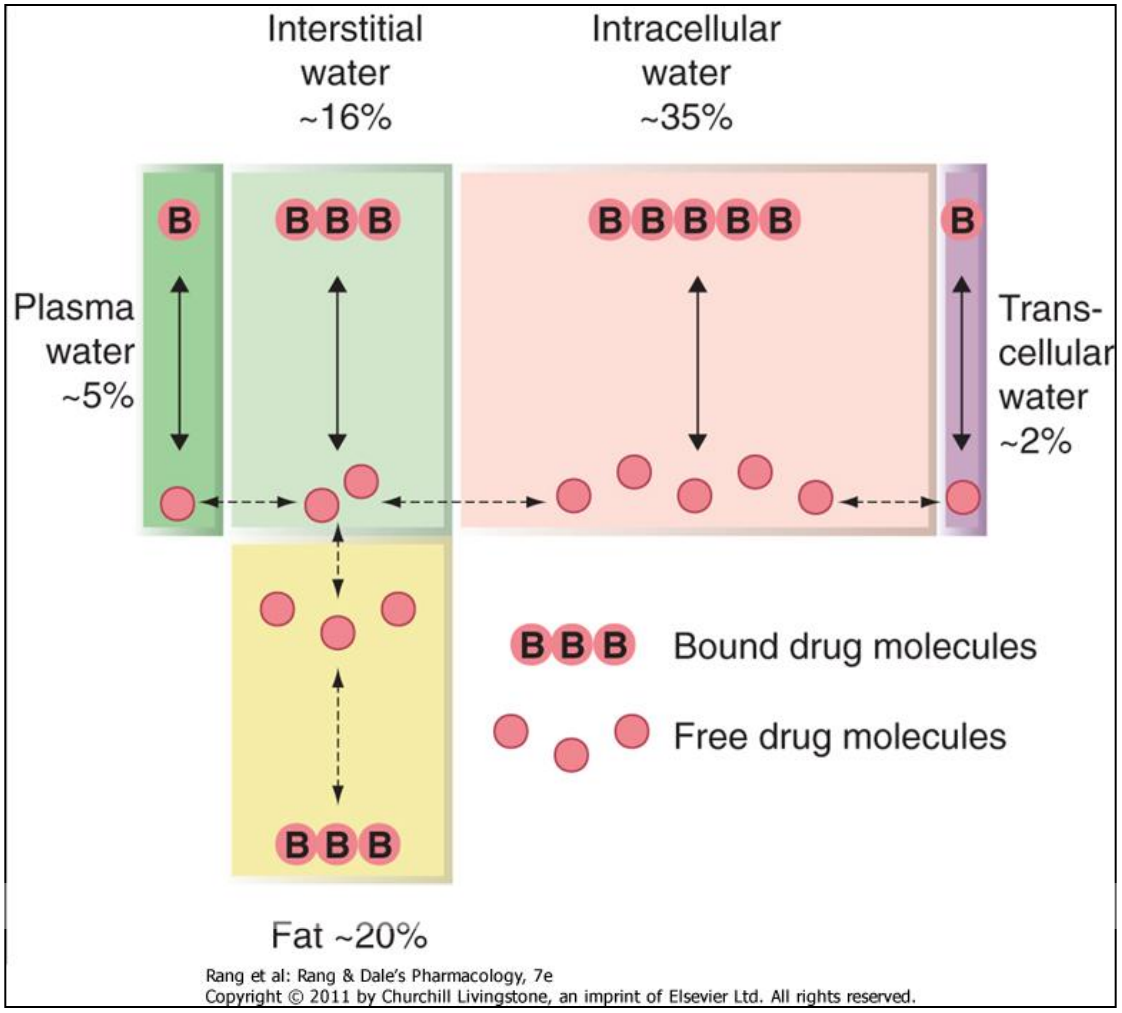


Partitioning into body fat and other tissues

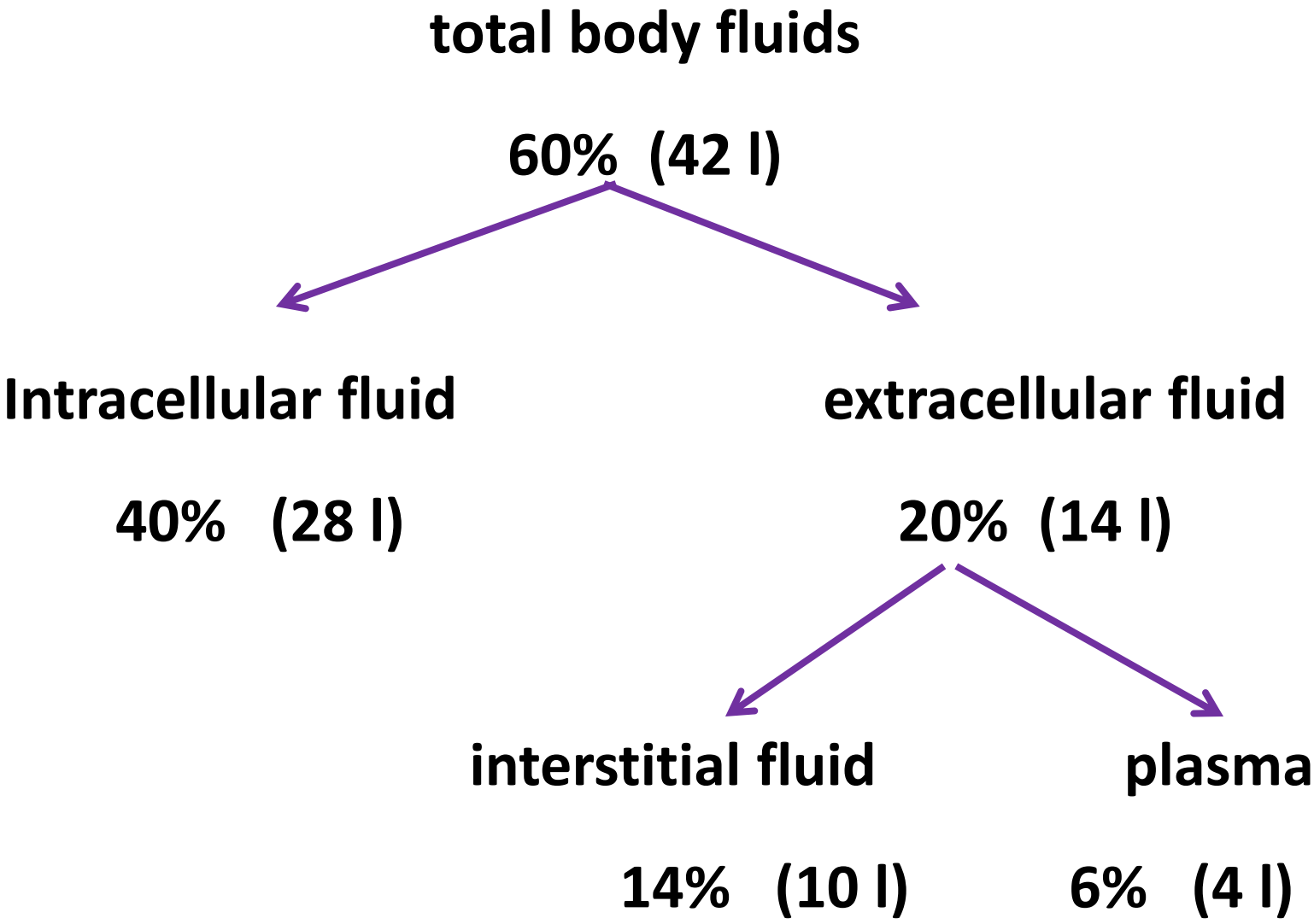
A large, nonpolar compartment. Fat has low blood supply—less than 2% of cardiac output, so drugs are delivered to fat relatively slowly

- For practical purposes: partition into body fat important following acute dosing only for a few highly lipid-soluble drugs and environmental contaminants which are poorly metabolized and remain in body for long period of time

The main body fluid compartments, expressed as a percentage of body weight



Water compartment



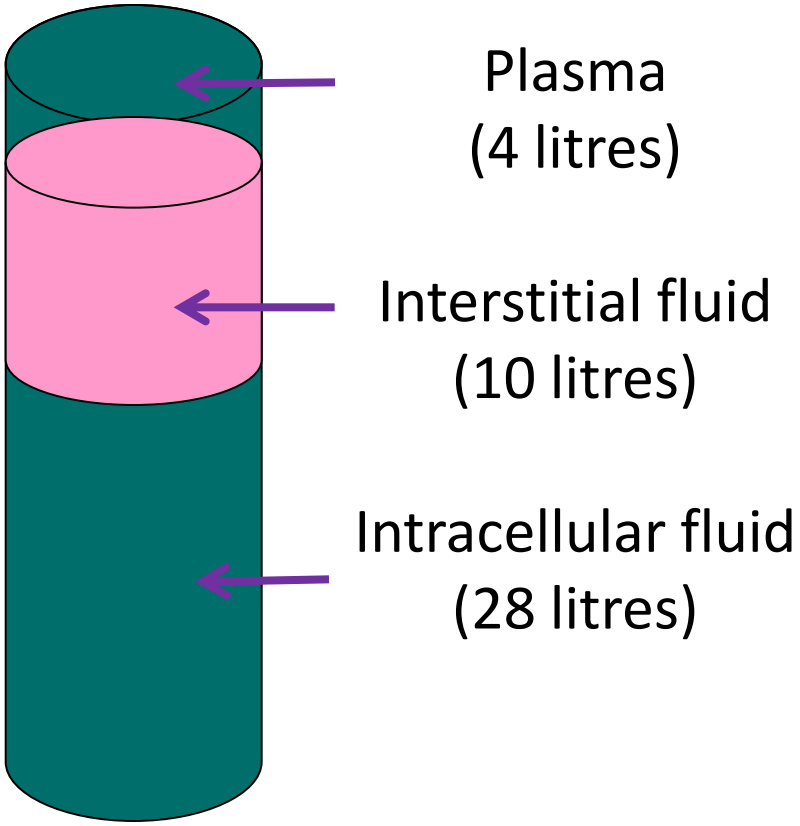
Apparent distribution volume (Vd)

Drug is distributed into following compartments

Plasma

Interstitial fluid

Intracellular fluid



Volume of Distribution

Apparent volume of distribution is the theoretical volume that would have to be available for drug to disperse in if the concentration everywhere in the body were the same as that in the plasma or serum, the place where drug concentration sampling generally occurs.

Volume of Distribution

- C = D/V

  V_d is the apparent volume of distribution

  C= [drug] in plasma at some time

  D (Q) = total [drug] in system

$$V_d = \frac{Q}{C_p}$$

V_d gives one as estimate of how well the drug is distributed. $V_d < 0.071$ L/kg indicate the drug is mainly in the circulatory system.

$V_d > 0.071$ L/kg indicate the drug has entered specific tissues.

