USMLE REVIEW SERIES IN PHARMACOLOGY

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General Pharmacologic Principles

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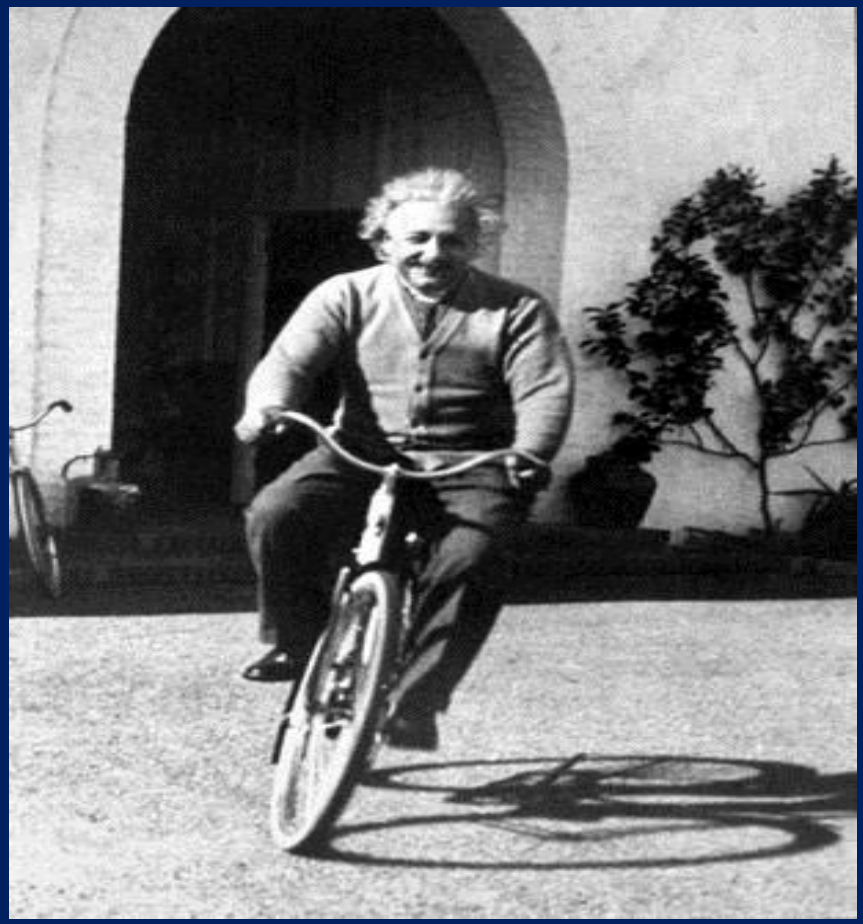
Albert Einstein

- Life is like riding a bicycle. To keep your balance, you must keep moving.



In Santa Barbra, 1933

Biomedical Sciences "A CHESS GAME APPROACH"

General Principles In Pharmacology Objectives

- State in words what is meant by the terms,

  Pharmacology, Pharmacodynamics

  Pharmacokinetics, Pharmaceutics,

  Pharmacotherapeutics and Pharmacognosy

- Define the term pK_a both mathematically and in words.

- Write the Henderson-Hasselbalch equation.

Objectives(Cont'd)

- Demonstrate how the Henderson-Hasselbalch equation shows how the state of ionization of a group on a molecule will vary with pH.
- Distinguish the term pharmacokinetics from pharmacodynamics.
- Identify the processes comprising the acronym ADME and classify those processes as relating to pharmacokinetics pharmacodynamics.

General Principles In Pharmacology Objectives(Cont'd)

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- State the overall objective of drug biotransformation.
- Identify the primary location of drug biotransformation and define the term first pass effect.
- Describe the role of cytochrome P450 enzymes in drug biotransformation.
- Explain enzyme induction and enzyme inhibition and how these processes may affect plasma levels of a drug.
- Explain how biotransformation can lead to toxic and active metabolites.

Objectives(Cont'd)

- Distinguish between Phase I and Phase II biotransformation reactions.
- Identify the various types of Phase I biotransformation reactions and their common purpose.
- Identify the molecules or groups involved in Phase II biotransformation reactions.

General Principles In Pharmacology Objectives

- 5
  - ➢

- Define the term ‘prodrug’ and give examples of prodrug use to meet different goals.

- Explain the differing effects of metabolism on drugs and prodrugs in cases where metabolizing enzymes are induced or inhibited.

Objectives(Cont'd)

- Describe distinguishing characteristics of agonists, partial agonists,

  and antagonists.

- Define the terms affinity, efficacy and selectivity in the context of drug-receptor interactions.

- Distinguish reversible and irreversible inhibition based on analysis of graphs.

Pharmacologic Principles

Drug

- Any chemical that affects the processes of a living organism

Pharmacology

- The study or science of drugs

Pharmacologic Principles

- Pharmacokinetics
- Pharmacodynamics
- Pharmaceutics
- Pharmacotherapeutics
- Pharmacognosy

Pharmacologic Principles

Pharmacodynamics

- The study of what the drug does to the body:
  - The mechanism of drug actions in living tissues

Pharmacologic Principles

Pharmaceutics

- The study of how various drug forms influence pharmacokinetic and pharmacodynamic activities

Pharmacologic Principles

Pharmacotherapeutics

- The use of drugs and the clinical indications for drugs to prevent and treat diseases

Pharmacologic Principles

Pharmacognosy

- The study of natural (plant and animal) drug sources

Pharmacokinetics vs. Pharmacodynamics(Con'd)

- Pharmacodynamics
- Action of the chemical on the body ("What the drug does to the body")

- Process: Biological ligands acting on their molecular targets in the body.

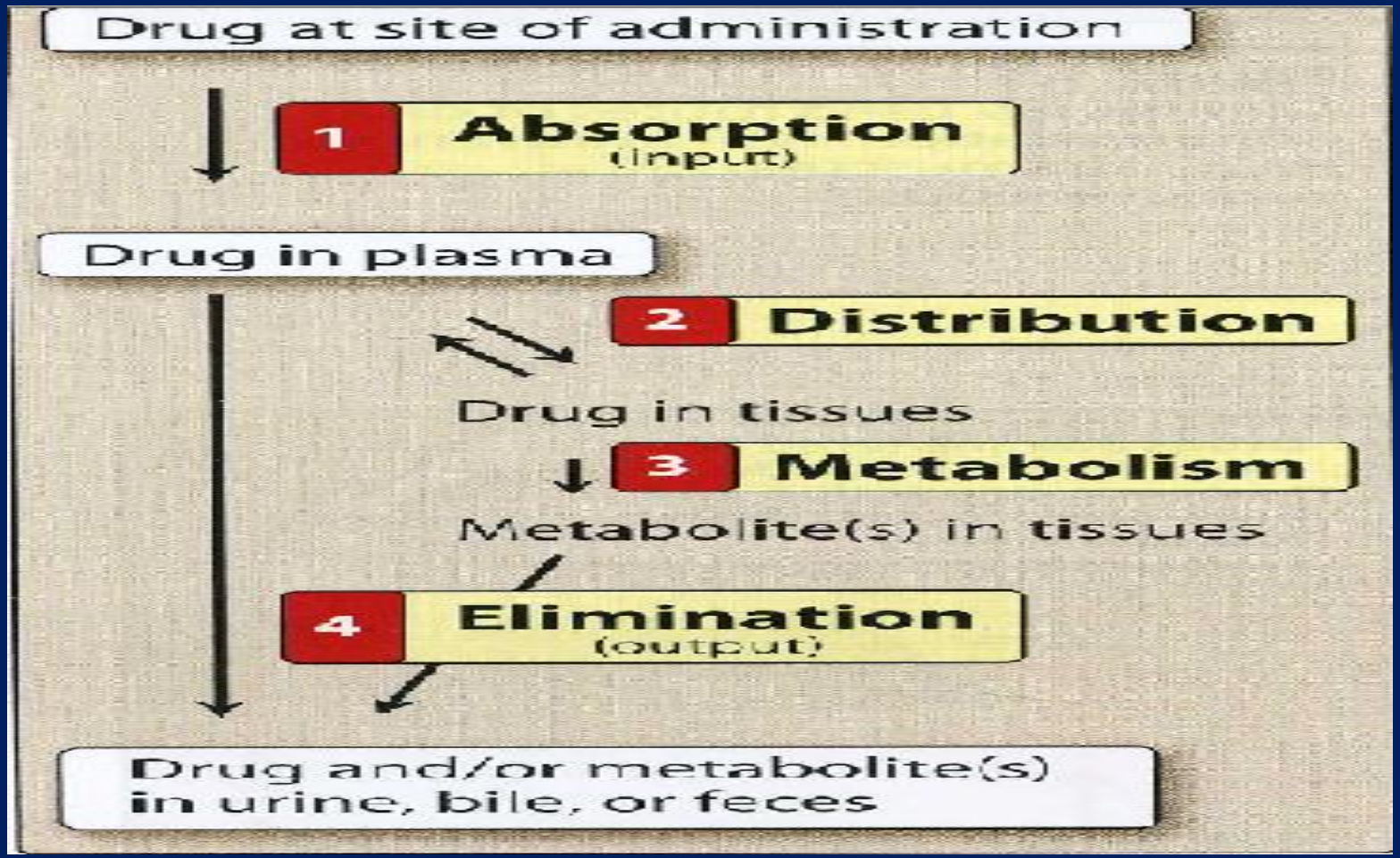
- ***Output: Biological response***

Pharmacologic Principles

Pharmacokinetics

- The study of what the body does to the drug:
  - Absorption
  - Distribution
  - Metabolism
  - Excretion

Pharmacokinetics



Schematic representation of absorption, distribution, metabolism and elimination

Lippinicott's Illustrated Reviewes in Pharmacology, 2006

Pharmacokinetics (cont'd)

Biotransformation and Elimination of Drugs(Cont'd)

- The major objective of drug biotransformation reactions in the body is **to make nonpolar drugs more polar** so that they may be more readily excreted.

Pharmacokinetics (cont'd)
ADME (Absorption, Distribution, Metabolism, Excretion)

- Majority of drugs exert their effects (*pharmacodynamics*) via interaction with specific receptor molecules within the body. However, prior to gaining access to these targets the drug must:

- Pass thru barriers (membranes)

- Avoid alternate sites of attachment and storage

- Avoid metabolic destruction prior to reaching site of action
- Be chemically stable at various pH levels

- All 4 of these barriers will affect a drug's *pharmacokinetics.*

Pharmacokinetics (cont'd)

- When the drug reaches the desired site of action (enabling a *pharmacodynamic* response):

- Drug + Receptor → Drug receptor complex

Pharmacological response

Pharmacokinetics (cont'd)

Biotransformation and Elimination of Drugs

- There are two primary ways in which drugs are eliminated from the body:

➢ They may be excreted in the urine or feces (i.e., excreted unchanged); or

➢ They may be metabolized or biotransformed and then excreted. (in some cases, drugs may be eliminated in other ways such as through respiration or through sweating, but these methods are decidedly in the minority).

Pharmacokinetics (cont'd)

Biotransformation and Elimination of Drugs(Cont'd)

- Drugs are biotransformed prior to excretion primarily because they are not polar enough to be excreted in the urine or feces.

- The major objective of drug biotransformation reactions in the body is to make nonpolar drugs more polar so that they may be more readily excreted.

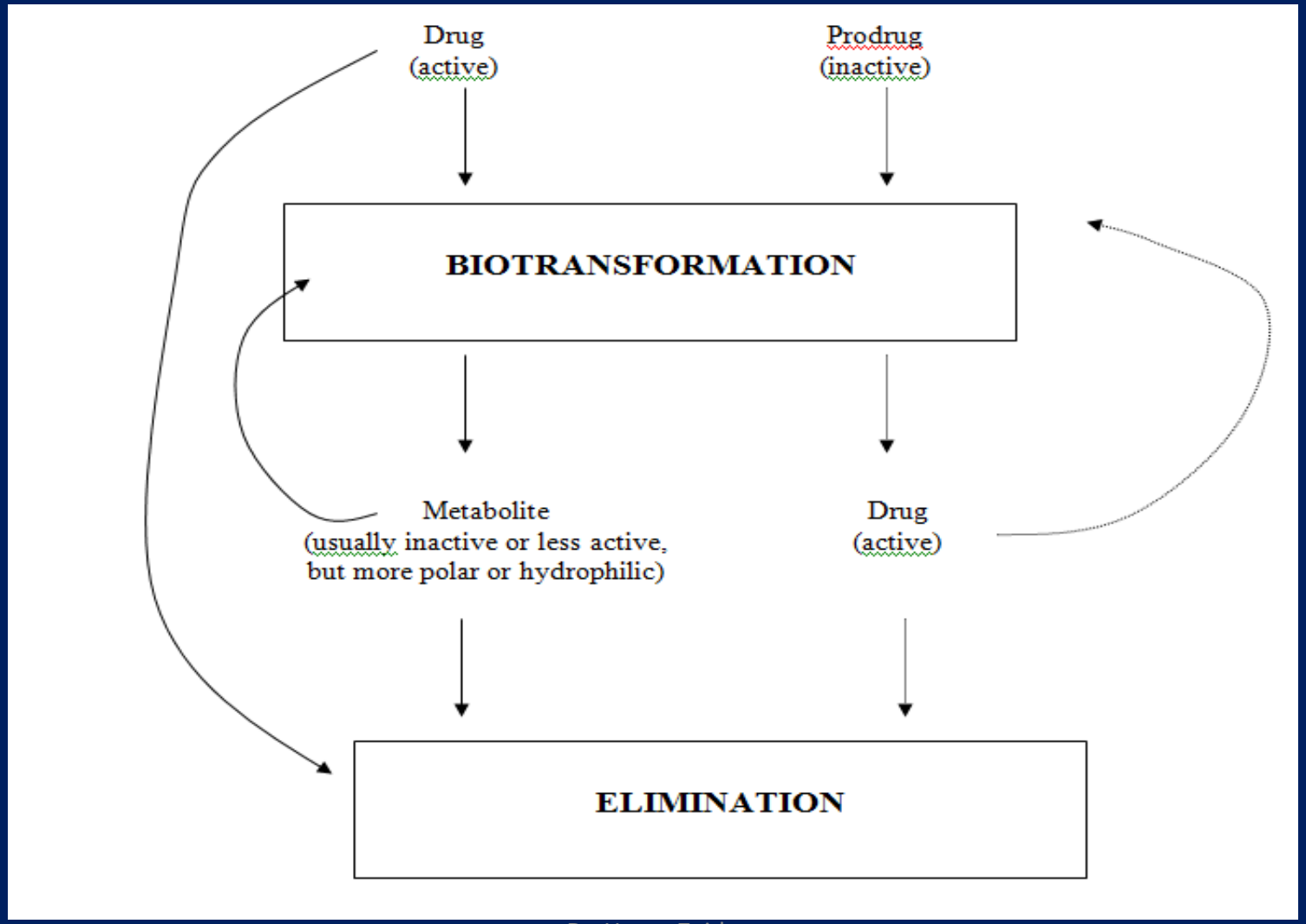
Pharmacokinetics (cont'd)

Biotransformation and Elimination of Drugs(Cont'd)

- Biotransformation results not only in making a drug more soluble for excretion, but also often produces a metabolite that is no longer capable of producing a therapeutic response.
- In some cases, however, the drug itself is inactive and the process of biotransformation results in the active compound.