Important Concepts

- VD is a theoretical Volume and determines the loading dose
- Clearance is a constant and determines the maintenance dose
- CL = kVD
- CL and VD are independent variables
- k is a dependent variable

Volume of Distribution

- An abstract concept
- Gives information on HOW the drug is distributed in the body
- Used to calculate a loading dose

Loading Dose

$$\textbf{Dose} = \textbf{Cp}_{\textbf{(Target)}} \times \textbf{VD}$$

Question

- What Is the is the loading dose required fro drug A if;
- Target concentration is 10 mg/L
- VD is 0.75 L/kg
- Patients weight is 75 kg

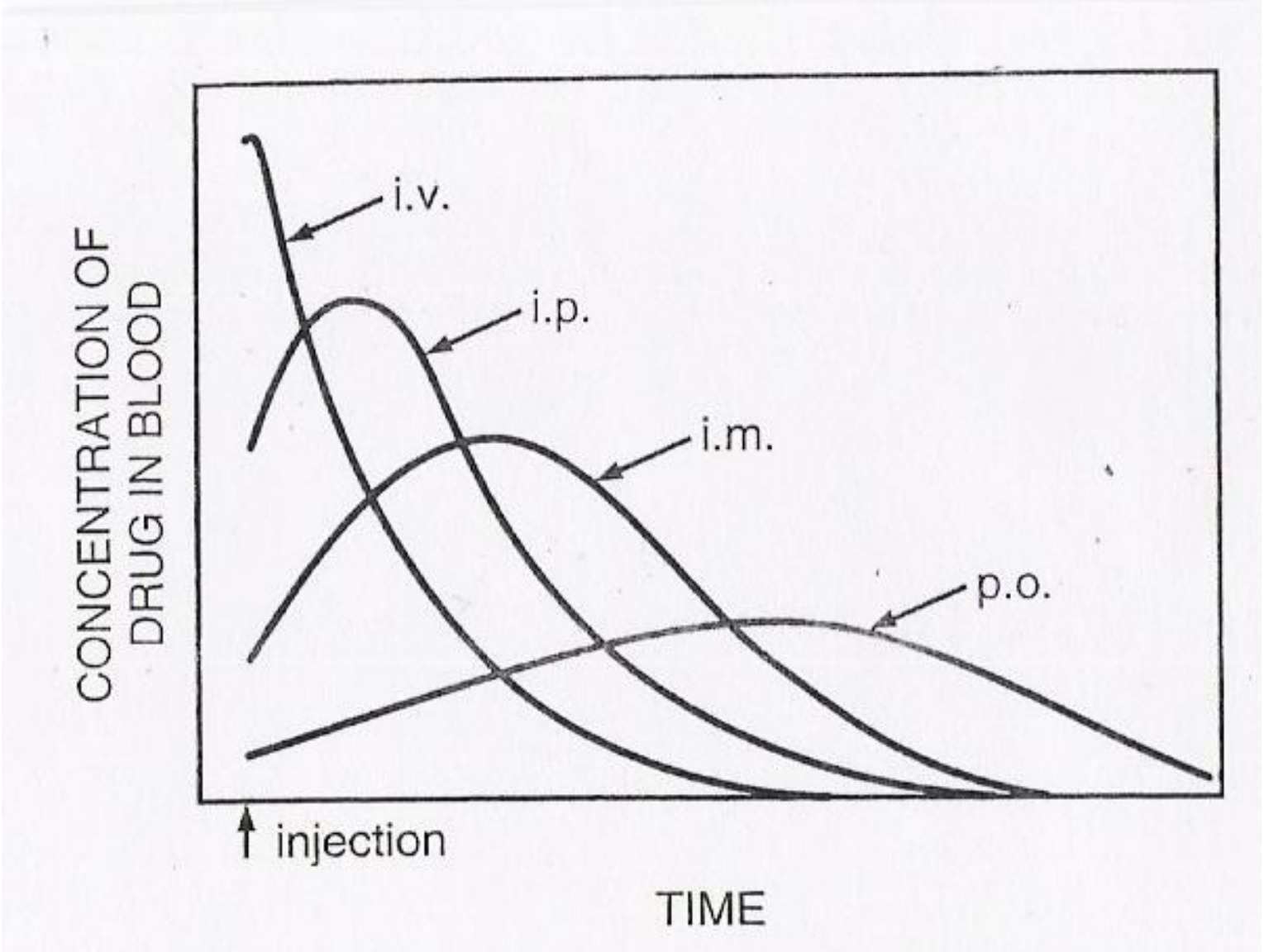
Answer: Loading Dose of Drug A

- Dose = Target Concentration x VD
- VD = 0.75 L/kg x 75 kg = 56.25 L
- Target Conc. = 10 mg/L
- Dose = 10 mg/L x 56.25 L
- = 565 mg
- This would probably be rounded to 560 or even 500 mg.

IMPORTANT EFFECTS OF pH PARTITIONING - Acetazolamide vs $NaHCO_3$

- urinary acidification will accelerate the excretion of weak bases and retard that of weak acids; alkalinisation has the opposite effects
- increasing plasma pH (by addition of $NaHCO_3$) will cause weakly acidic drugs to be extracted from the CNS into the plasma; reducing plasma pH (by administering a carbonic anhydrase inhibitor) will cause weakly acidic drugs to be concentrated in the CNS, increasing their toxicity

Route of Administration Determines Bioavailability (AUC)



AUC: An Indicator of Bioavailability

- Dose is proportional to [drug] in tissues.
- [drug], in turn, is proportional to the Area Under the Curve in a Concentration-decay curve.
- Thus, we have k = dose/AUC
- Because oral administration is full of barriers, the fraction, F, that is *available* by entering the general circulation, may not be significant.
- Thus, FD = k(AUC)

  or k = FD/AUC

- Combining these 2 equations gives us:

$$FD_{po}/AUC_{po} = D_{iv}/AUC_{iv}$$

- And thus, $F = \frac{AUC_{po} D_{iv}}{AUC_{iv} D_{po}}$

- More generally, the relative bioavailability,

$$F = \frac{AUC_{A} Dose_{B}}{AUC_{B} Dose_{A}}$$

AUC: IV Administration

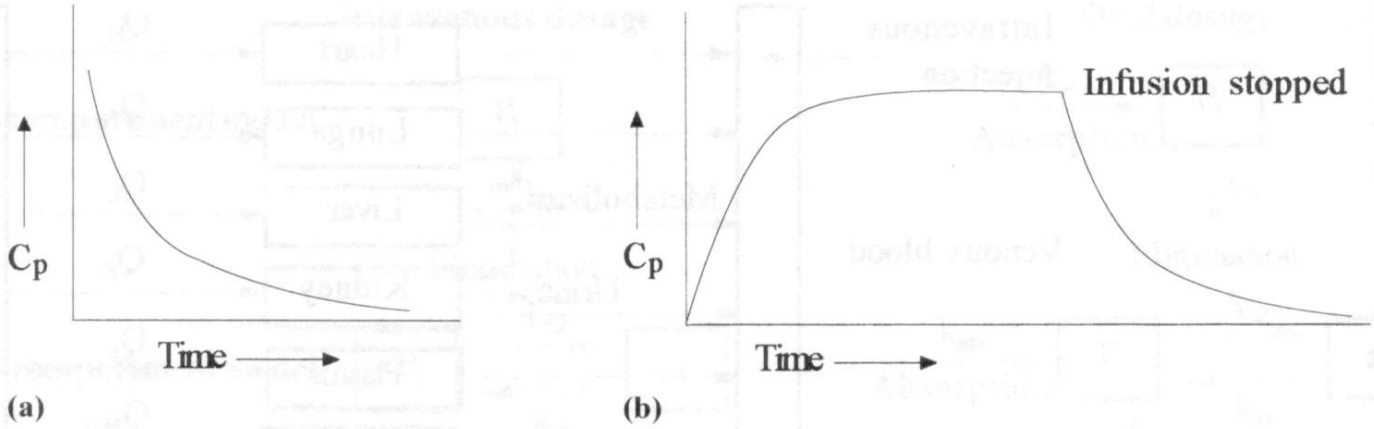


Figure 5.8. The variation of the concentration of a drug in the plasma (C_p) with time when administered by (a) a rapid single intravenous injection and (b) intravenous infusion. With rapid intravenous injections the graph does not show the time taken to carry out the injection; it is normally taken as being spontaneous. In these cases the curve starts at the point where the first plasma concentration measurements were taken.

AUC

- For IV bolus, the AUC represents the total amount of drug that reaches the circulatory system in a given time.
- Dose = CL_T AUC

AUC: Oral Administration

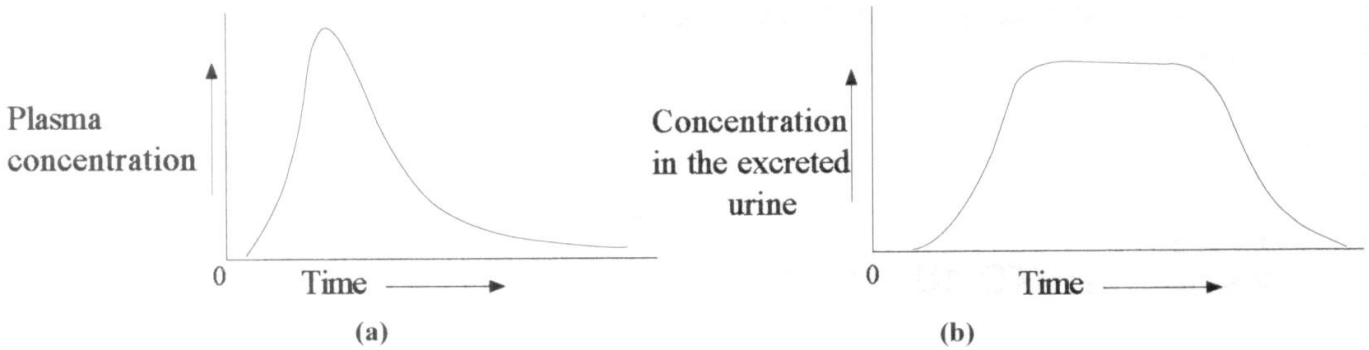


Figure 5.1. Typical variations in the concentration of a drug with time in samples of (a) plasma and (b) urine after the administration of a single oral dose of the drug at time zero. In both cases the precise shape of the graph will depend on the drug being studied.

Bioavailability

- The fraction of the dose of a drug (F) that enters the general circulatory system,

$$F = \frac{\text{amount of drug that enters systemic circulation}}{\text{Dose administered}}$$

$$F = AUC/Dose$$

Bioavailability

- A concept for oral administration
- Useful to compare two different drugs or different dosage forms of same drug

- Rate of absorption depends, in part, on rate of dissolution (which in turn is dependent on chemical structure, pH, partition coefficient, surface area of absorbing region, etc.) Also first-pass metabolism is a determining factor

Table 3–3. Routes of administration, bioavailability, and general characteristics.