Pharmacokinetics (cont'd)

Biotransformation and Elimination of Drugs(Cont'd)



Pharmacokinetics (cont'd)

Biotransformation and Elimination of Drugs(Cont'd)

- **Prodrugs**
-
- A "Pro"drug is an inactive compound that is administered and then transformed into an active substance by either chemical or metabolic means
- Prodrugs are designed to take advantage of absorption or metabolic properties to provide more optimal drug therapy.

Pharmacokinetics (cont'd)
Biotransformation and Elimination of Drugs(Cont'd)

- Prodrugs can be activated in various places (e.g. stomach, intestine, liver, blood, inside cells) and in various ways (cleavage of groups, biotransformation, addition of phosphates)

Pharmacokinetics (cont'd)

Biotransformation and Elimination of Drugs(Cont'd)

- In this case, the drug acts as a prodrug and must be biotransformed in order to have a therapeutic response.

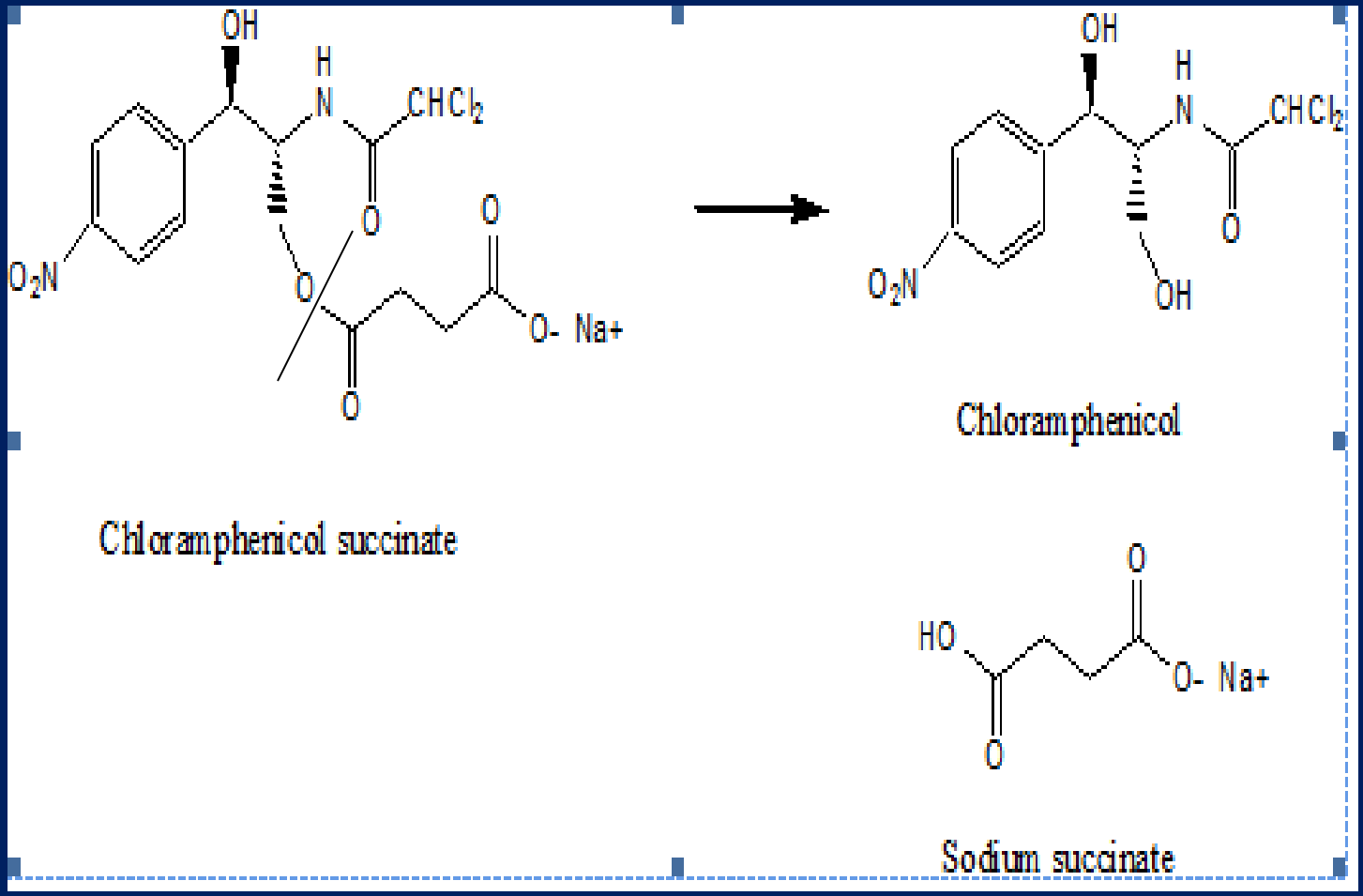
Biotransformation and Elimination of Drugs(Cont'd)

Prodrugs(Cont'd)

- **Examples of Prodrugs**

- Chloramphenicol succinate – esterified form is more soluble and can be administered IV – esterases in blood release active form (i.e. chloramphenicol itself)
-

Examples of Prodrugs Chloramphenicol succinate(Cont'd)



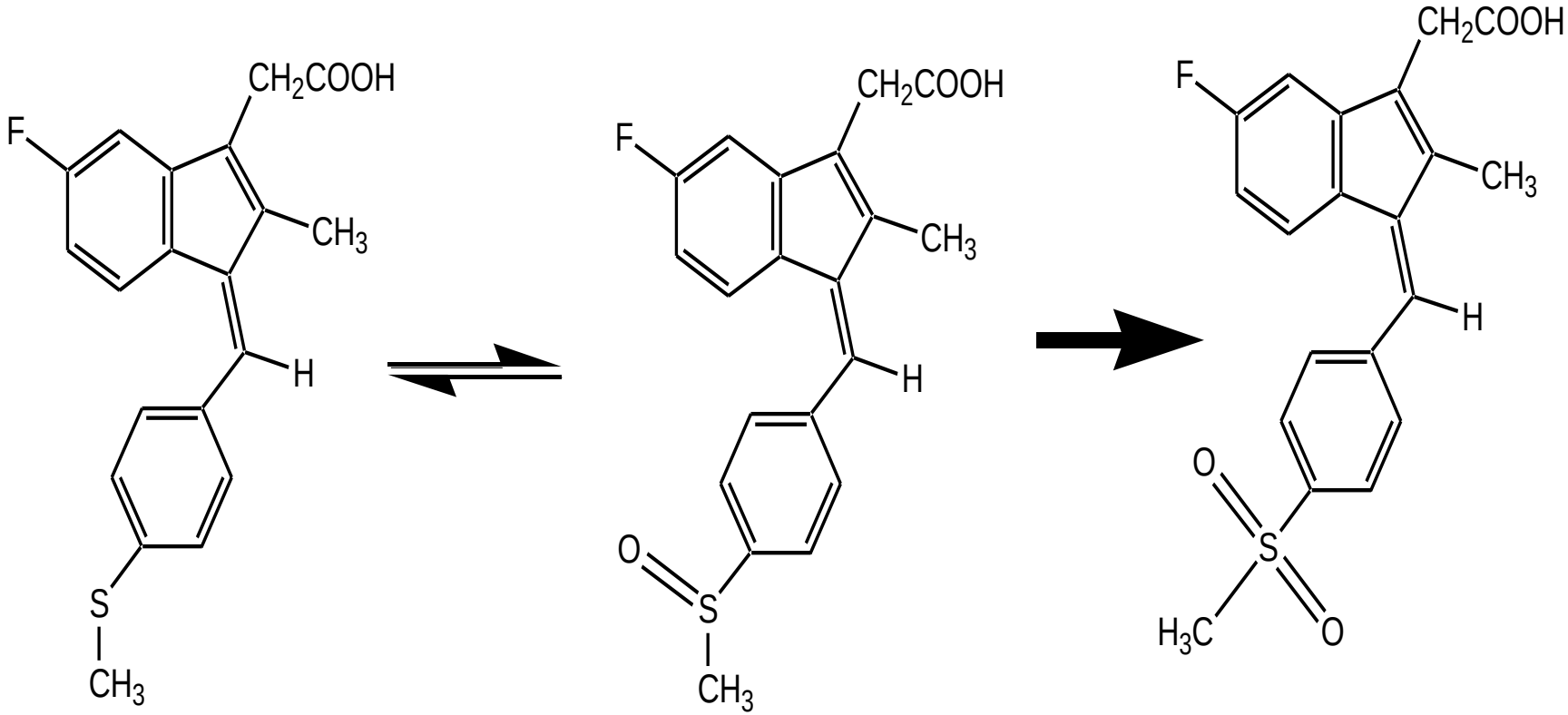
Biotransformation and Elimination of Drugs(Cont'd)

Examples of Prodrugs (Cont'd)

- Sulindac – (A drug that have anti-inflammatory and analgesic activity) in its active form (sulfide) causes significant GI irritation when administered orally . If the suldinac in its inactive form is absorbed from the GI tract and reduced by enzymes in the liver, the active form will be available only after absorption thus by passing the GI tract and reducing GI distress.

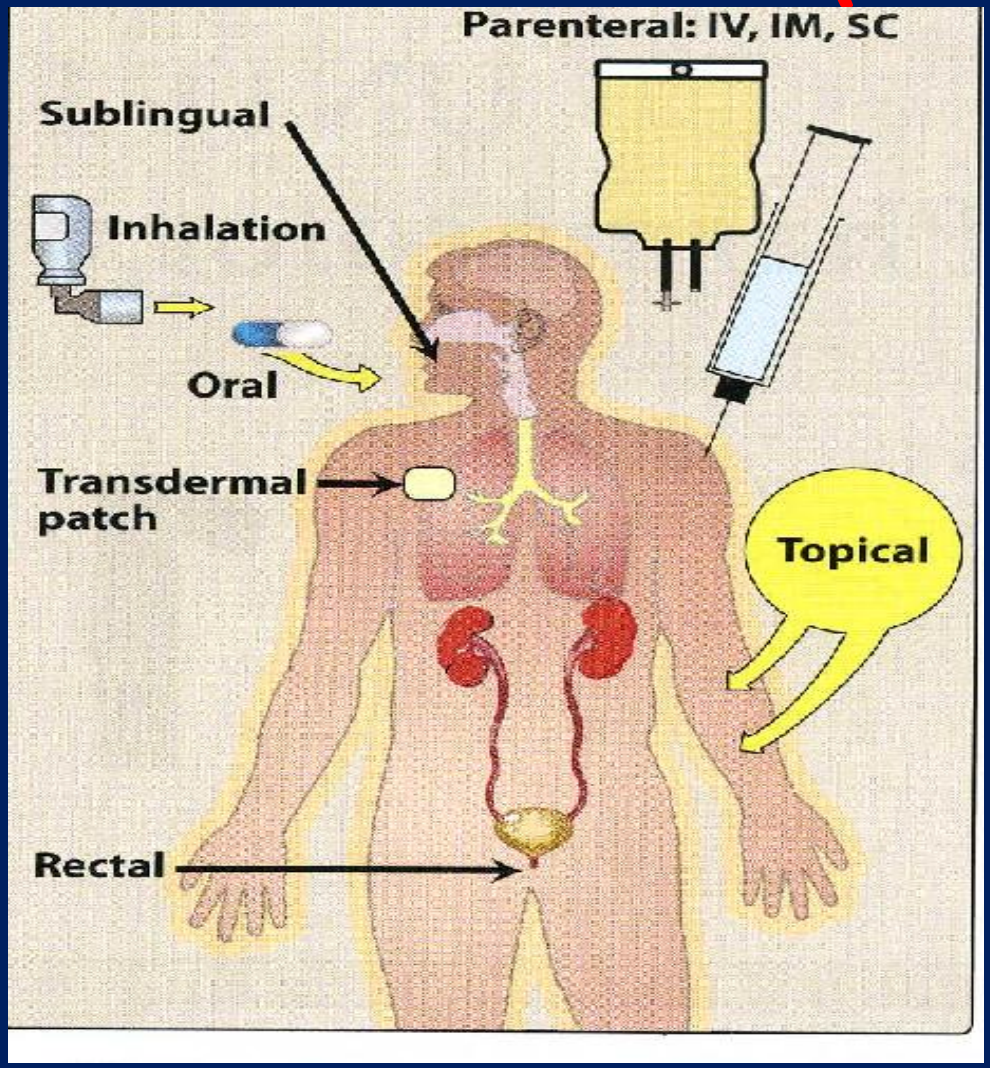
Biotransformation and Elimination of Drugs(Cont'd)

Examples of Prodrugs (Cont'd)



Sulfide (active) Sulindac (inactive) Sulfone (inactive)

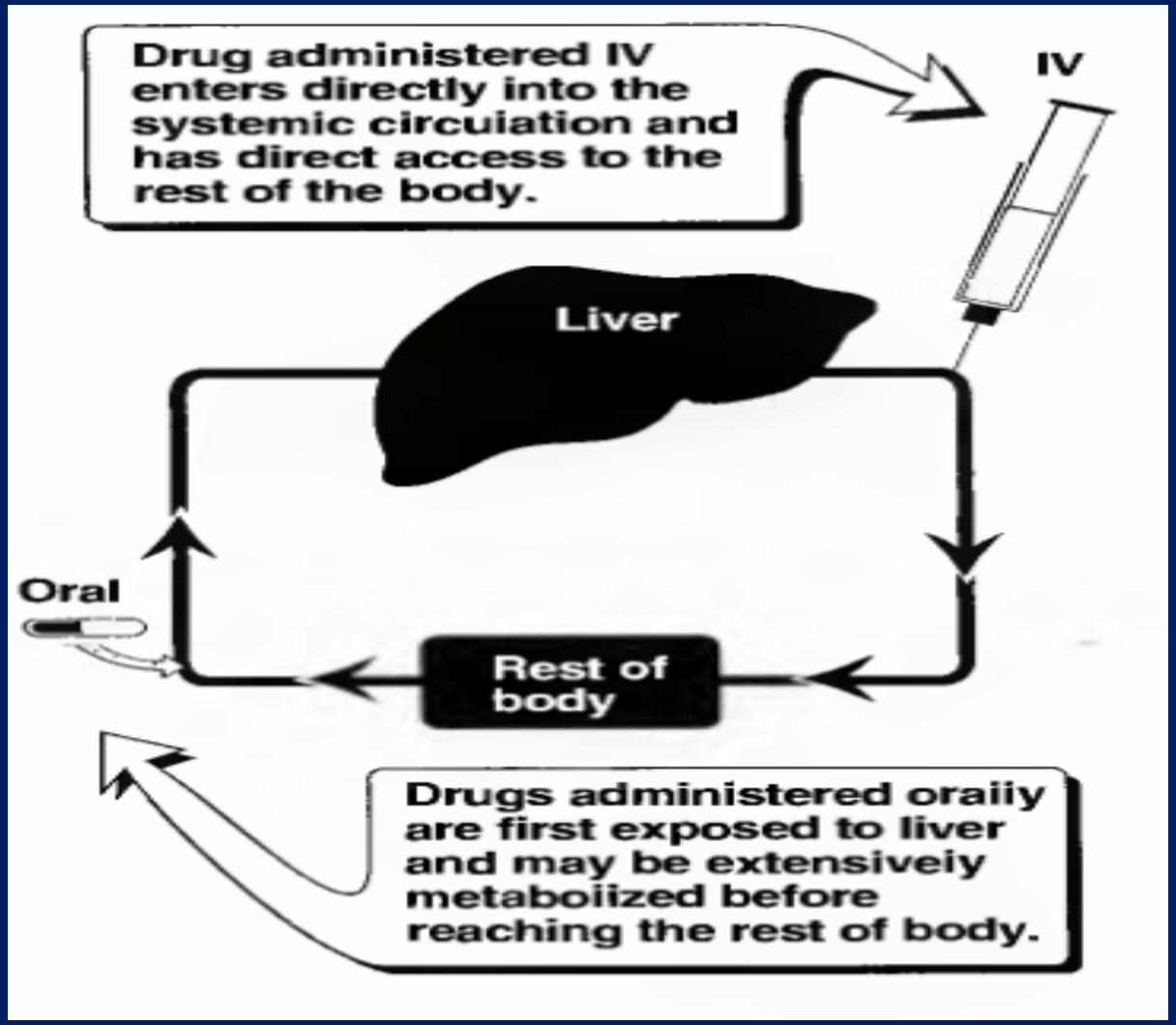
Pharmacokinetics (cont'd)



Routes of drug administration

Lippincott's Illustrated Reviewes in Pharmacology, 2008

Pharmacokinetics (cont'd)

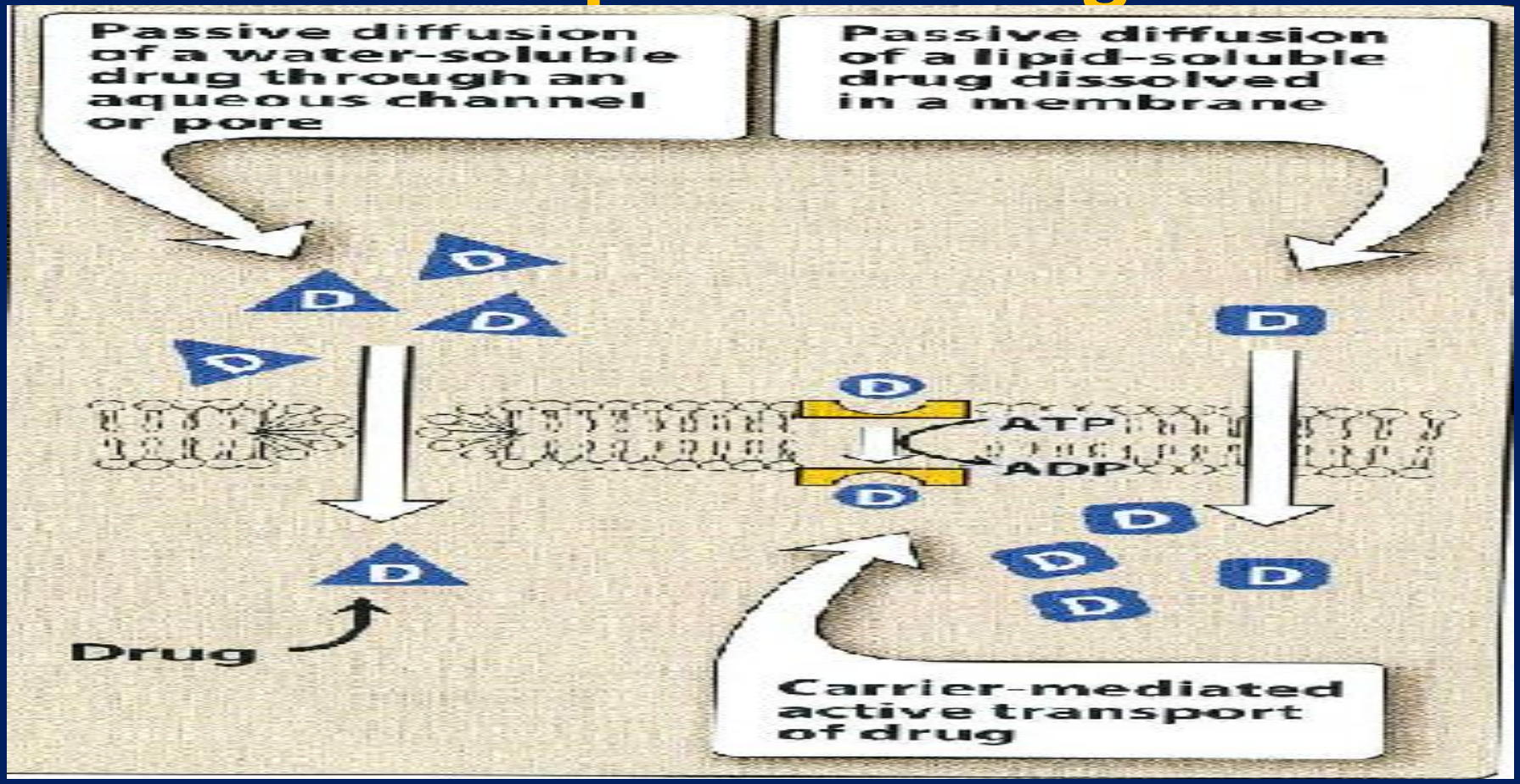


First-pass mechanism can occur with orally administered drugs

Reproduced from Lippicott's, 2007

Pharmacokinetics (cont'd)

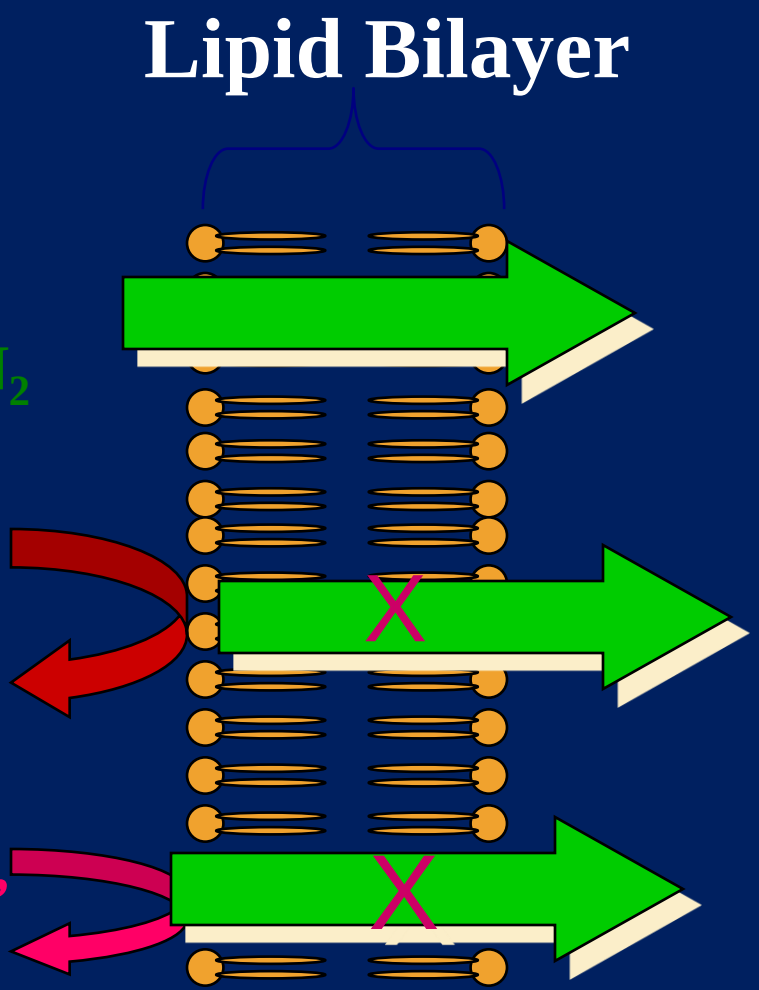
Absorption of Drugs



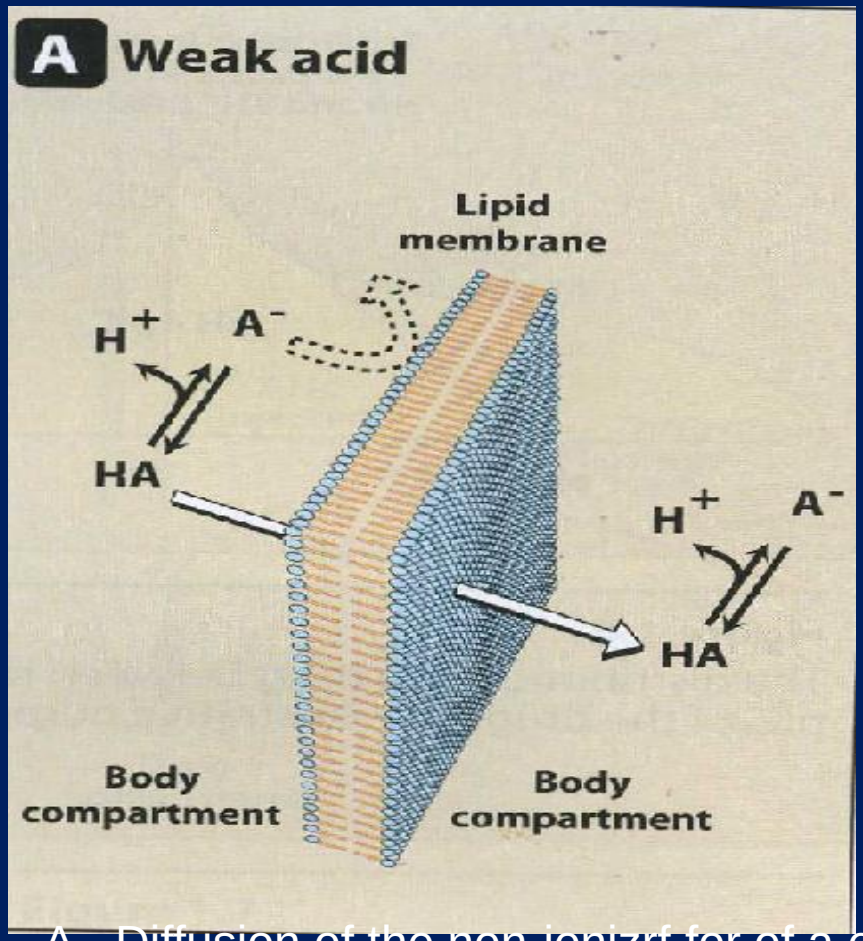
Schematic representation of drugs crossing a cell memebrane of an epithelial cell of GI

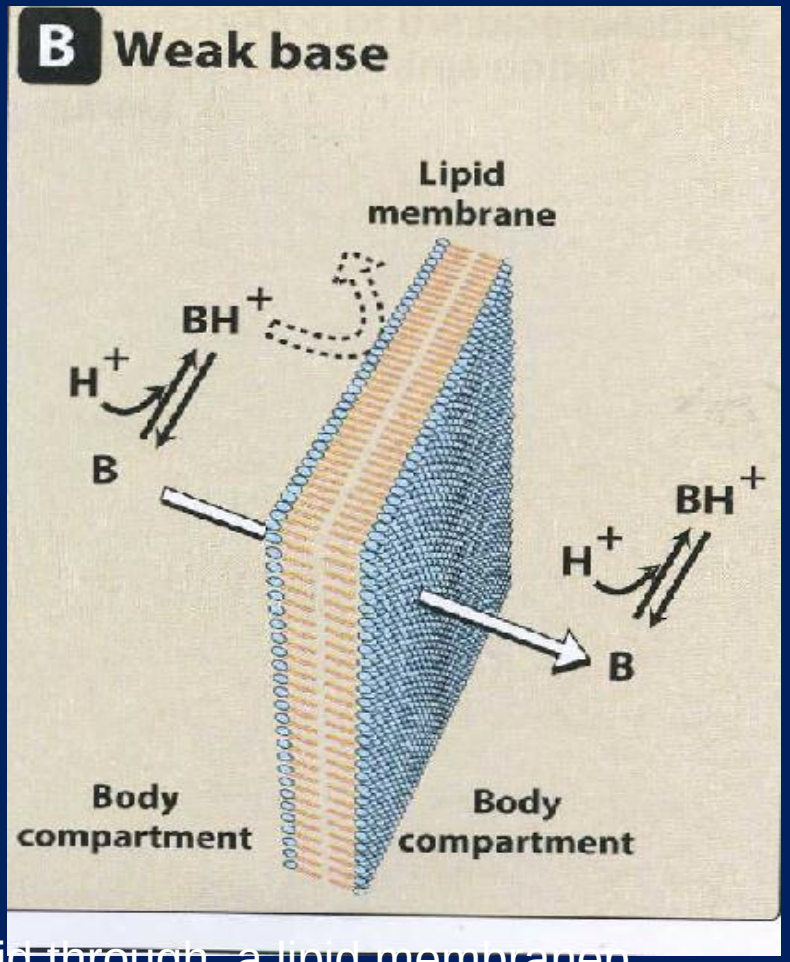
Lippincott's Illustrated Reviewes in Pharmacology, 2008