Route	Bioavailability (%)	Characteristics
Intravenous	100 (by definition)	Most rapid onset
Intramuscular	75 to ≤100	Large volumes often feasible; may be painful
Subcutaneous	75 to ≤100	Smaller volumes than IM; may be painful
Oral	5 to <100	Most convenient; first-pass effect may be significant
Rectal	30 to <100	Less first-pass effect than oral
Inhalation	5 to <100	Often very rapid onset
Transdermal	80 to ≤100	Usually very slow absorption; used for lack of first-pass effect; prolonged duration of action

The Effect of the Liver First Pass

- F = 1-E, where E is fraction of the dose elim via the liver.
- $Cl_{tot} = D/AUC$
- $Cl_{hep} = Cl_{tot} - Cl_{ren}$
- $Cl_{hep} = E \times LBF$, which is liver blood flow or $E = Cl_{hep}/LBF$
- Combining the 1st eq with the last gives

$$F = 1-E = \frac{1-Cl_{hep}}{LBF}$$

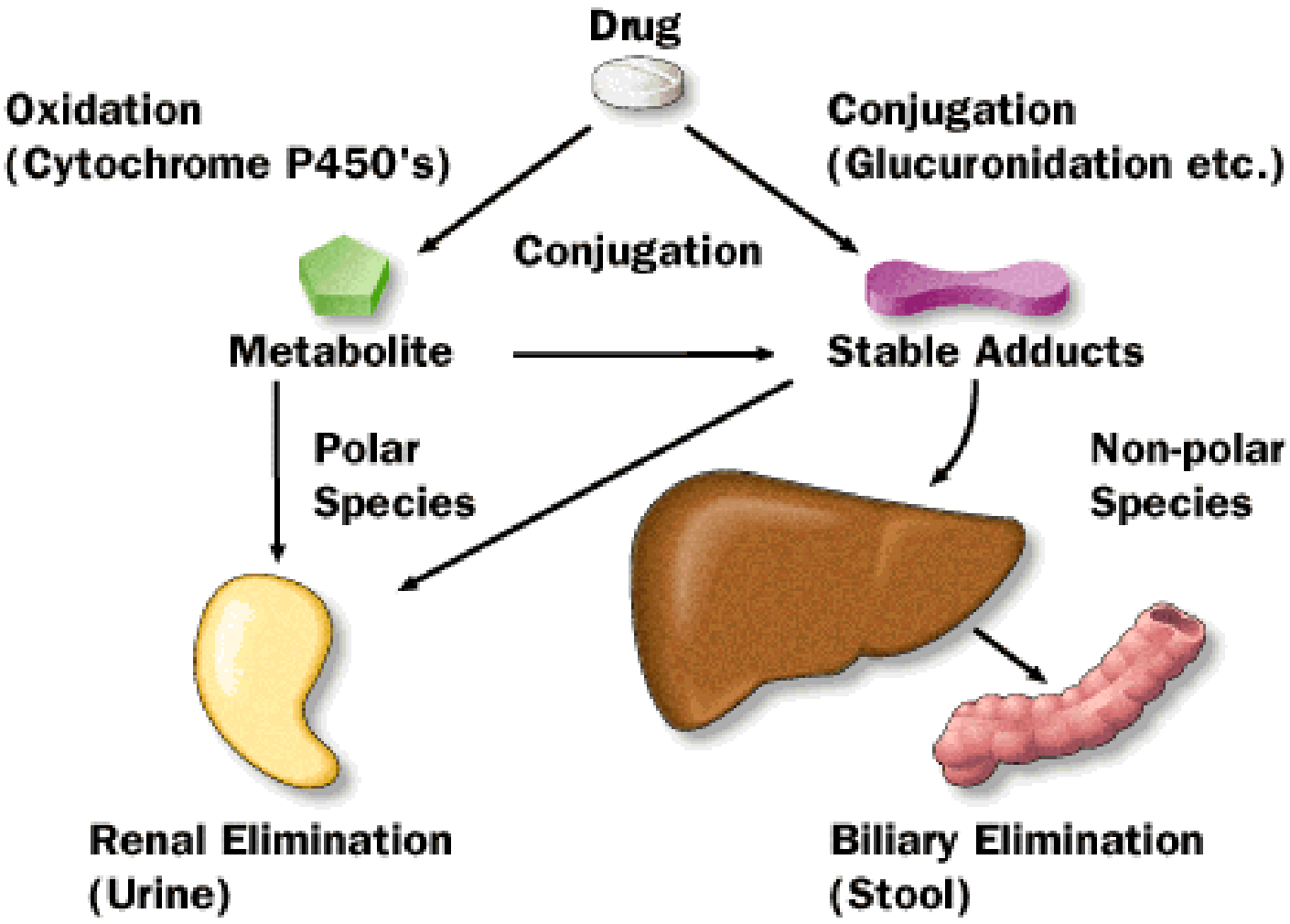
Rowland's Equation

- $F = 1-E = \frac{1-Cl_{hep}}{LBF}$

This very useful equation calculates the magnitude of the effect of the liver's 1st pass of an oral dose and, more precisely, to predict it from and i.v. test.

Thus, if $E < 0.10$, then, clearly, bioavailability $F > 0.90$.

Drug metabolism



Elimination by the Liver

- Metabolism - major

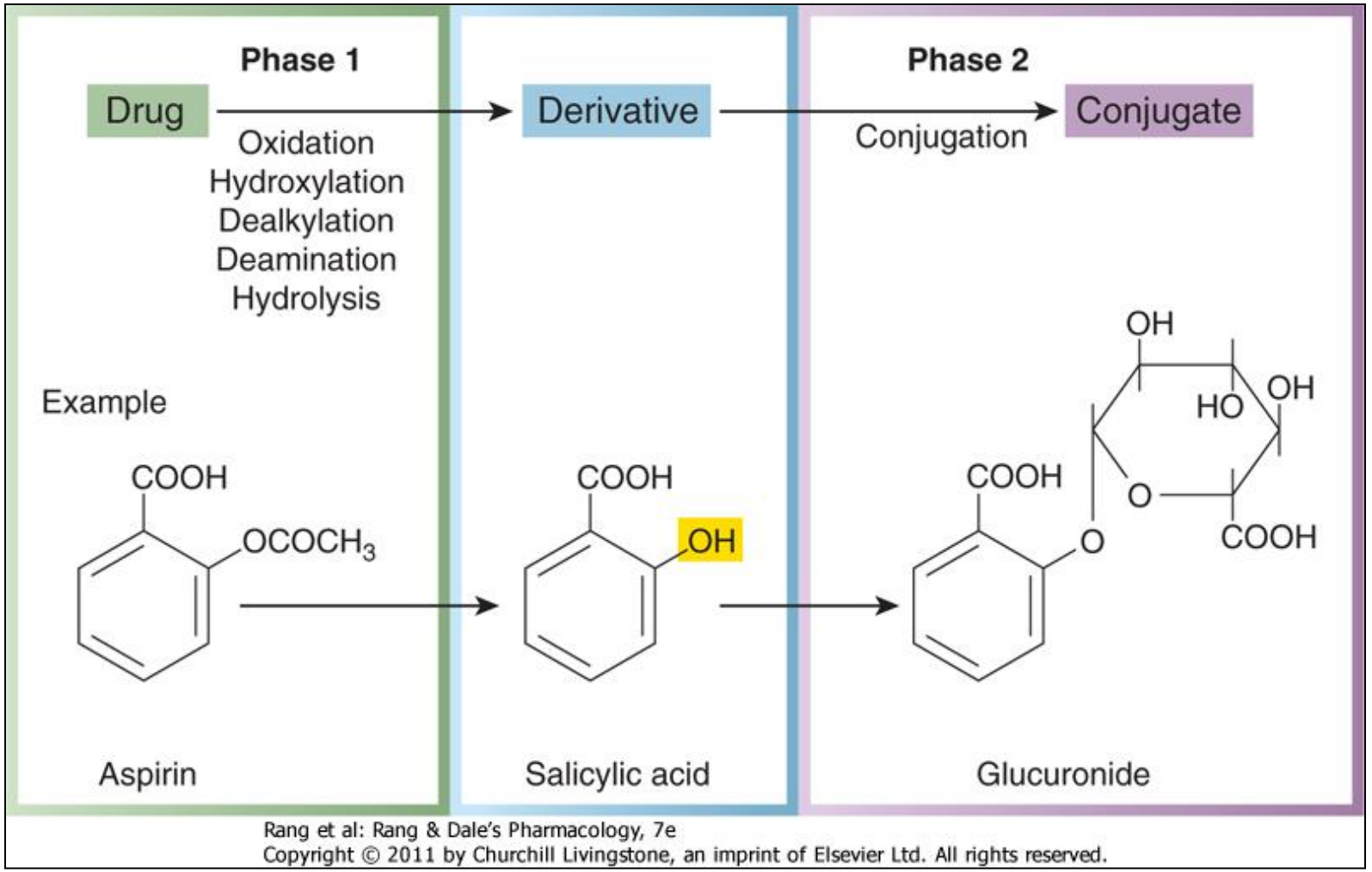
  1) Phase I and II reactions

  2) Function: change a lipid soluble to more water soluble molecule to excrete in kidney

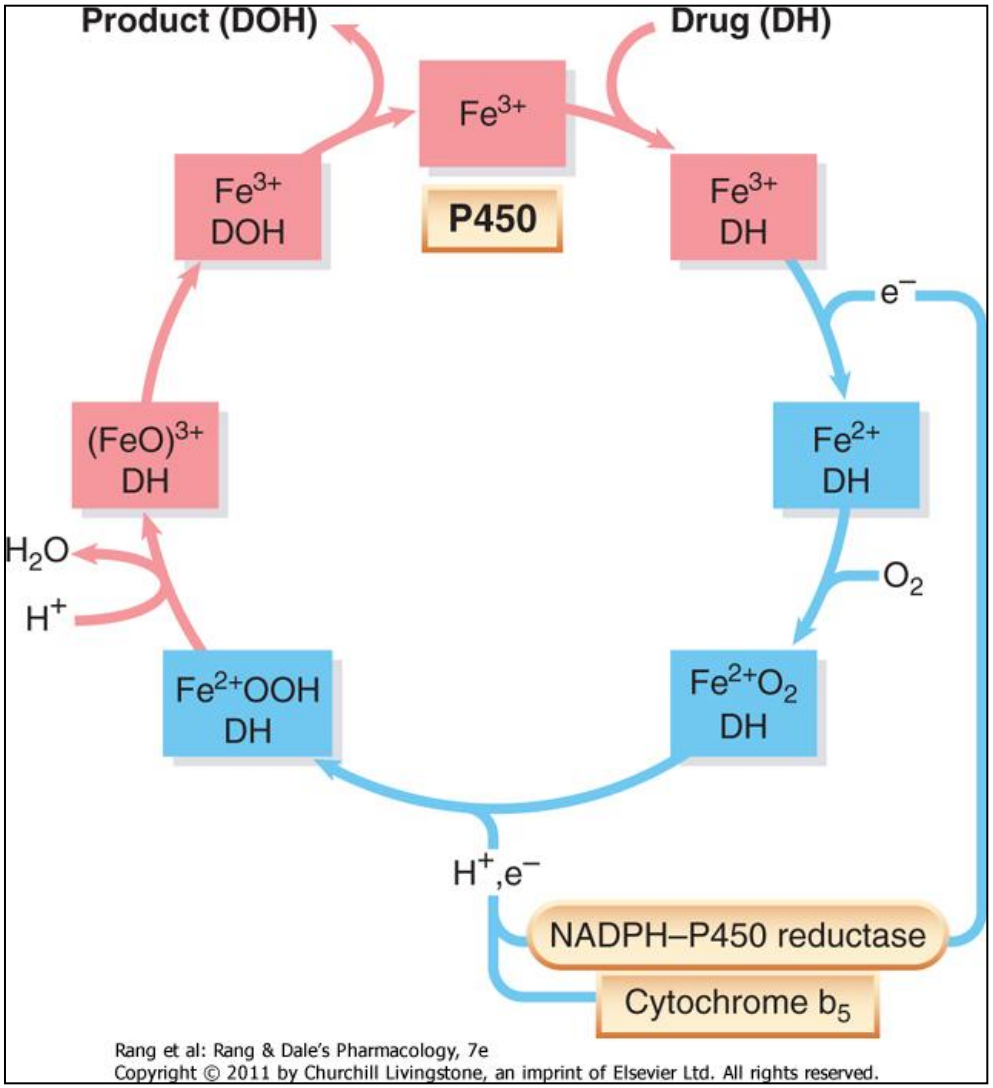
  3) Possibility of active metabolites with same or different properties as parent molecule