Membranes and Absorption



Pharmacokinetics (cont'd)Absorption of Drugs



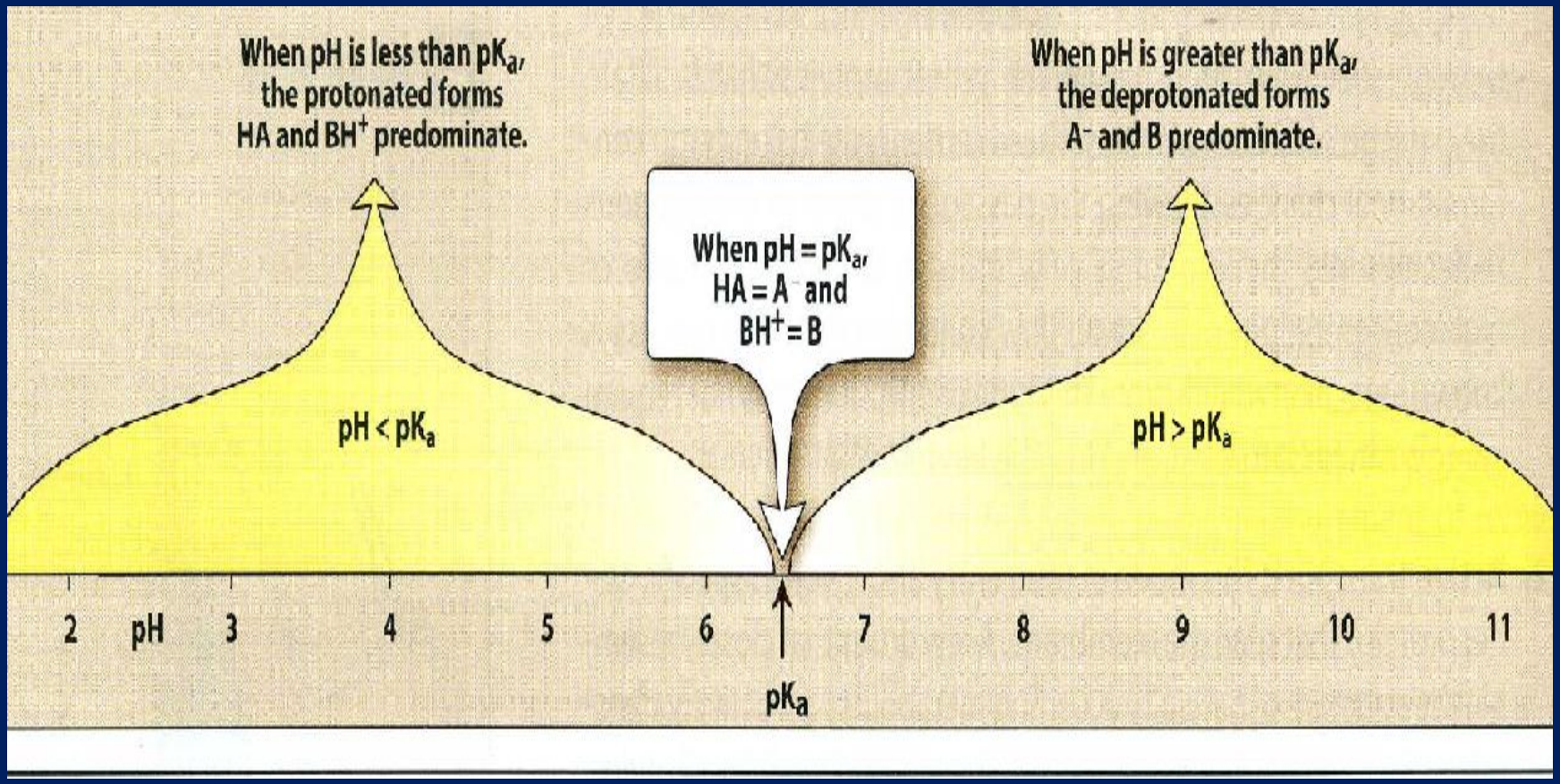


A. Diffusion of the non-ionizrf for of a eak acid through a lipid membranep,
B. Diffusion of the non Ionized form of a weak base through a lipid membrane

Lipicott's Illustrated Reviews in Pharmacology

Pharmacokinetics (cont'd)

Distribution of Drugs



The distribution of a drug between its ionized and non-ionized forms, pKa value for the drug is 6.5

Lippincott's Illustrated Reviews in Pharmacology

Factors Affecting Absorption

- Absorbing surface
- Blood flow
- pH
- Disease states
- Interactions with food, other drugs
- Drug pka
- Concentration
- Contact time at the absorption surface

Factors Affecting Absorption(Cont'd)

Determination of how much drug will be found on either side of a membrane: The relationship of pK_a and the ratio of acid-base concentrations to pH is expressed by the Henderson-Hasselbalch equation[3]:

$$pH = pK_a + \log \frac{[\text{non-protonated species}]}{[\text{protonated species}]}$$

For acids: $$pH = pK_a + \log \frac{[A^-]}{[HA]}$$

For bases: $$pH = pK_a + \log \frac{[B]}{[BH^+]}$$

Reproduced from Lippicott's, 2008

How much drug will be found on either side of the membrane?

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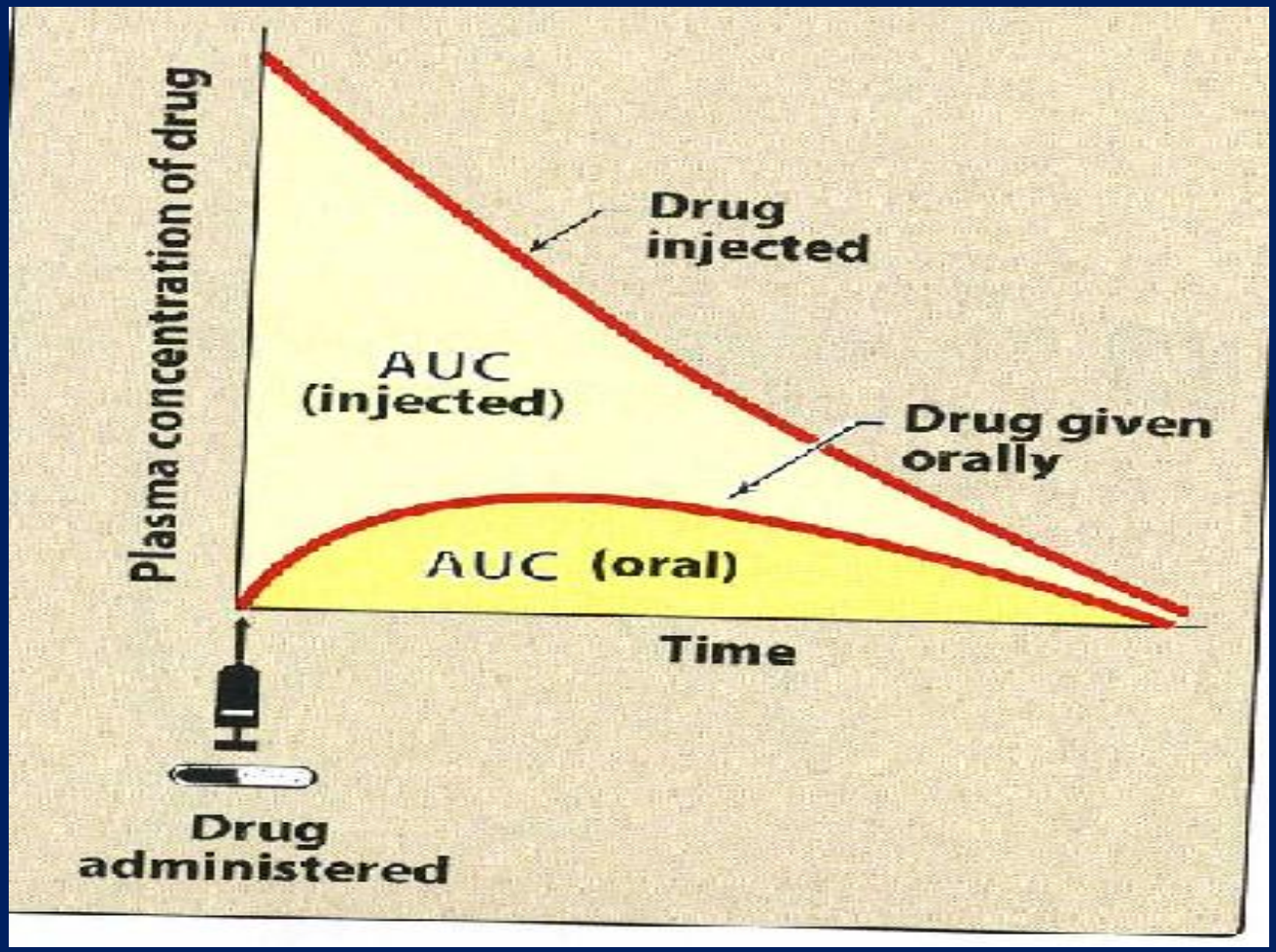
For bases: $$pH = pK_a + \log \frac{[B]}{[BH^+]}$$

Pharmacokinetics (cont'd)

Determination of Bioavailabilty of a drug



Distribution

- Rate of perfusion
- Plasma protein (albumin) binding
- Accumulation in tissues
- Ability to cross membranes
  - Blood-brain barrier
  - Placental barrier

Pharmacokinetics: Distribution

The transport of a drug in the body by the bloodstream to its site of action.

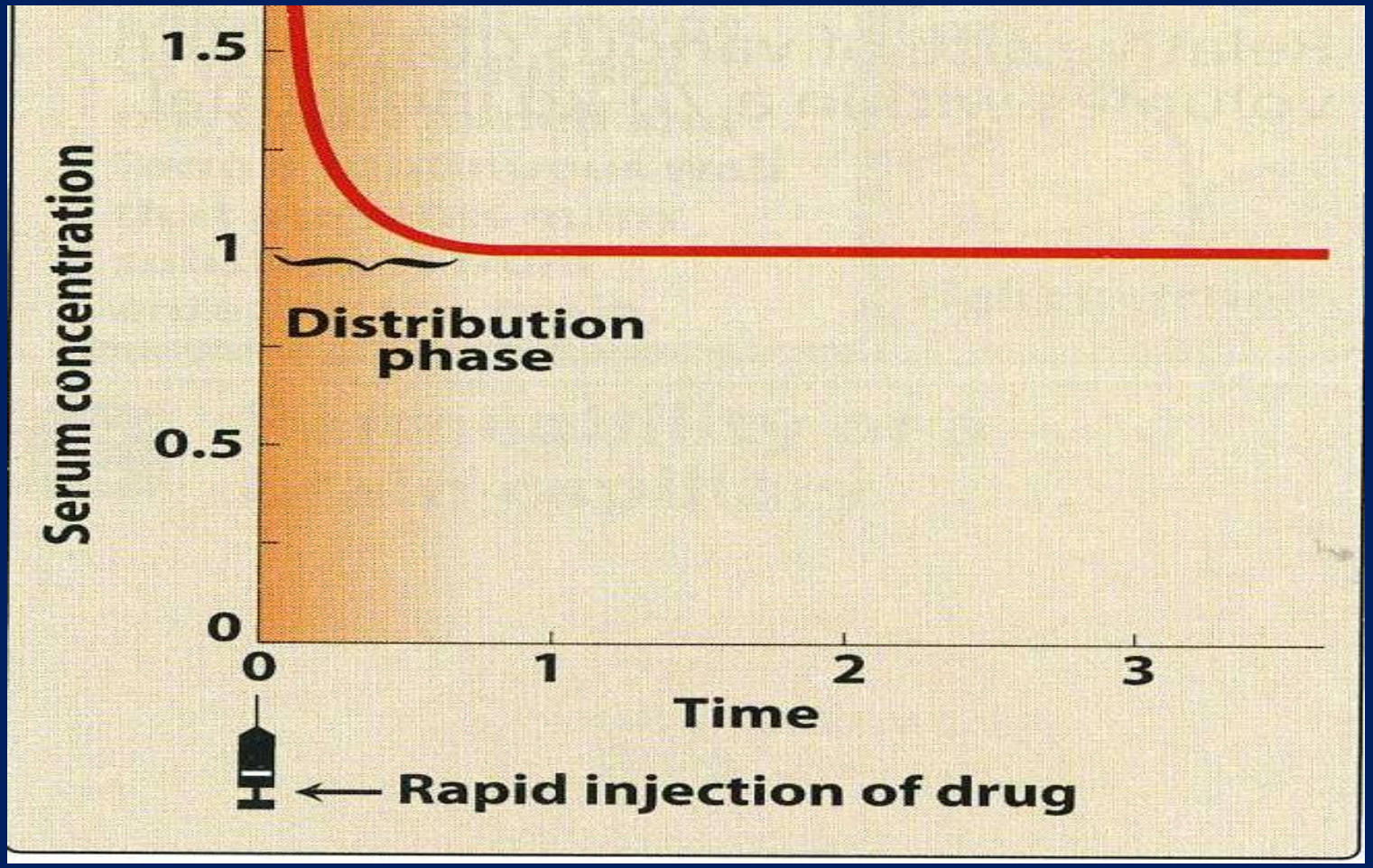
- Protein-binding
- Water soluble vs. fat soluble
- Blood-brain barrier
- Areas of rapid distribution: heart, liver, kidneys, brain
- Areas of slow distribution: muscle, skin, fat

Pharmacokinetics: Bioavailability

- The rate at which a drug leaves its site of administration, and the extent to which absorption occurs.
  - Bioavailability
  - Bioequivalent

Pharmacokinetics (cont'd)

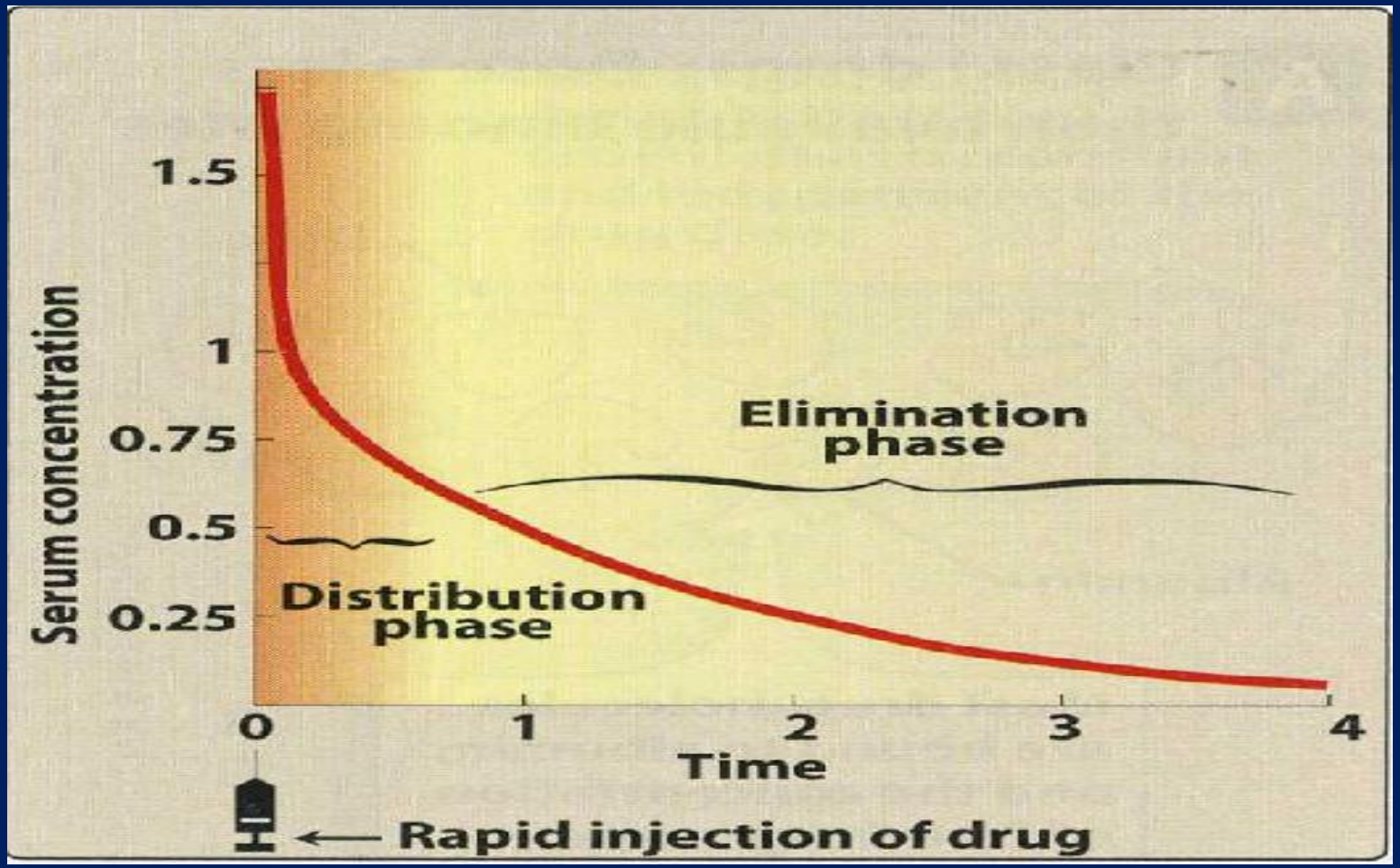
Apparent volume of distribution



Drug concentrations in serum after a single injection of drug at time =O, Assume the drud is not eliminated