- Biliary Secretion – active transport, 4 categories

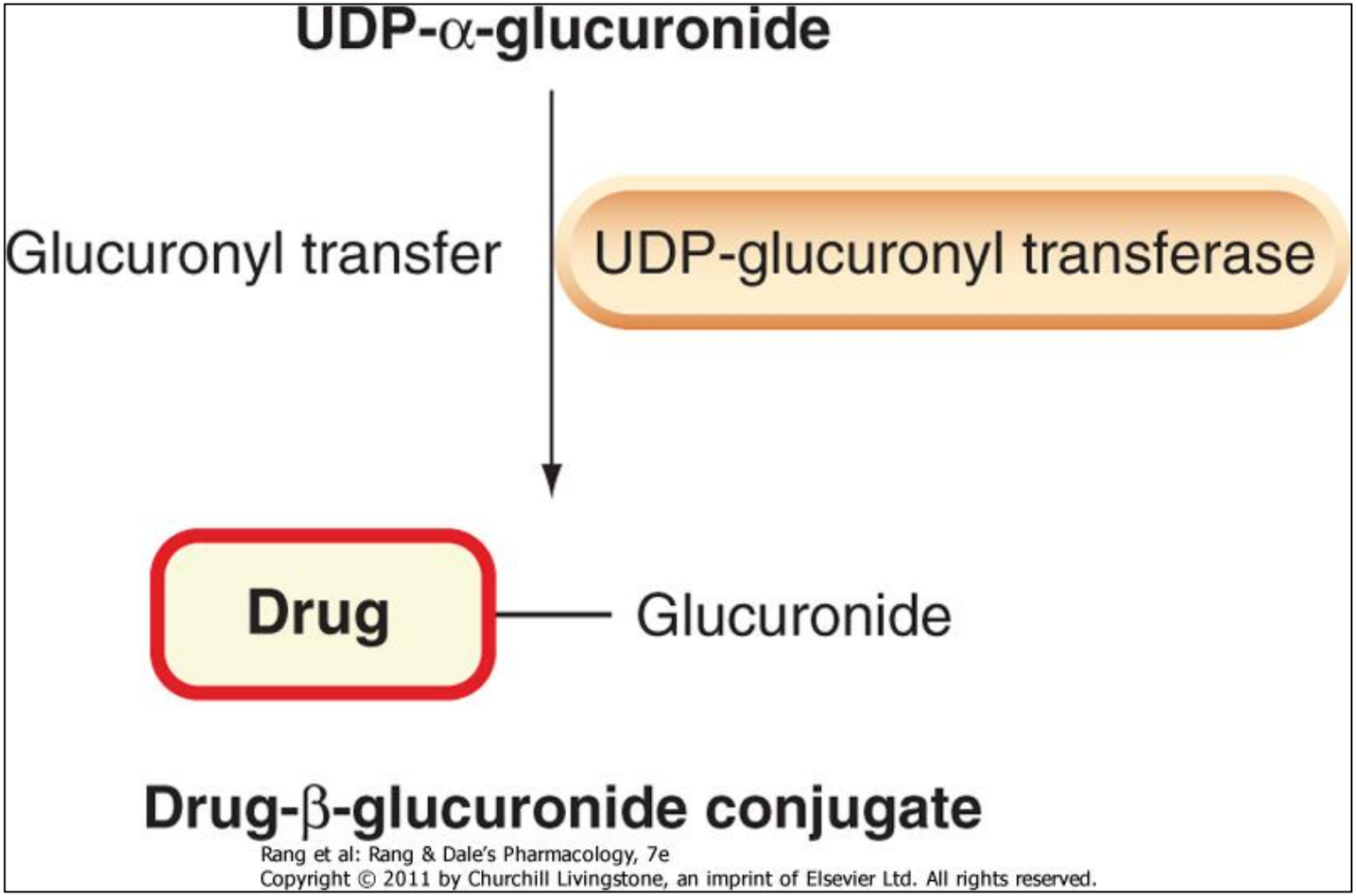
Two phases of drug metabolism



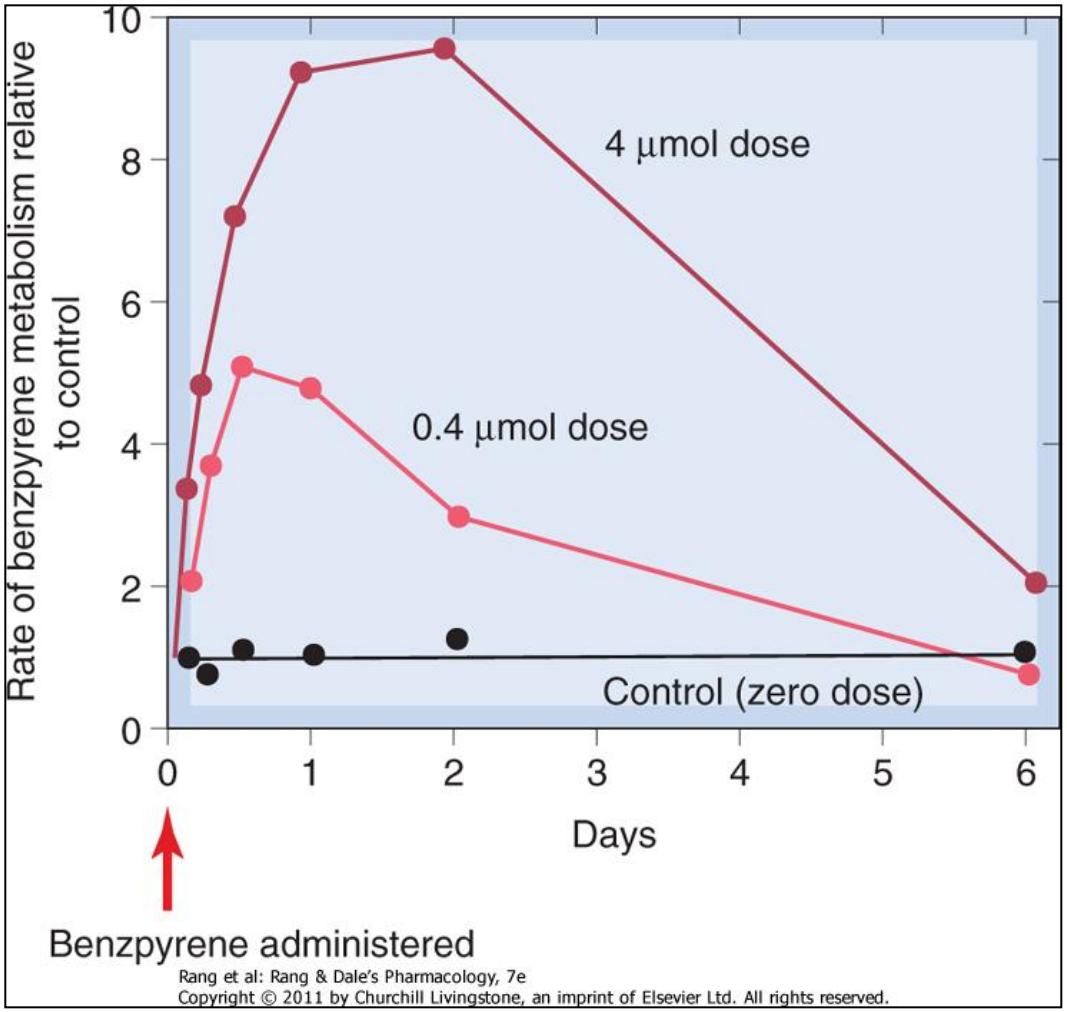
Monooxygenase P450 system



Glucuronide conjugation reaction



Stimulation of hepatic metabolism of benzpyrene



Liver P450 systems

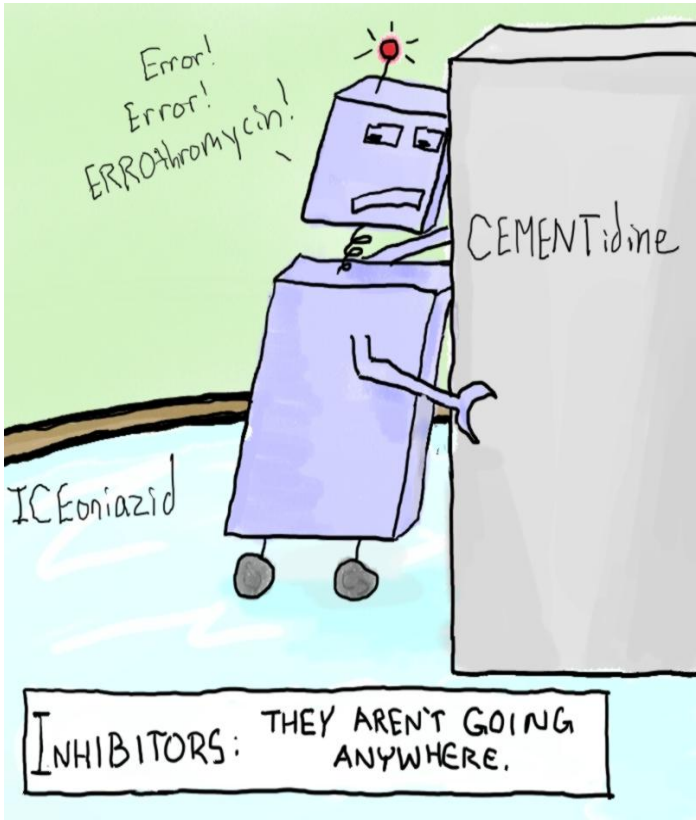
- Liver enzymes inactivate some drug molecules
  - First pass effect (induces enzyme activity)
- P450 activity is genetically determined:
  - Some persons lack such activity → leads to higher drug plasma levels (adverse actions)
  - Some persons have high levels → leads to lower plasma levels (and reduced drug action)
- Other drugs can interact with the P450 systems
  - Either induce activity (apparent tolerance)
  - Inactivate an enzyme system

P450 Interactions

- Substrate: Is the drug metabolized via a specific hepatic isoenzyme?
- Inhibitor: does a specific drug inhibit a specific hepatic isoenzyme?
  - Would expect this to interfere with drug inactivation
- Inducer: does a specific drug enhance a specific hepatic isoenzyme?
  - Would expect this to speed up drug inactivation

Inhibitors

- cimetidine, macrolids, ketoconazol, grapefruit juice...
- increase concentration
- prolong (increase) drug effects
- inhibit creation of active metabolite from pro-drug (effect is decreased)



Inducers

- barbiturates, rifampicin, fenytoin, carbamazepin, smoking
- increase drug metabolism (decrease concentration)
- shorten and decrease the effect
- in pro-drugs opposite

Drug-CYP Interactions

Enzyme (CYP)	Substrate	Inhibitor	Inducer
1A2	Clozapine, haloperidol	Cimetidine	Tobacco smoke
2B6	Bupropion	Thiotepa	Phenobarbital
2C19	Citalopram	Fluoxetine	Prednisone
2C9	Fluoxetine	Paroxetine	Secobarbital
2D6	Most ADs, APs	CPZ, ranitidine	Dexamethasone
2E1	Gas anesthetics	Disulfiram	Ethanol
3A4,5,7	Alprazolam	Grapefruit juice	Glucocorticoid

http://www.georgetown.edu/departments/pharmacology/clinlist.html

Elimination of drugs from the body

MAJOR

KIDNEY
filtration
secretion
(reabsorption)

LIVER
metabolism
secretion

MINOR

LUNGS
exhalation

OTHERS
mother's milk
sweat, saliva etc.

Elimination by the Kidney

- Excretion - major

  1) glomerular filtration

  glomerular structure, size constraints, protein binding

  2) tubular reabsorption/secretion

  - acidification/alkalinization,

  - active transport, competitive/saturable, organic acids/bases
  - protein binding

- Metabolism - minor

Renal Elimination

- Glomerular filtration: molecules below 20 kDa pass into filtrate. Drug must be free, not protein bound.
- Tubular secretion/reabsorption: Active transport. Followed by passive and active. DP=D + P. As D transported, shift in equilibrium to release more free D. Drugs with high lipid solubility are reabsorbed passively and therefore slowly excreted. Idea of ion trapping can be used to increase excretion rate---traps drug in filtrate.

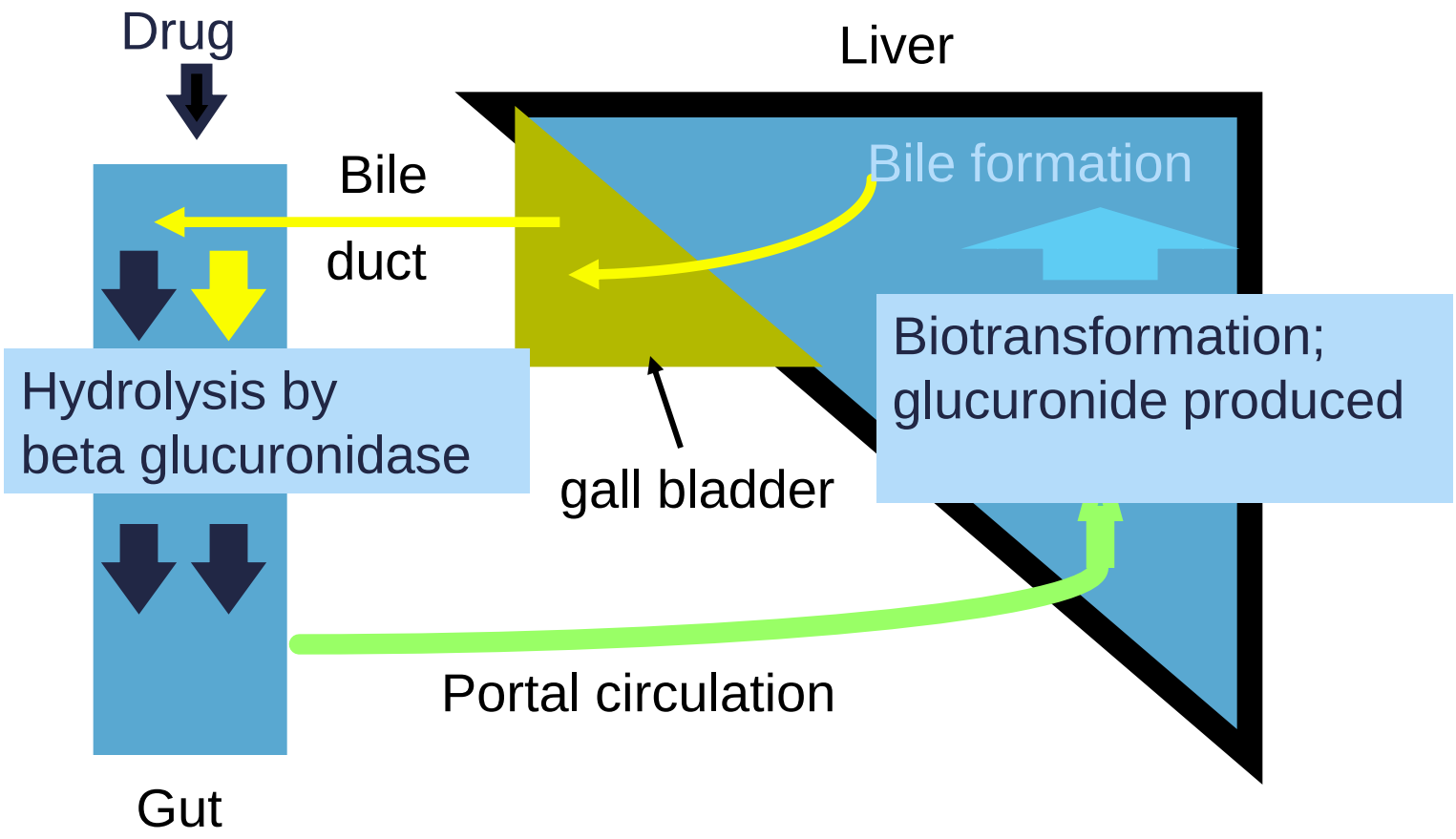
Special ways of excretion

- Excretion into maternal milk (breast-feeding)
- Excretion by stool (less)
- Lungs - volatile agents (general anaesthetics))
- sweat, saliva, tears

Excretion via bile

- anions, cations, neutral agents (m.w. > 300)
- agents with m.w. < 300 are reabsorbed from bile - conjugates (glucuronides) via bile into intestine
- re-absorption into portal vein and body
- enterohepatal circulation
- prolonged stay of drug and its effect in the body

The Enterohepatic Shunt



Types of Kinetics Commonly Seen

Zero Order Kinetics

- Rate = k
- $C = C_o - kt$
- Constant rate of elimination regardless of $[D]_{plasma}$
- C vs. t graph is LINEAR

First Order Kinetics

- Rate = k C
- $C = C_o e^{-kt}$
- Rate of elimination proportional to plasma concentration. Constant ***fraction*** of drug eliminated per unit time.
- C vs. t graph is NOT linear, decaying exponential. Log C vs. t graph is linear.

Conc. *vs*. time plots

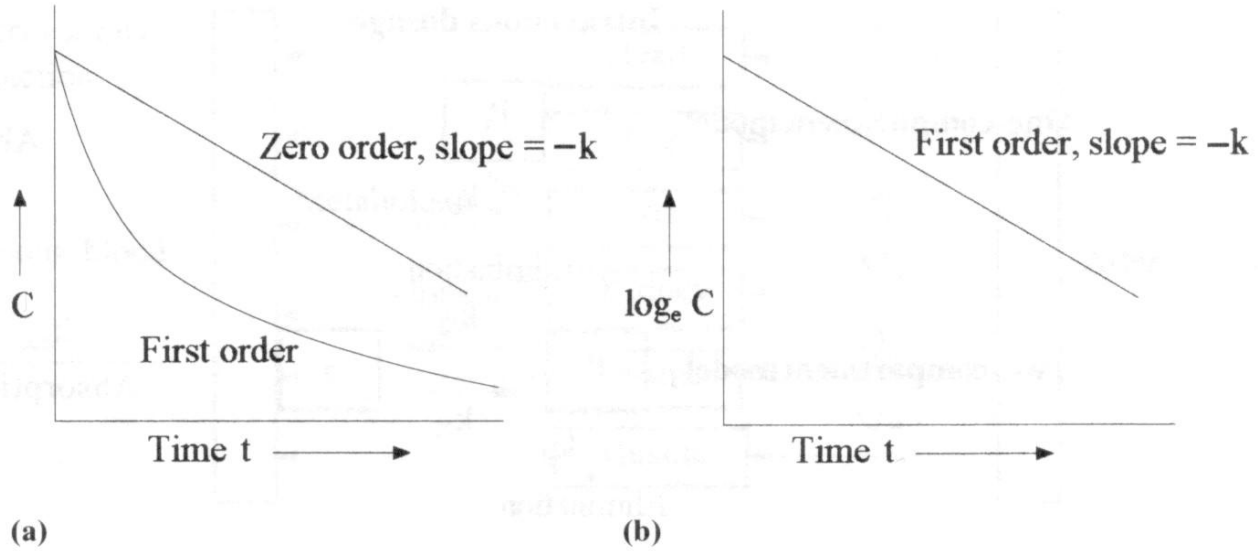


Figure 5.5. (a) Zero- and first-order concentration–time plots and (b) first-order log$_e$ concentration–time plots.

$C = C_o - kt$ $\ln C = \ln C_o - kt$

Example of Zero Order Elimination: Pharmacokinetics of Ethanol

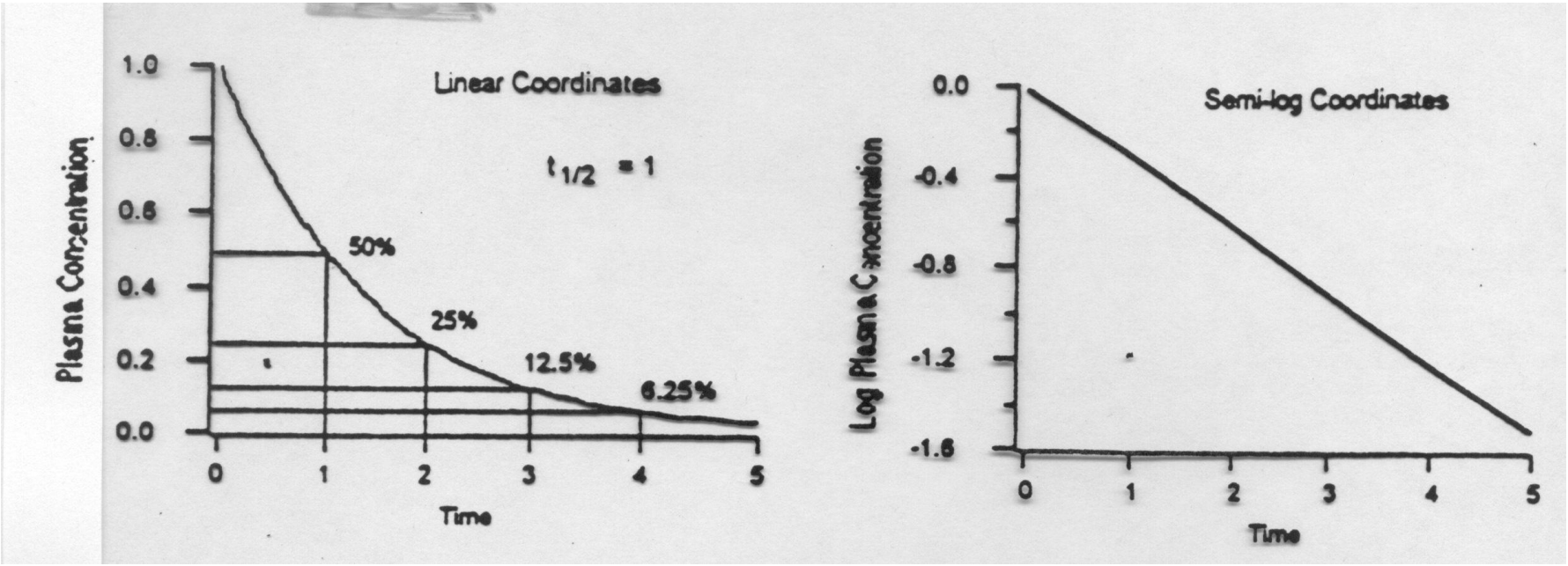
- Ethanol is distributed in total body water.
- Mild intoxication at 1 mg/ml in plasma.
- How much should be ingested to reach it?

  Answer: 42 g or 56 ml of pure ethanol (V_dXC)

  Or 120 ml of a strong alcoholic drink like whiskey
- Ethanol has a constant elimination rate = 10 ml/h
- To maintain mild intoxication, at what rate must ethanol be taken now?

  at 10 ml/h of pure ethanol, or 20 ml/h of drink.

First-Order Kinetics



To reiterate: Comparison

- Zero Order Elimination
  - [drug] decreases linearly with time
  - Rate of elimination is constant
  - Rate of elimination is independent of [drug]
  - No true $t_{1/2}$
- First Order Elimination
  - [drug] decreases exponentially w/ time
  - Rate of elimination is proportional to [drug]
  - Plot of log [drug] or ln[drug] vs. time are linear
  - $t_{1/2}$ is constant regardless of [drug]

Clearance

- Ability of organs of elimination (e.g. kidney, liver to “clear” drug from the bloodstream
- Volume of fluid which is completely cleared of drug per unit time
- Units are in L/hr or L/hr/kg
- Pharmacokinetic term used in determination of maintenance doses

Clearance

- Volume of blood in a defined region of the body that is cleared of a drug in a unit time.
- Clearance is a more useful concept in reality than $t_{1/2}$ or k_{el} since it takes into account blood flow rate.
- Clearance varies with body weight.
- Also varies with degree of protein binding.