Lippincott's Illustrated Reviewes in Pharmacology

Pharmacokinetics (cont'd)



Drug concentrations in serum after a single injection of drug at time =O. Assume that the drugs distributes and is eliminiate

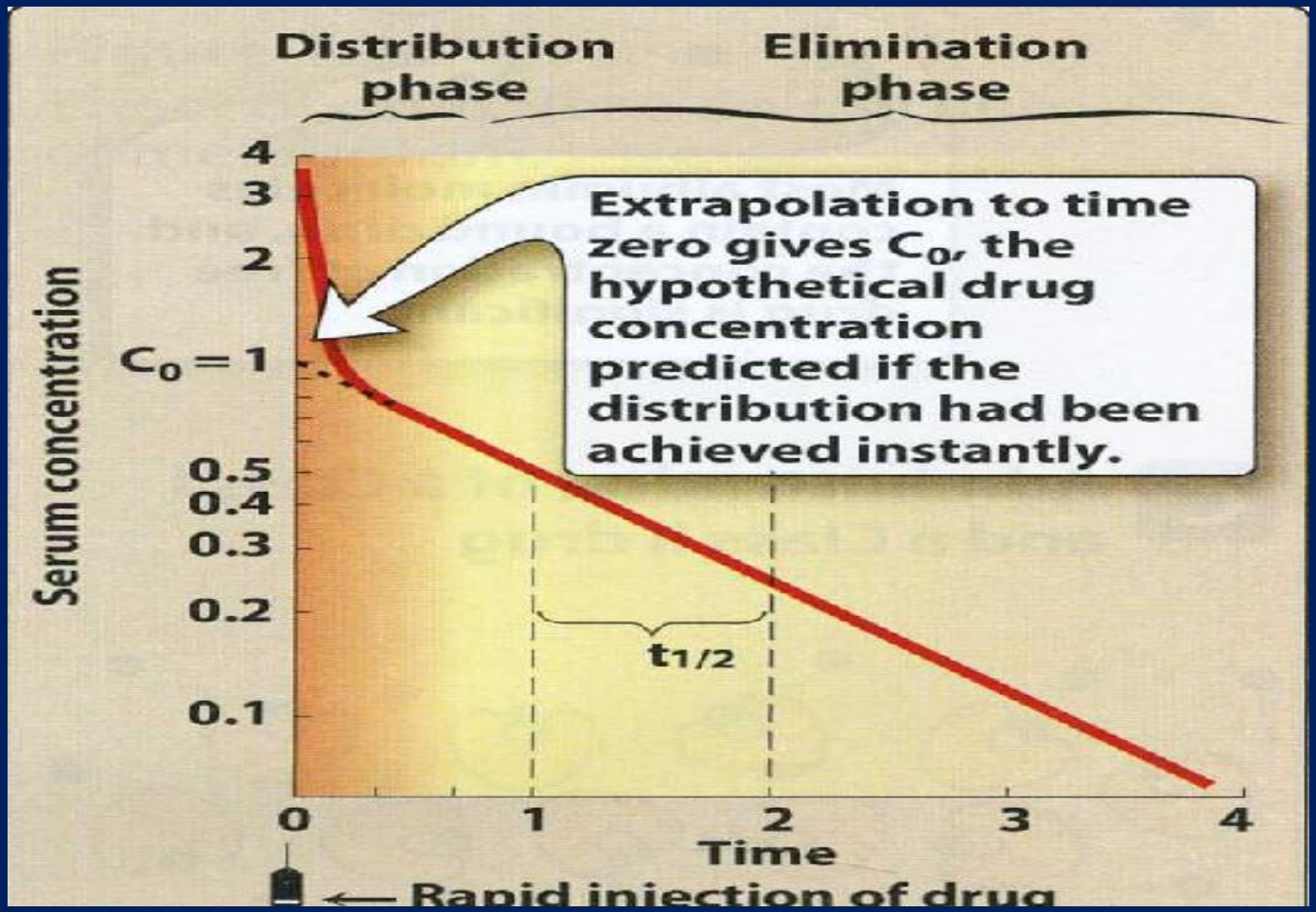
Determination of Apparent volume of distribution

$$C = D/V_d \quad \text{or} \quad V_d = D/C$$

C = Plasma concentration of drug
D = Total amount of drug in the body

Reproduced from Lippicott's, 2007

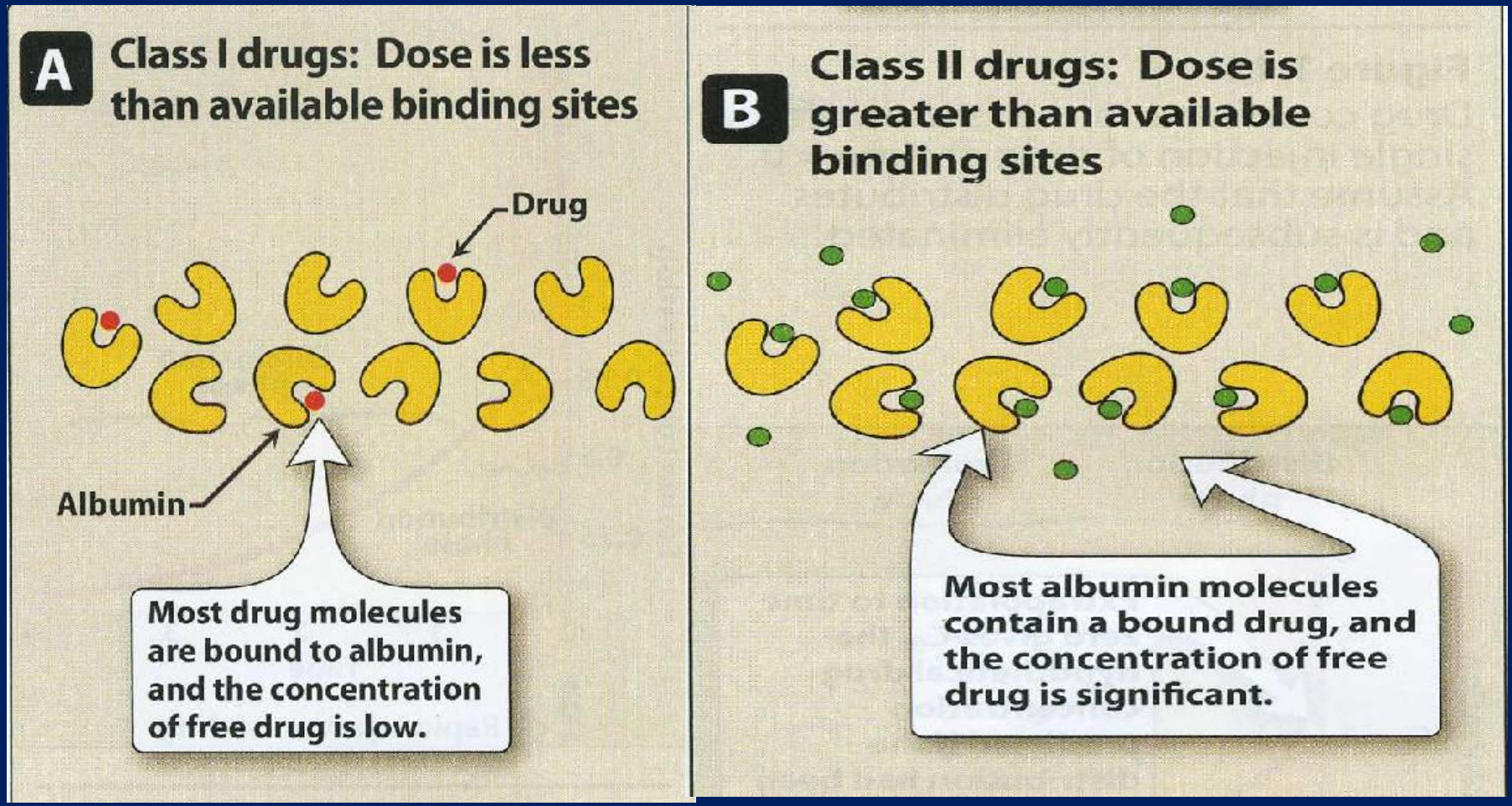
Pharmacokinetics (cont'd)



Drug concentrations in serum after a single injection of drug at time =O.

Reproduced from Lippicott's, 2007

Pharmacokinetics (cont'd)
Binding Drugs to Plasma proteins



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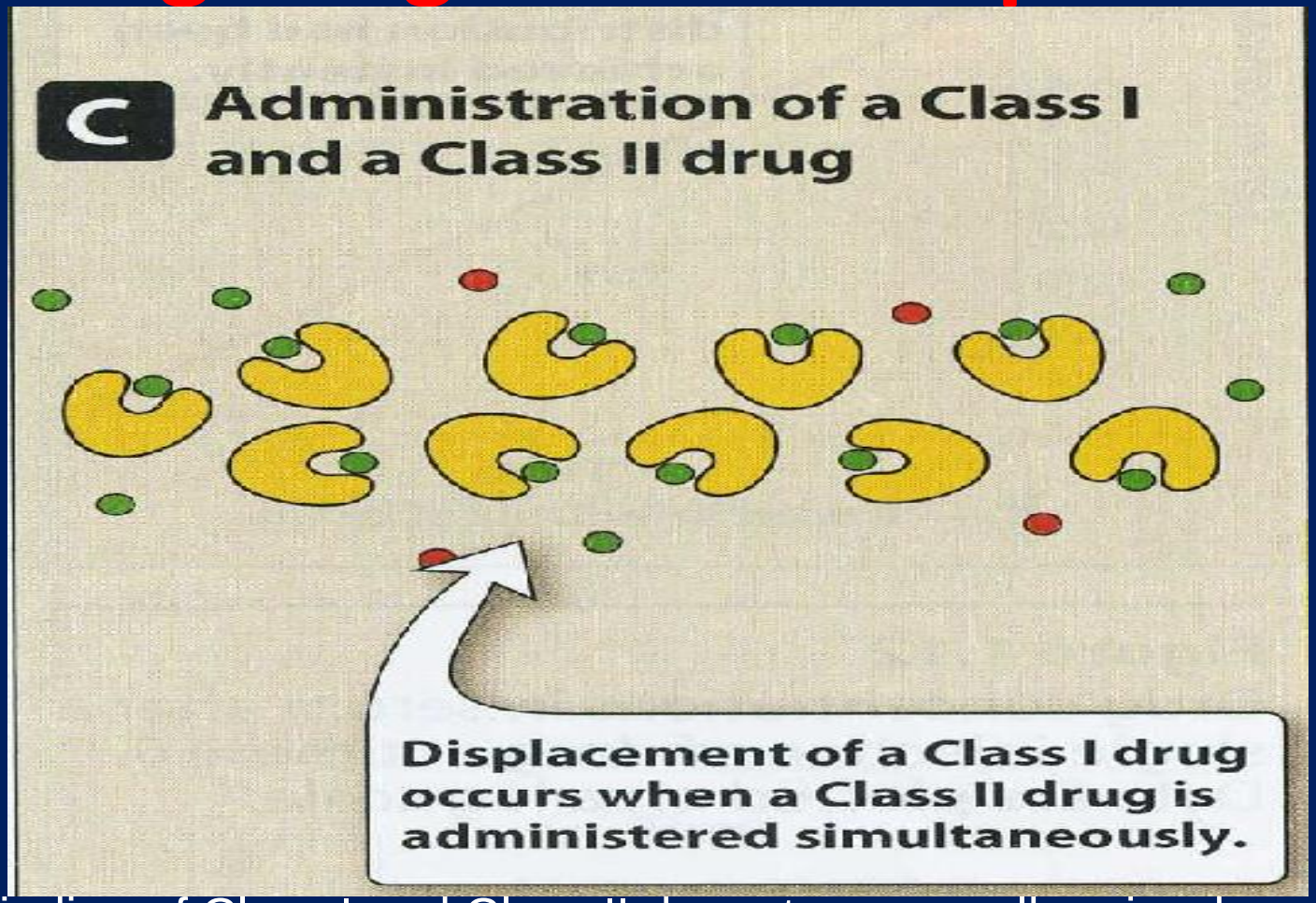
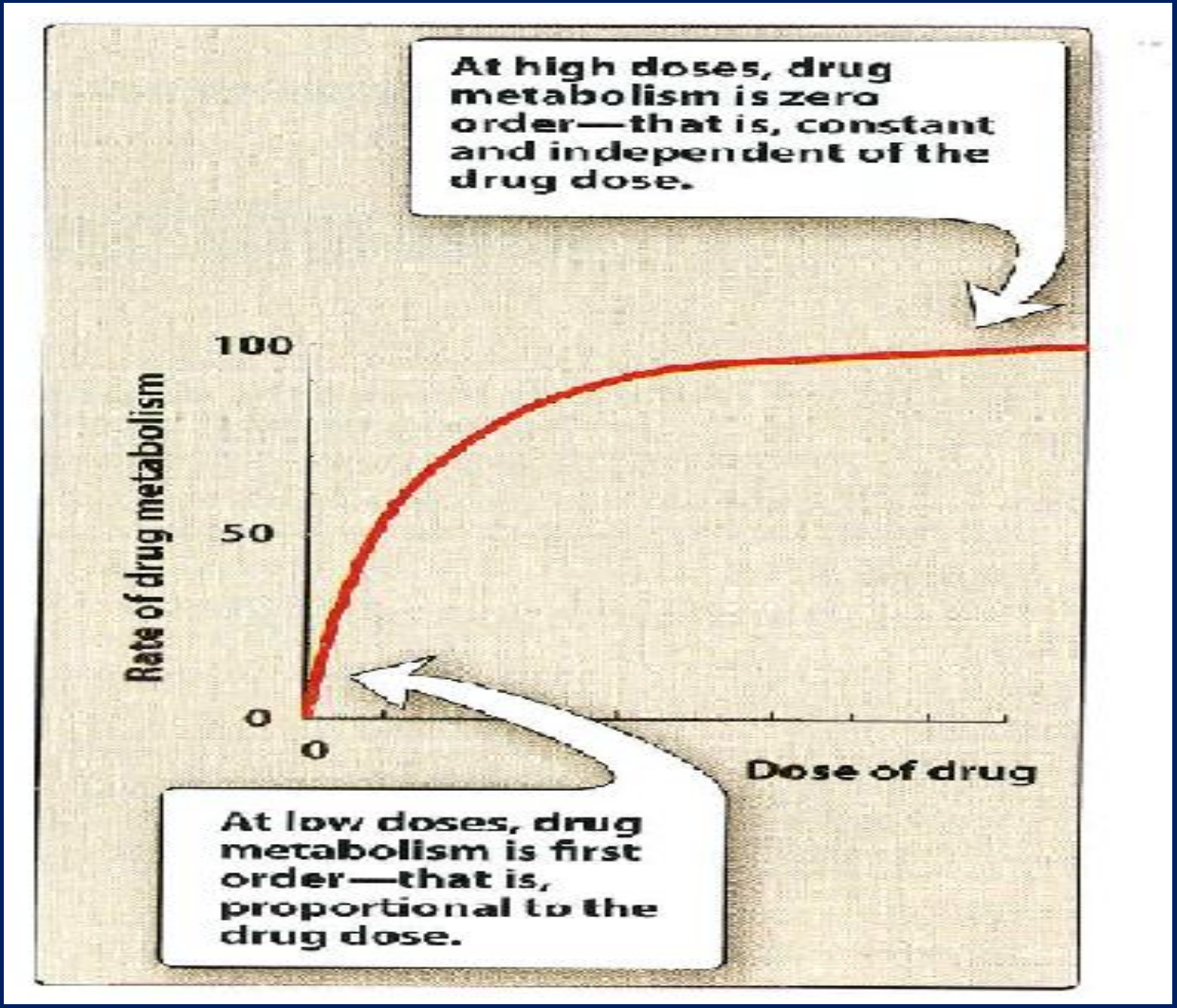
Pharmacokinetics (cont'd)
Binding Drugs to Plasma proteuns



Binding of Class I and Class II drugs to serum albumin when drugs are administered alone or together

Drug Metabolism

Pharmacokinetics (cont'd)
Effect of drug dose on the rate of Metabolism



Pharmacokinetics (cont'd)

Reactions of Drug Metabolism

Phase I

Phase I reactions function to convert lipophilic molecules into more

polar by introducing or unmasking polar functional group such as –OH, or,-NH_2

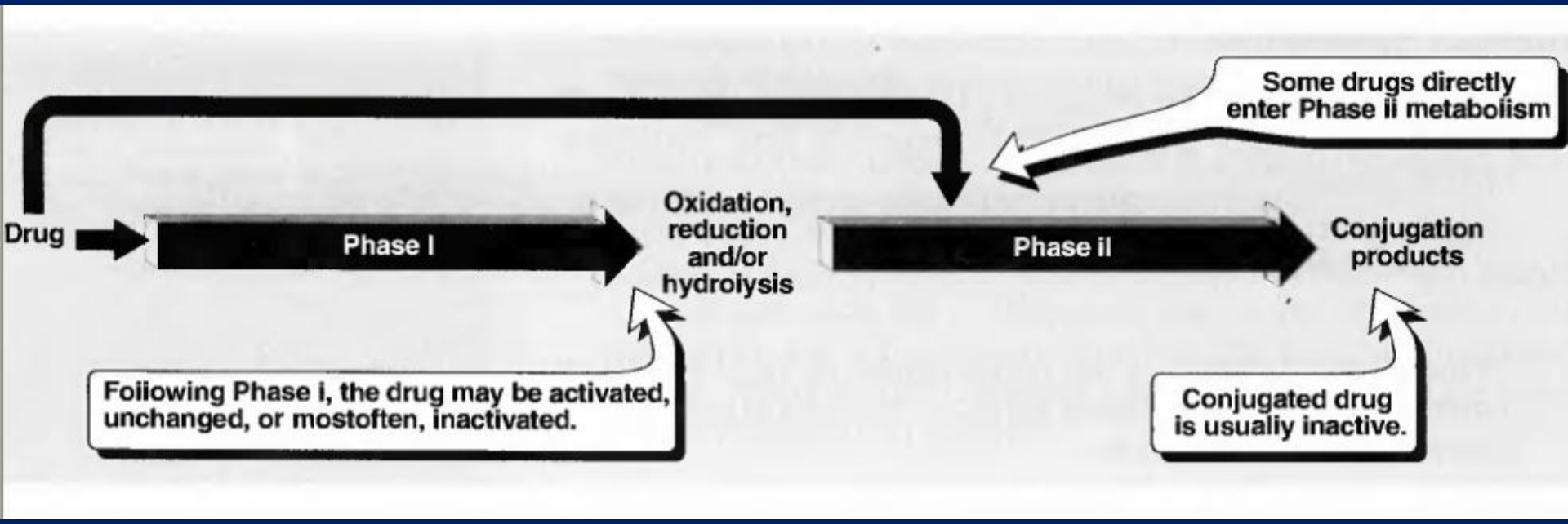
Phase I metabolism may increase, decrease, or leave unaltered

the drug's pharmacologic action.

Phase II

This phase consists of conjugation reactions

Pharmacokinetics (cont'd)



The biotransformation of drugs

Reproduced from Lippicott's, 2007

Metabolism (Biotransformation)

- Two effects
  - Transformation of drugs to less, or more active metabolite
  - Alteration of solubility
- Liver = primary site
- Liver disease
  - Slows metabolism
  - Prolongs effects

Cytochrome P_{450} Monooxygenase System

- The cytochrome P_{450} enzymes are heme-

  containing membrane proteins that are capable of catalyzing

  the following types of reactions:
-
- Aromatic and aliphatic hydroxylations
- N-, O-, and S- dealkylations
- N-oxidation
- Sulfoxidation
- N-hydroxylation
- Deamination

Pharmacokinetics (cont'd)

Isozyme: CYP2C9/10

COMMON SUBSTRATES	INDUCERS
Warfarin Phenytoin ibuprofen Toibutamide	Phenobarbitai Rifampin

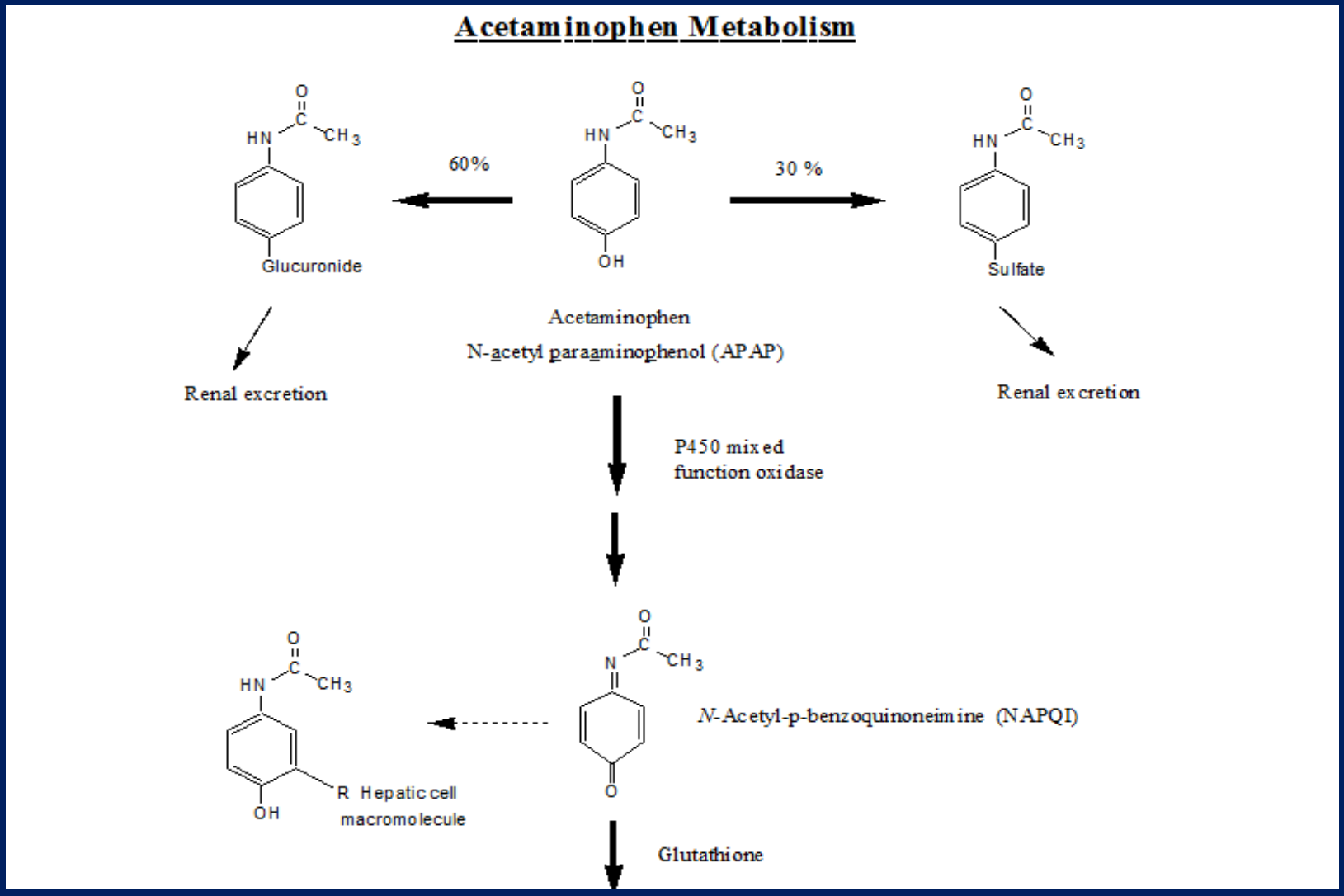
Isozyme: CYP2D6

COMMON SUBSTRATES	INDUCERS
Desipramine Imipramine Haloperidoi Propanoiol	

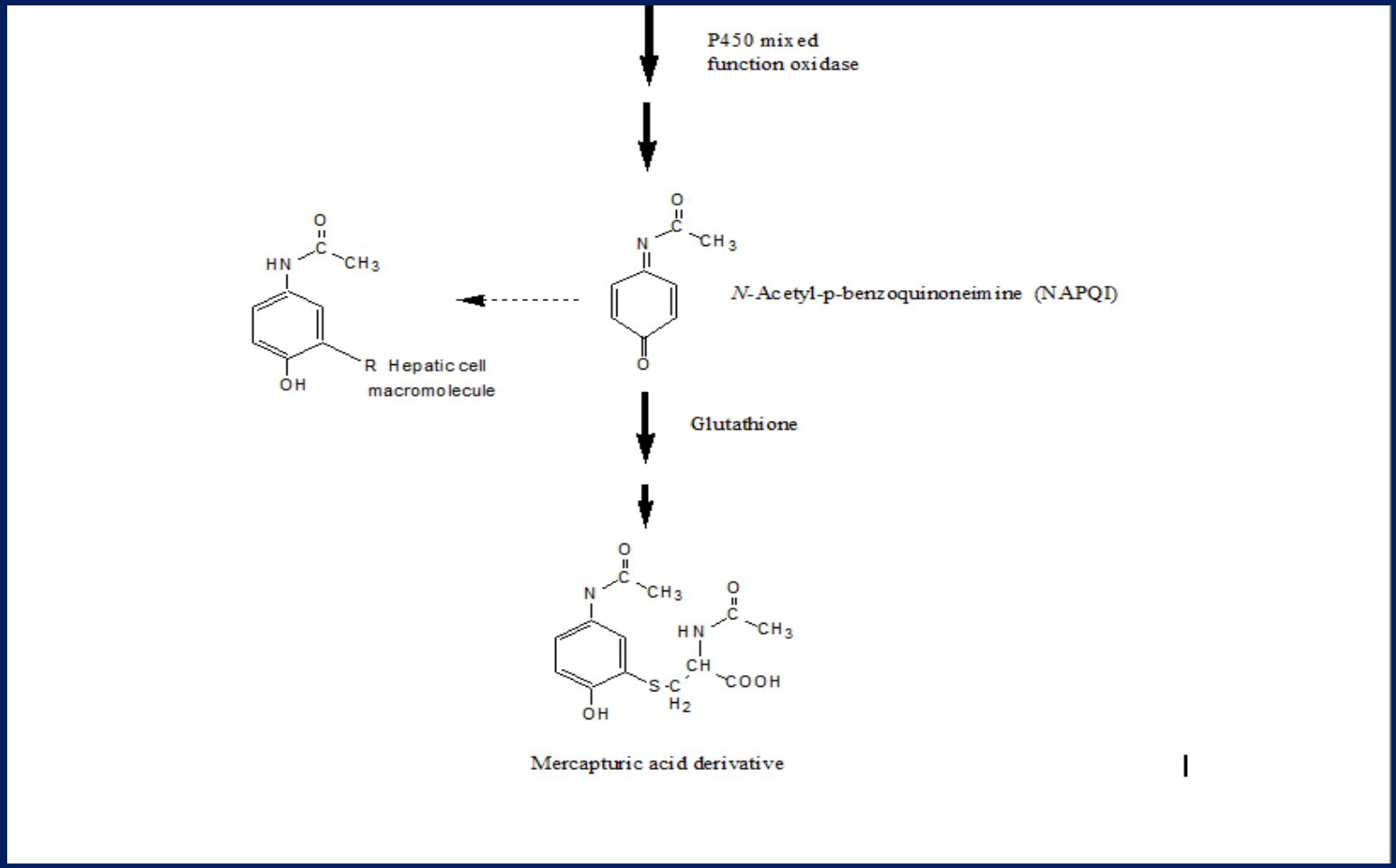
Isozyme: CYP3A4/5

COMMON SUBSTRATES	INDUCERS
Carbamazepine Cyclosporine Erythromycin Nifedipine Verapamii	Carbamazepine Dexamethasone Phenobarbital Phenytoin Rifampin

Pharmacokinetics (cont'd)