Clearance

- Rate of elimination = k_{el} D,
  - Remembering that C = D/V_d
  - And therefore D= C V_d
  - Rate of elimination = k_{el} C V_d
- Rate of elimination for whole body = CL_T C

Combining the two,

CL_T C = k_{el} C V_d and simplifying gives:

CL_T = k_{el} V_d

Maintenance Dose Calculation

- Maintenance Dose = CL x $CpSS_{av}$
- $CpSS_{av}$ is the target average steady state drug concentration
- The units of CL are in L/hr or L/hr/kg
- Maintenance dose will be in mg/hr so for total daily dose will need multiplying by 24

Question

- What maintenance dose is required for drug A if;
- Target average SS concentration is 10 mg/L
- CL of drug A is 0.015 L/kg/hr
- Patient weighs 75 kg

- Answer on next slide.

Answer

- Maintenance Dose = CL x $CpSS_{av}$
- CL = 0.015 L/hr/kg x 75 = 1.125 L/hr
- Dose = 1.125 L/hr x 10 mg/L
  = 11.25 mg/hr
- So will need 11.25 x 24 mg per day
  = 270 mg

Half-Life and k

- Half-life is the time taken for the drug concentration to fall to half its original value
- The elimination rate constant (k) is the fraction of drug in the body which is removed per unit time.

Drug Half-Life

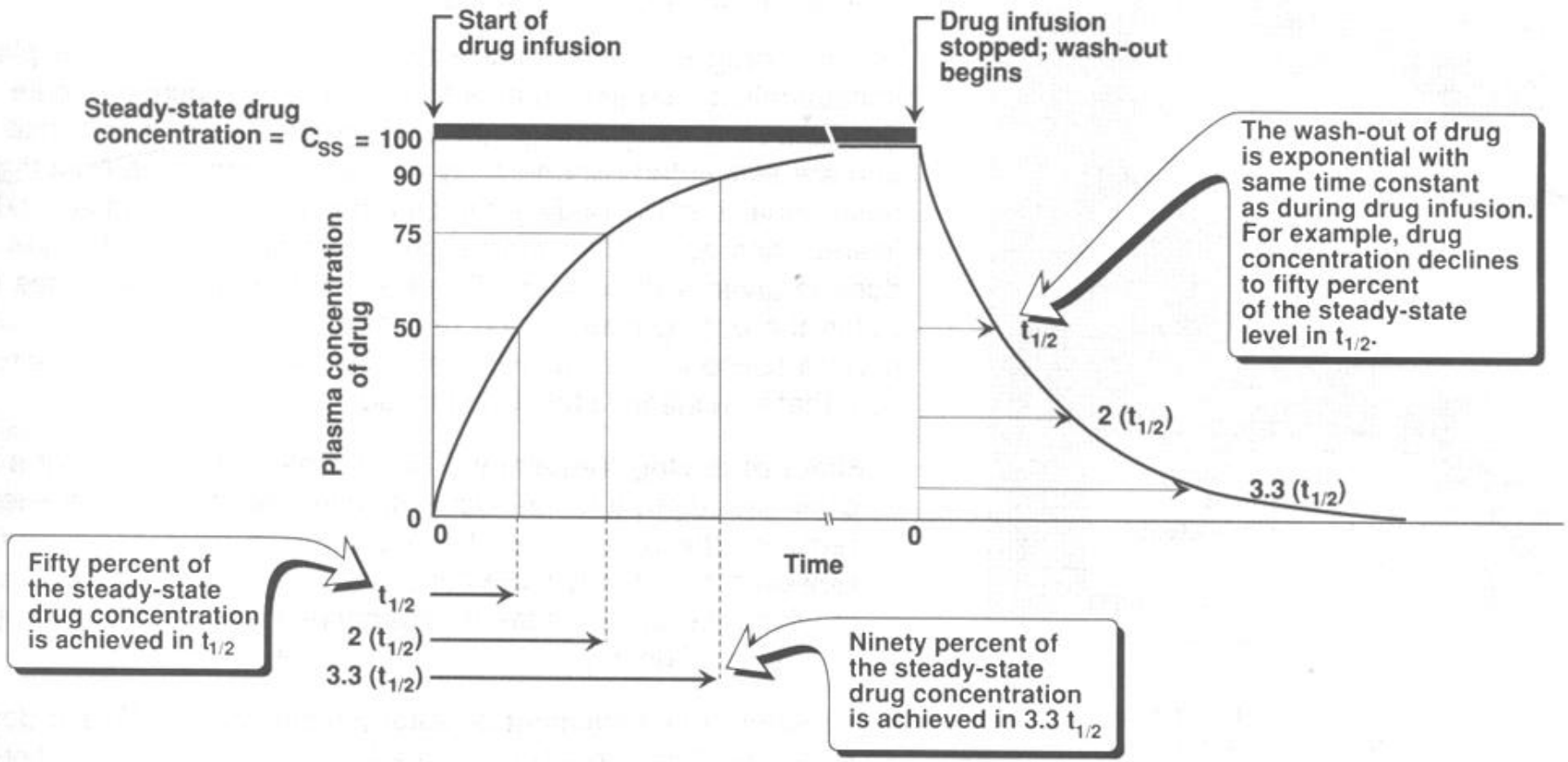
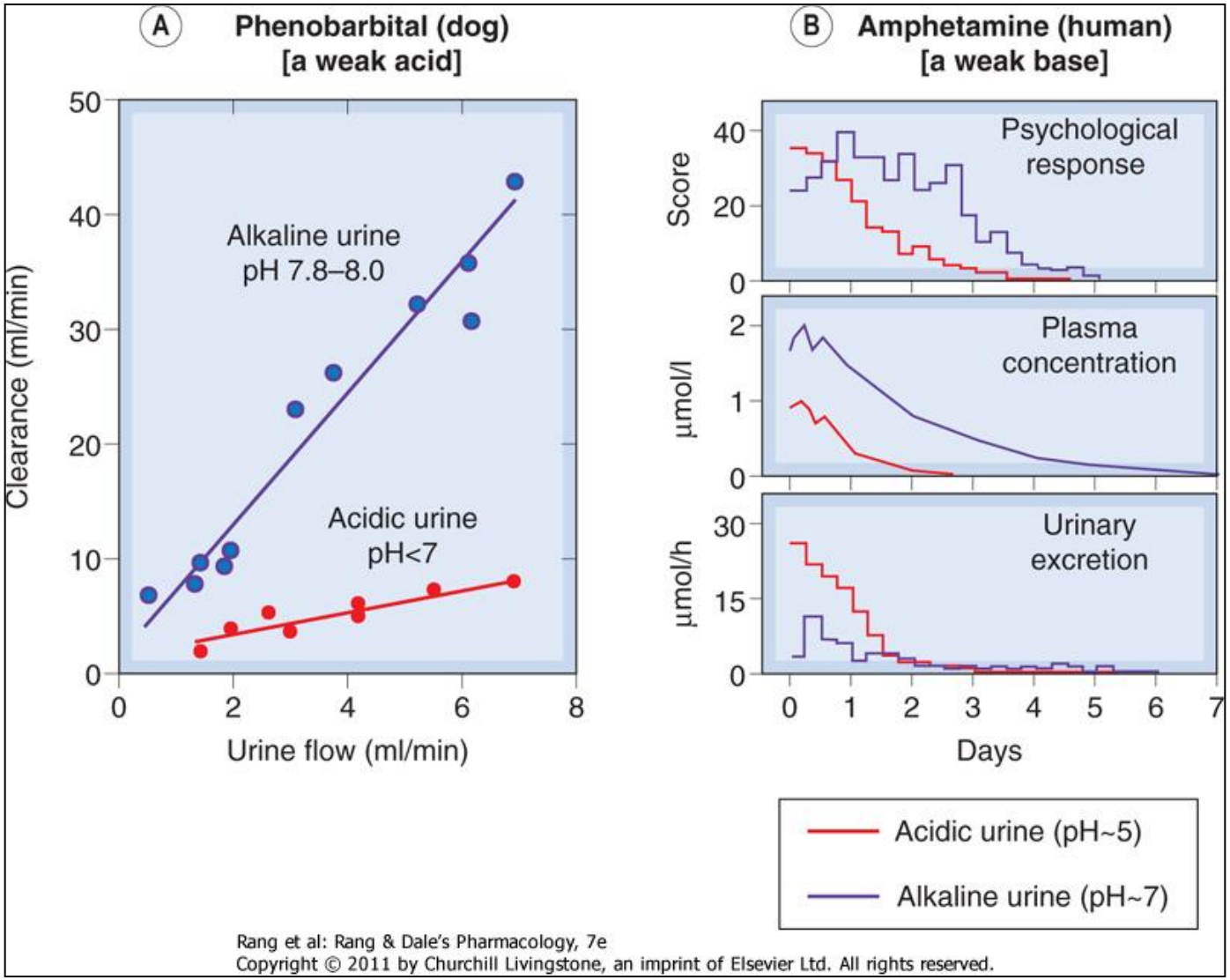
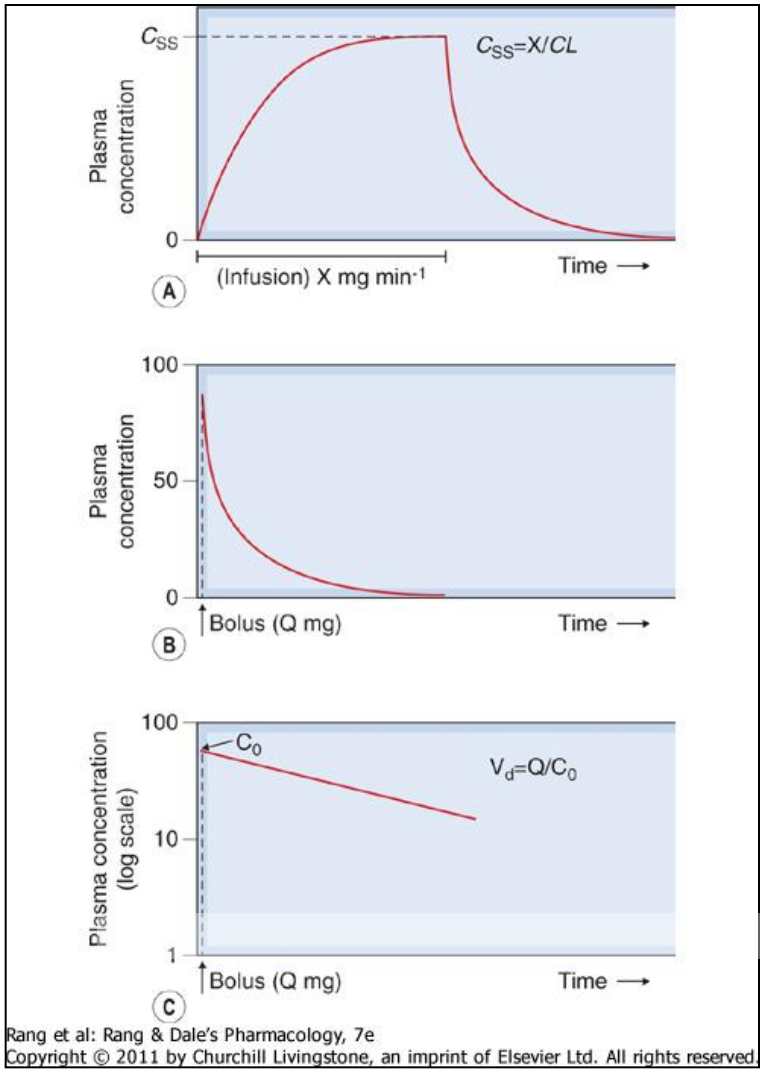


Figure 2.3
Rate of attainment of steady-state concentration of drug in plasma.