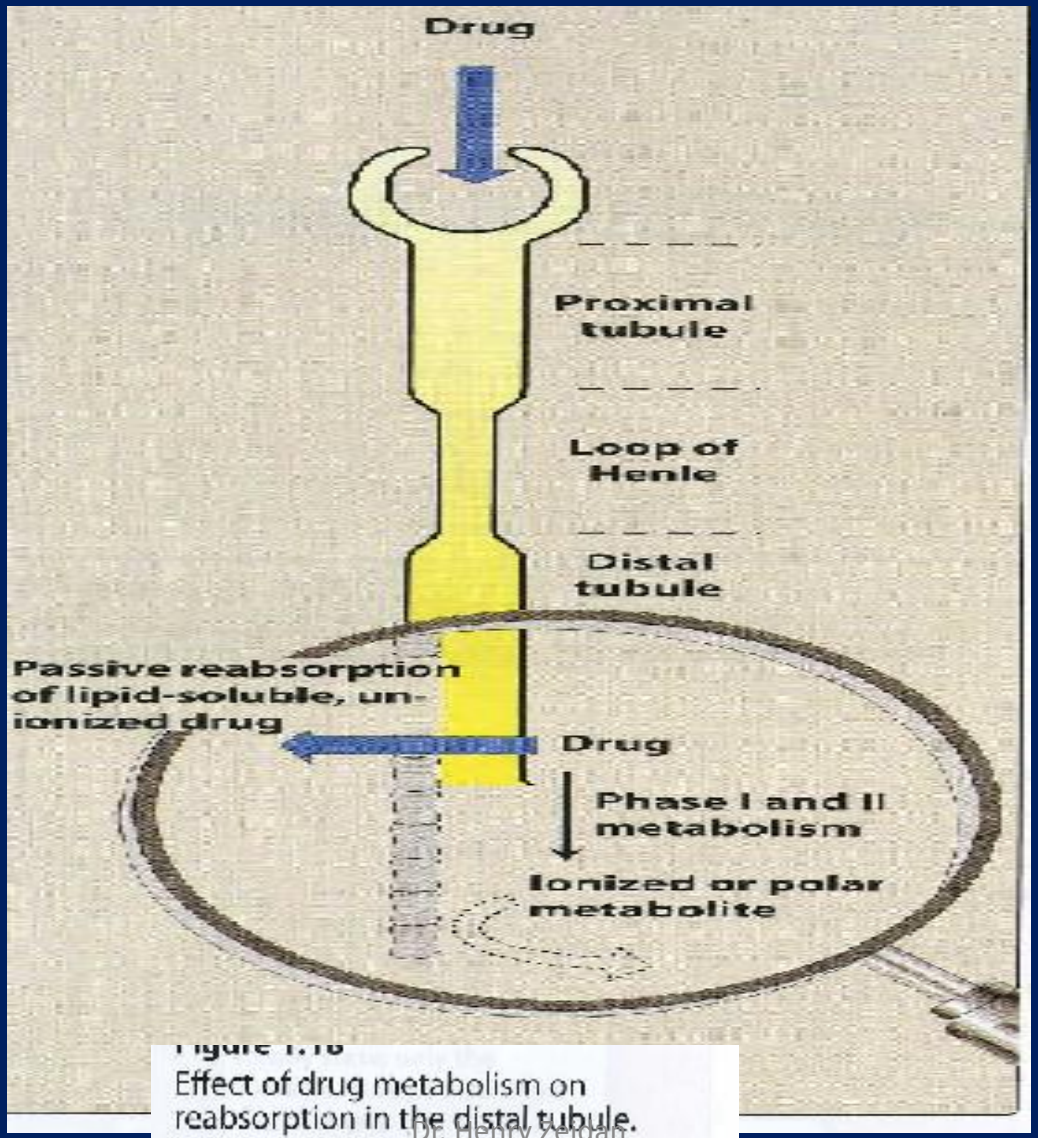
Pharmacokinetics (cont'd)



Elimination

- Kidneys = primary site
  - Mechanisms dependent upon:
    - Passive glomerular filtration
    - Active tubular transport
  - Partial reabsorption
  - Hemodialysis
- Renal disease
  - Slows excretion
  - Prolongs effects

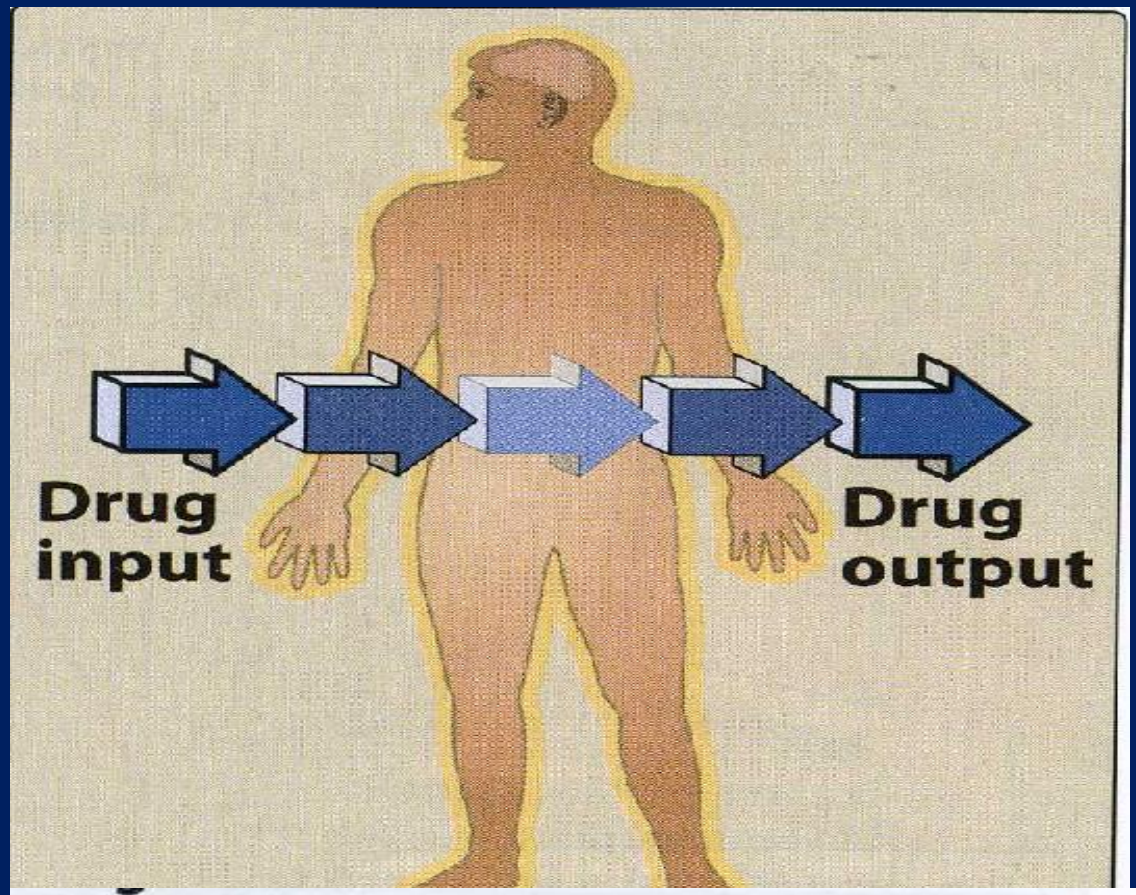
Elimination(Cont'd)



Effect of drug metabolism on reabsorption in the distal tubule.

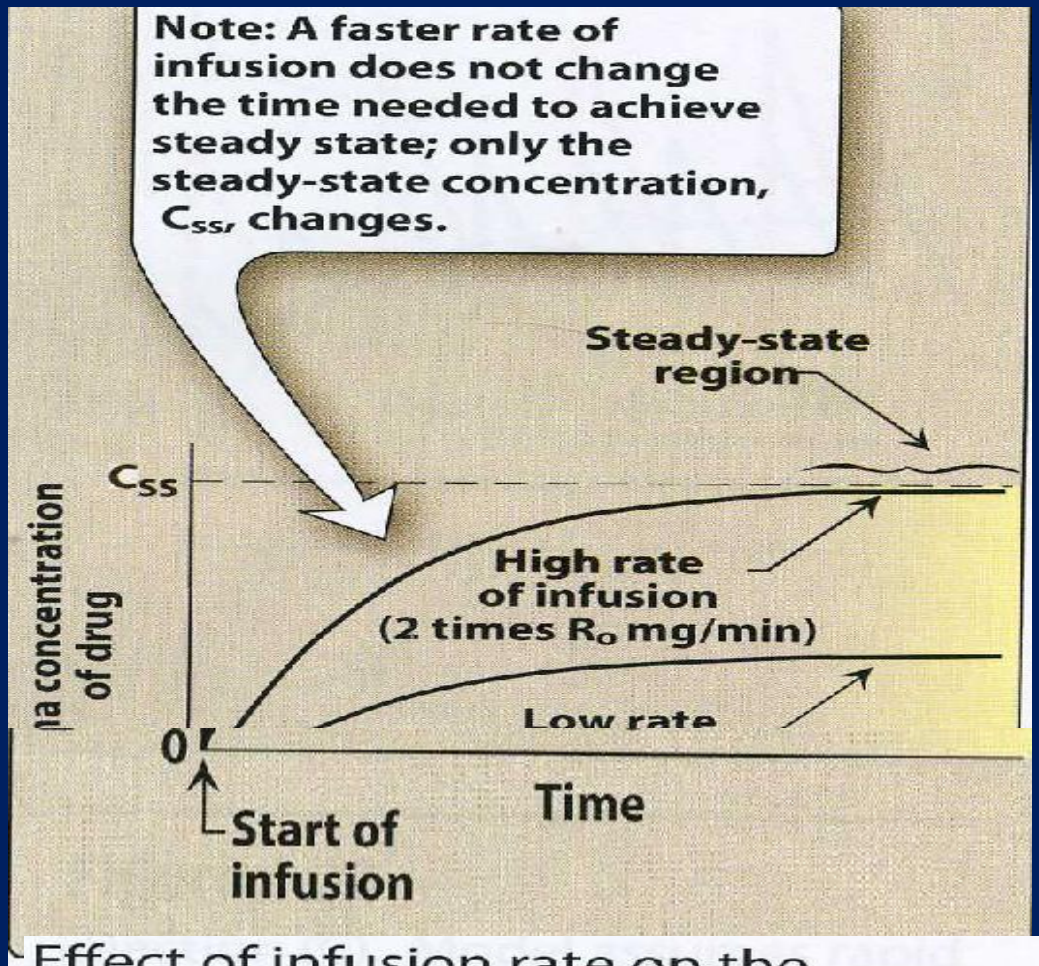
Kinetics of Continous Administrtion

Pharmacokinetics (cont'd)



At steady state, input (rate of infusion) equals output (rate of elimination).

Pharmacokinetics (cont'd)



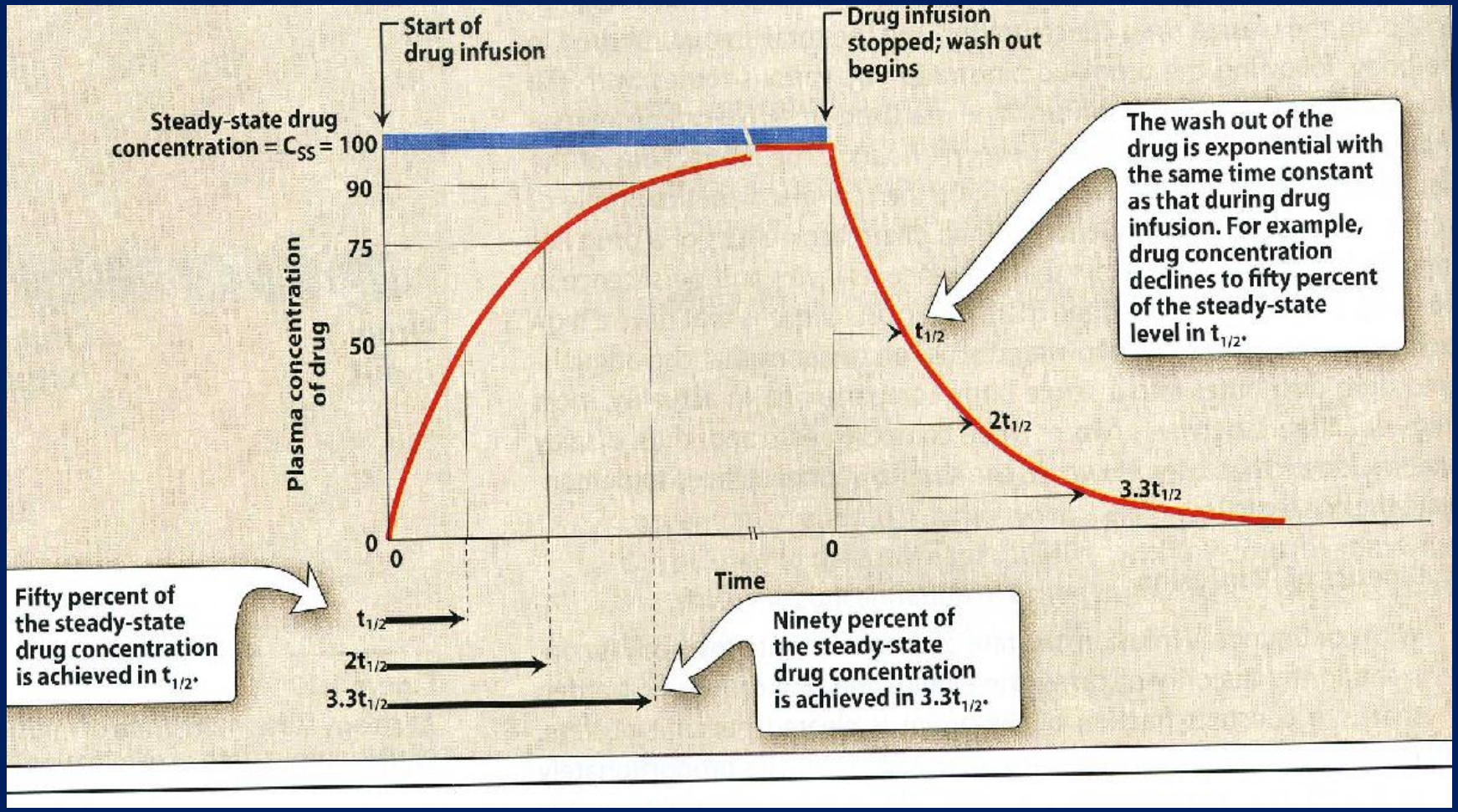
Effect of infusion rate on the steady-state concentration of drug in the plasma. (R_o = rate of infusion of a drug.)