The effect of urinary pH on drug excretion

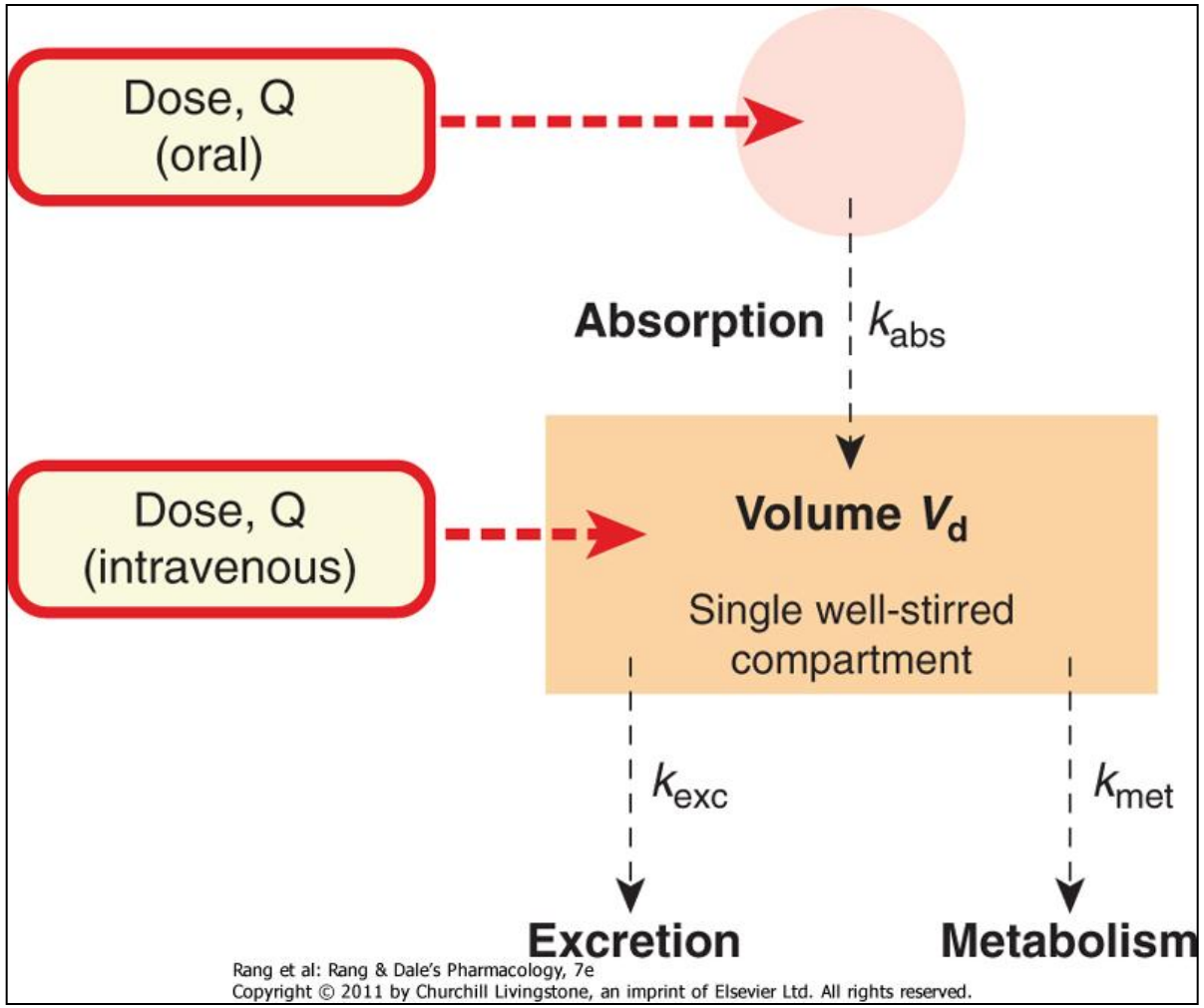


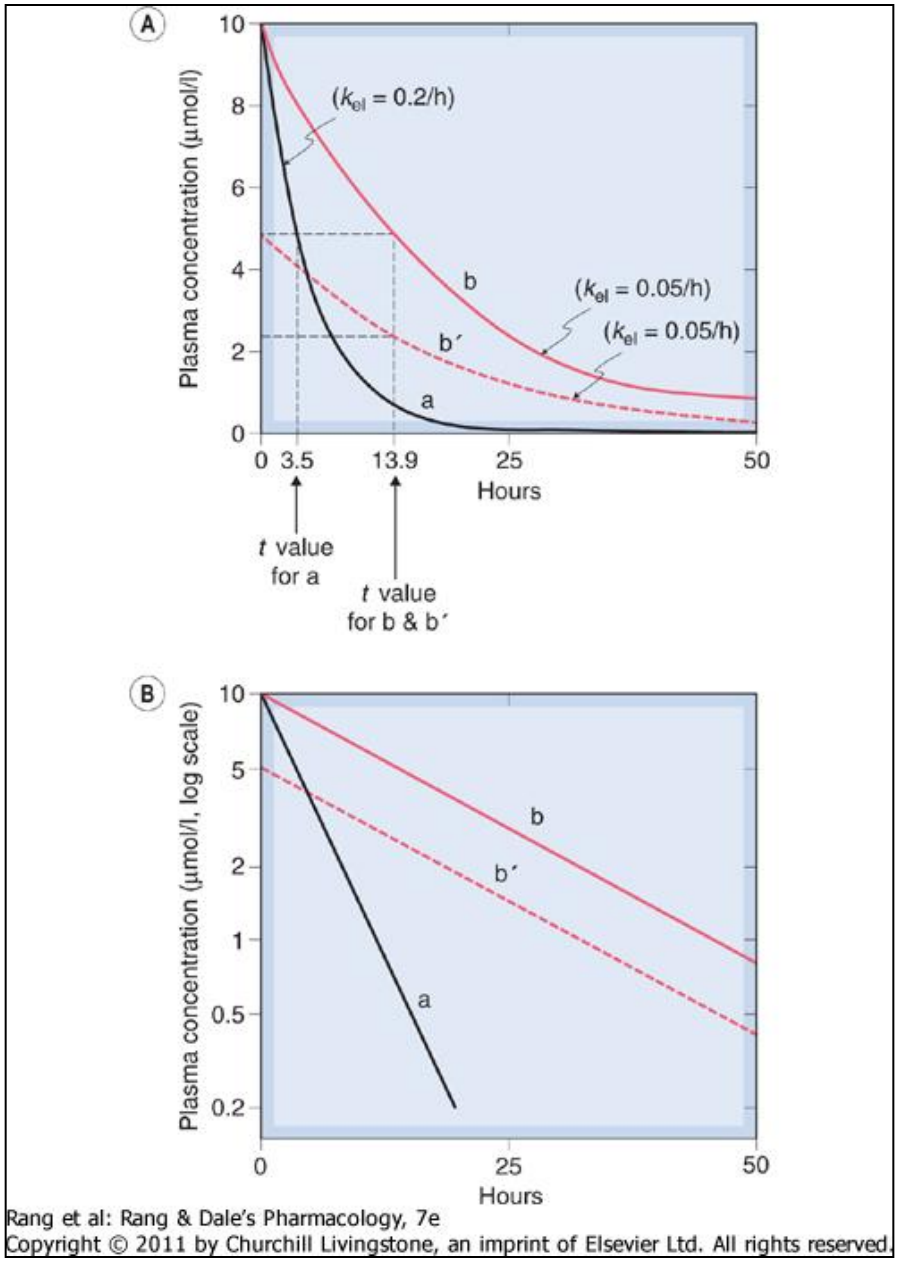
Plasma drug concentration-time curves



- A – intravenous infusion (rate x mg/min)
- B – intravenous bolus dose (Q mg)
- C – same as B plotted on logarithmic scale – by extrapolation – Co and ability to calculate Vd

Single-compartment pharmacokinetic model



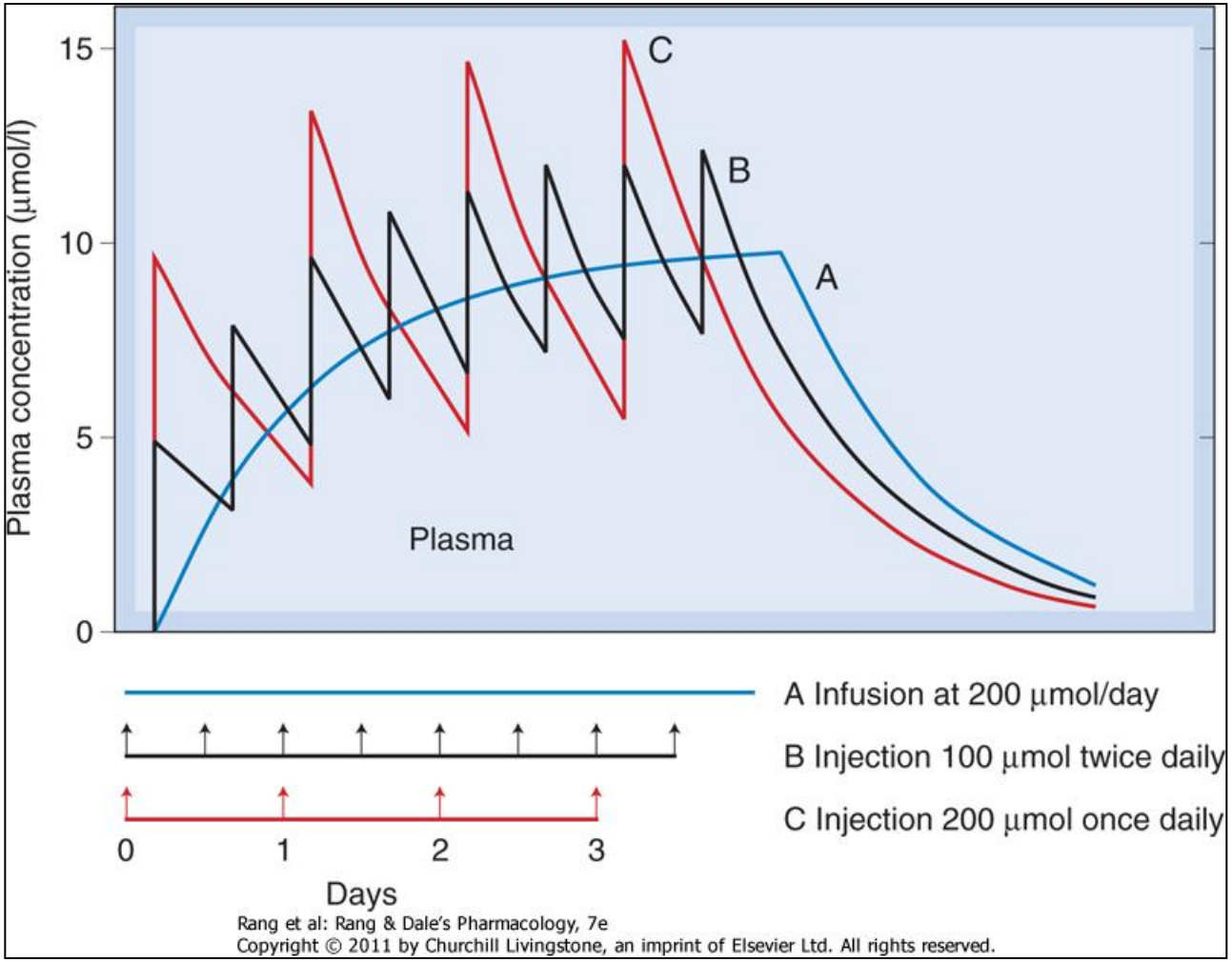


Predicted behaviour of single-compartment model following i.v. drug administration at time 0.

A – linear scale

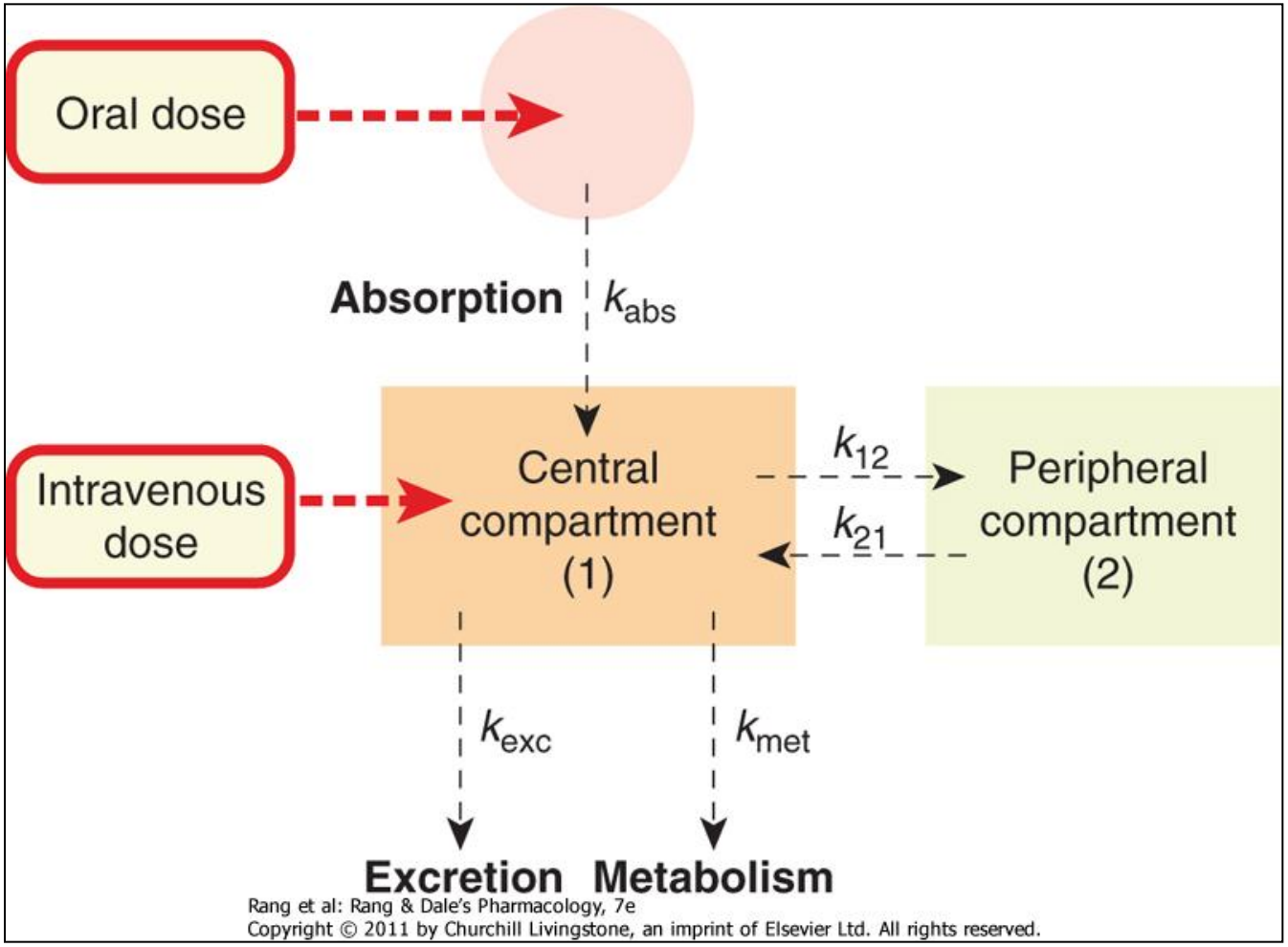
B – logarithmic scale

Predicted behaviour of single-compartment model with continuous or intermittent drug administration

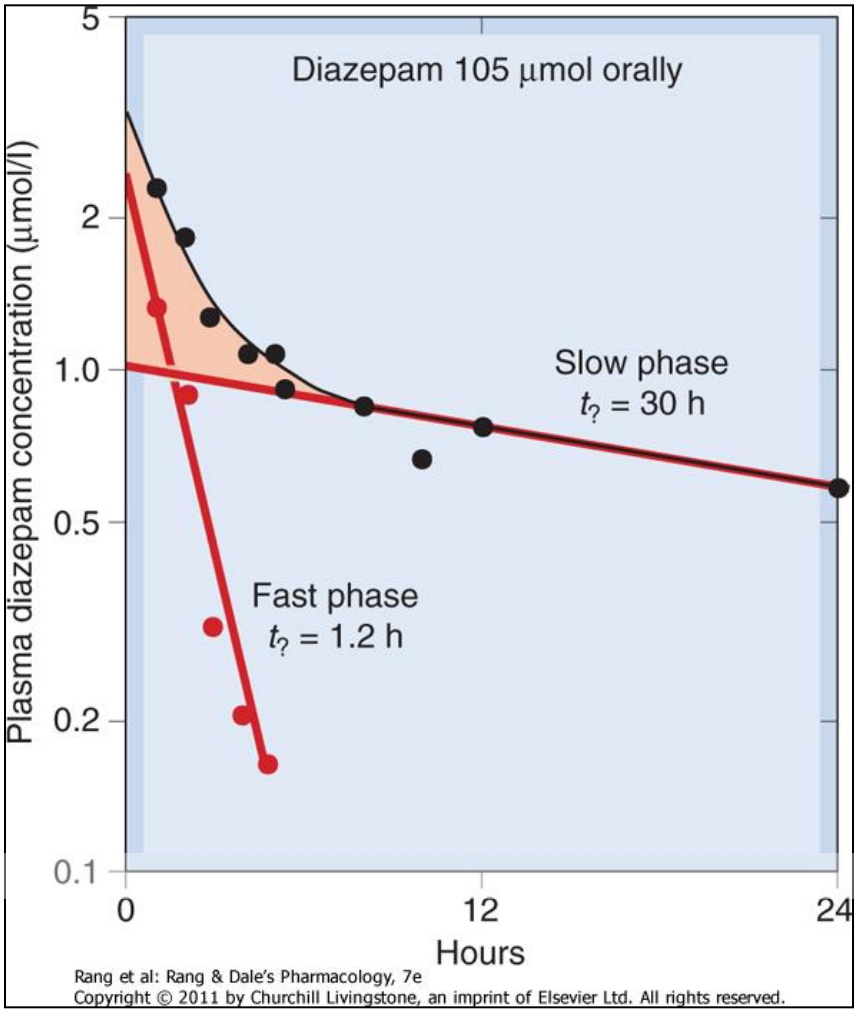


T1/2 – 17 h
VD – 20 l

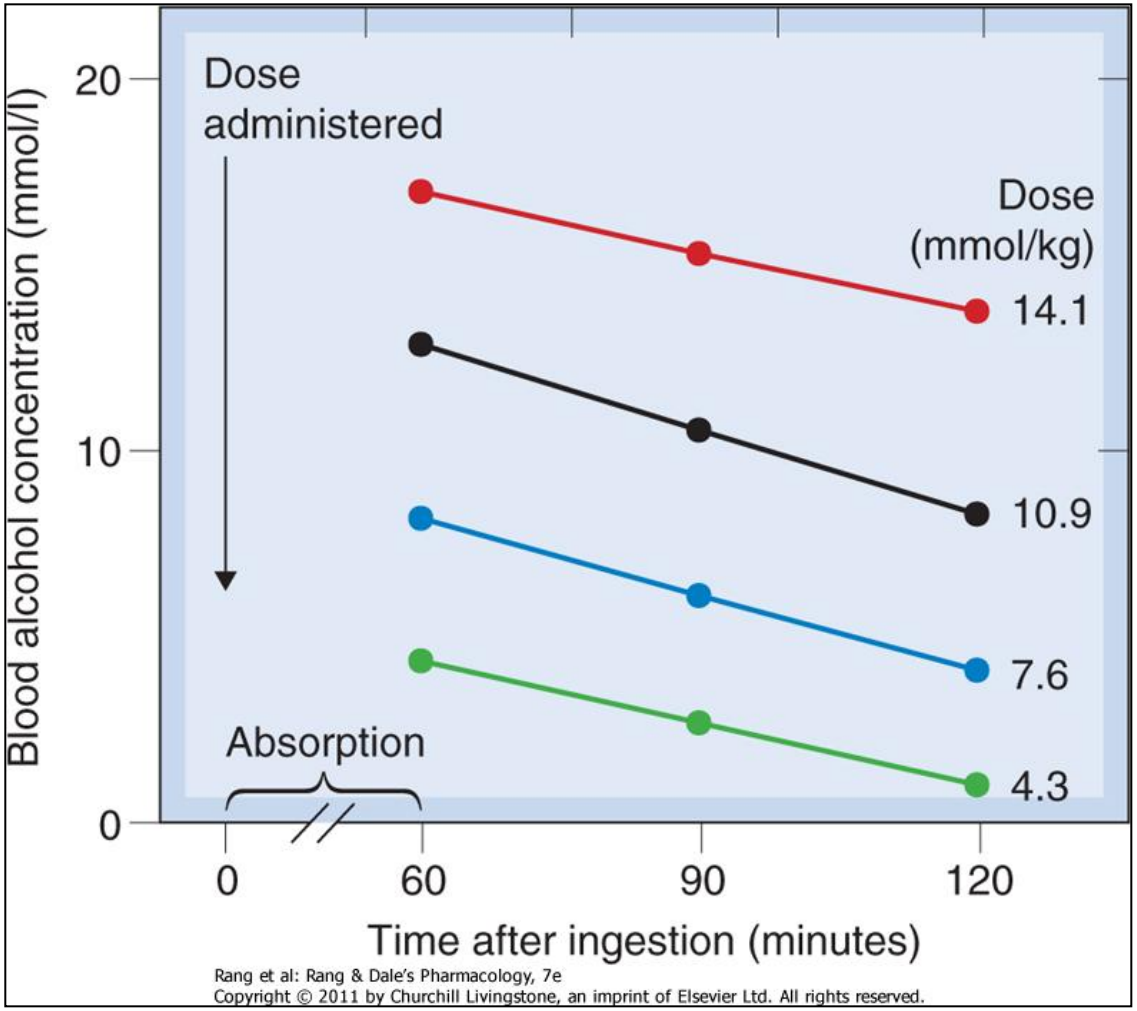
Two-compartment pharmacokinetic model



Two-compartment pharmacokinetic model – kinetics of diazepam elimination in humans following a single oral dose



Saturating kinetics of alcohol elimination in humans



Comparison of non-saturating and saturating kinetics for drugs given orally every 12 h.