Biological Half-life ($t_{1/2}$)

- Amount of time to eliminate 1/2 of total drug

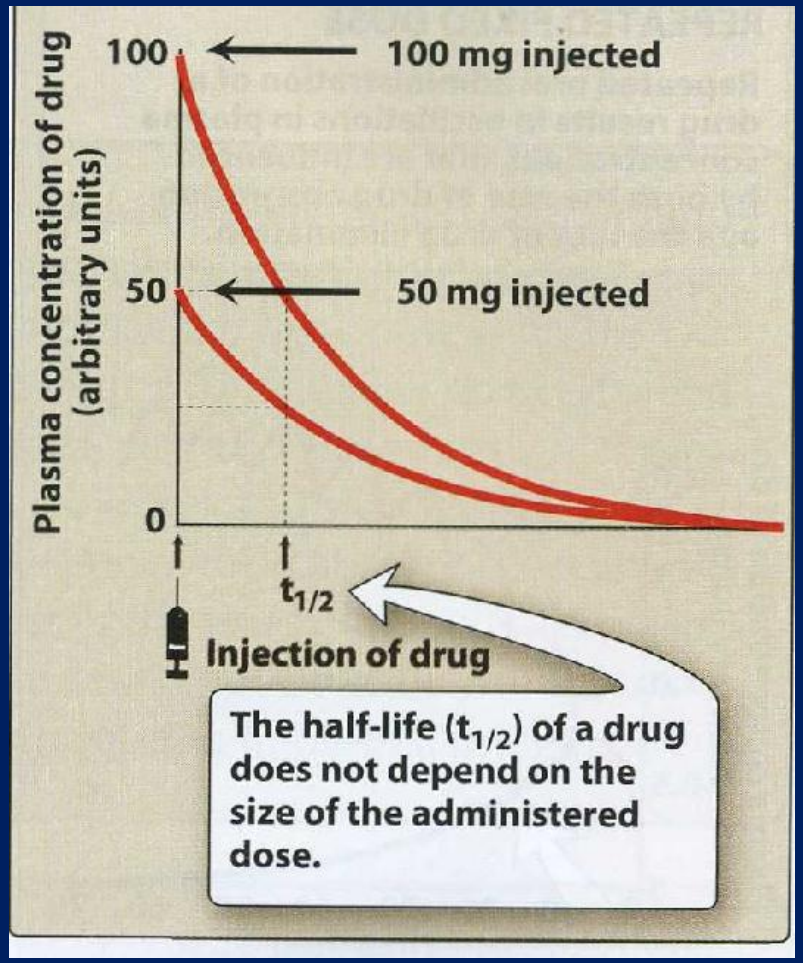
  amount Shorter $t_{1/2}$ may need more frequent doses.
- Hepatic disease may increase $t_{1/2}$

Pharmacokinetics (cont'd)

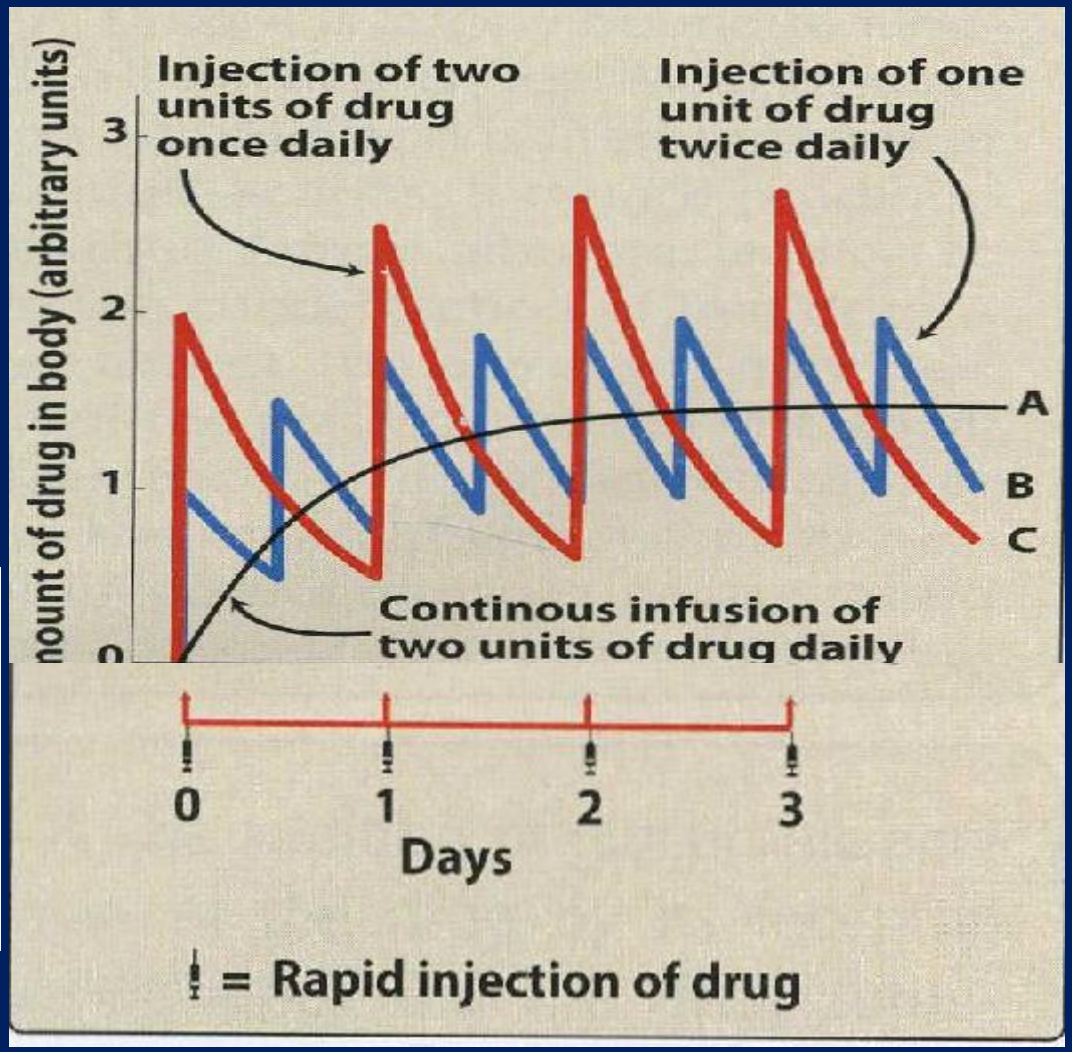


Rate of attainment of steady-state concentration of a drug in the plasma.

Pharmacokinetics (cont'd)

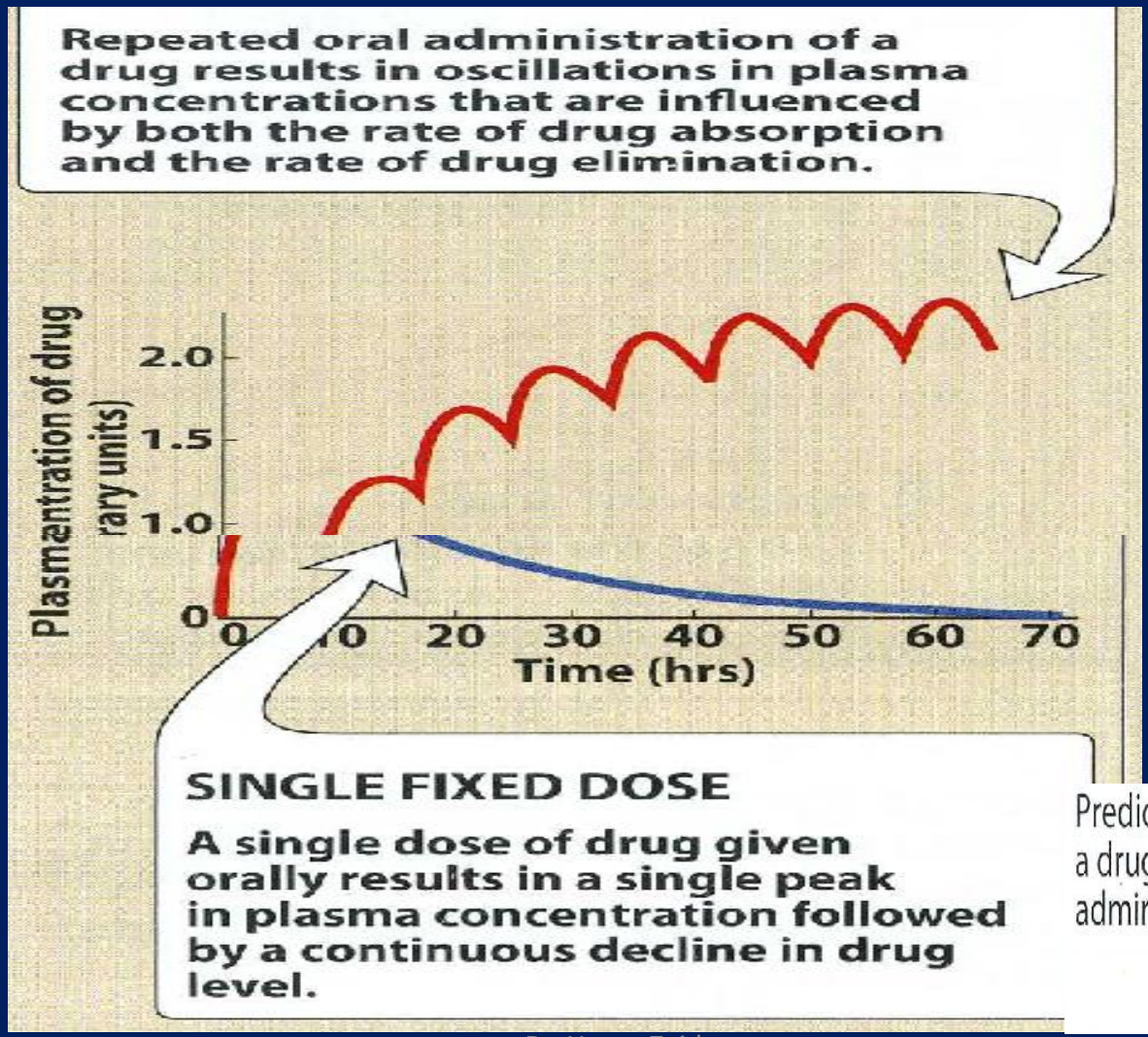


Pharmacokinetics (cont'd)



Predicted plasma concentrations of a drug given by infusion (A), twice-daily injection (B), or once-daily injection (C). Model assumes rapid mixing in a single body compartment and a half-life of twelve hours.

Pharmacokinetics (cont'd)



Predicted plasma concentrations of a drug given by repeated oral administrations.

Pharmacodynamics

Pharmacodynamics

- The biochemical and physiologic mechanisms of drug action

What the drug

does when it gets there?.

Drug Mechanisms

- Receptor interactions
- Non-receptor mechanisms

Pharmacodynamics: Mechanisms of Action

- Receptor interaction
- Enzyme interaction
- Nonspecific interactions

Non-receptor Mechanisms

- Actions on Enzymes
  - Enzymes = Biological catalysts
  - Drugs alter processes catalyzed by the enzymes
  - Examples
    - Cholinesterase inhibitors
    - Monoamine oxidase inhibitors

Non-receptor Mechanisms

- Combining With Other Chemicals
  - Antacids
  - Antiseptic effects of alcohol, phenol

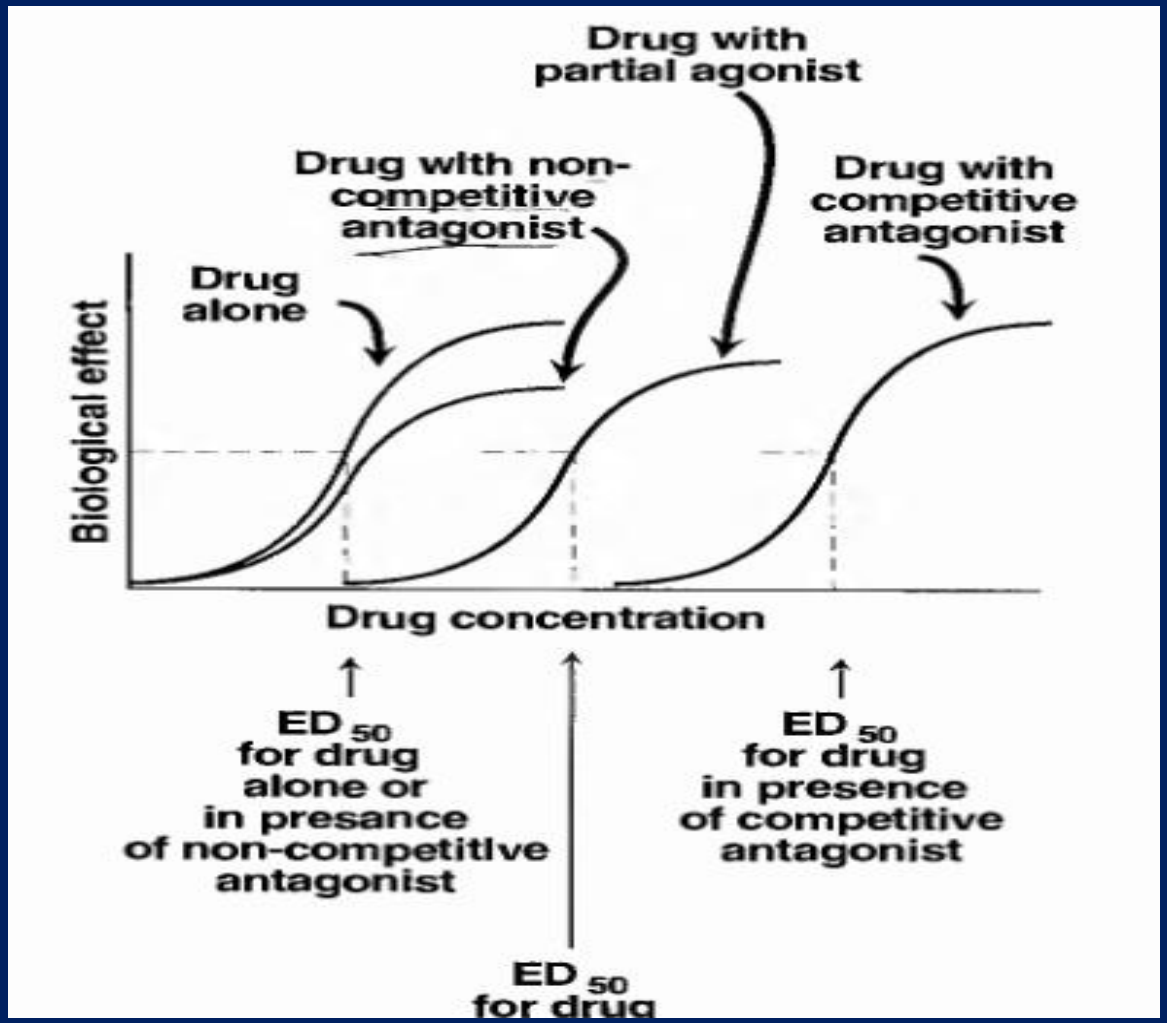
  - Chelation of heavy metals

  . Changing Cell Membrane Permeability

Non-receptor Mechanisms

- Anti-metabolites
  - Enter biochemical reactions in place of normal substrate “competitors”
  - Result in biologically inactive product
  - Examples
    - Some anti-neoplastics
    - Some anti-infectives

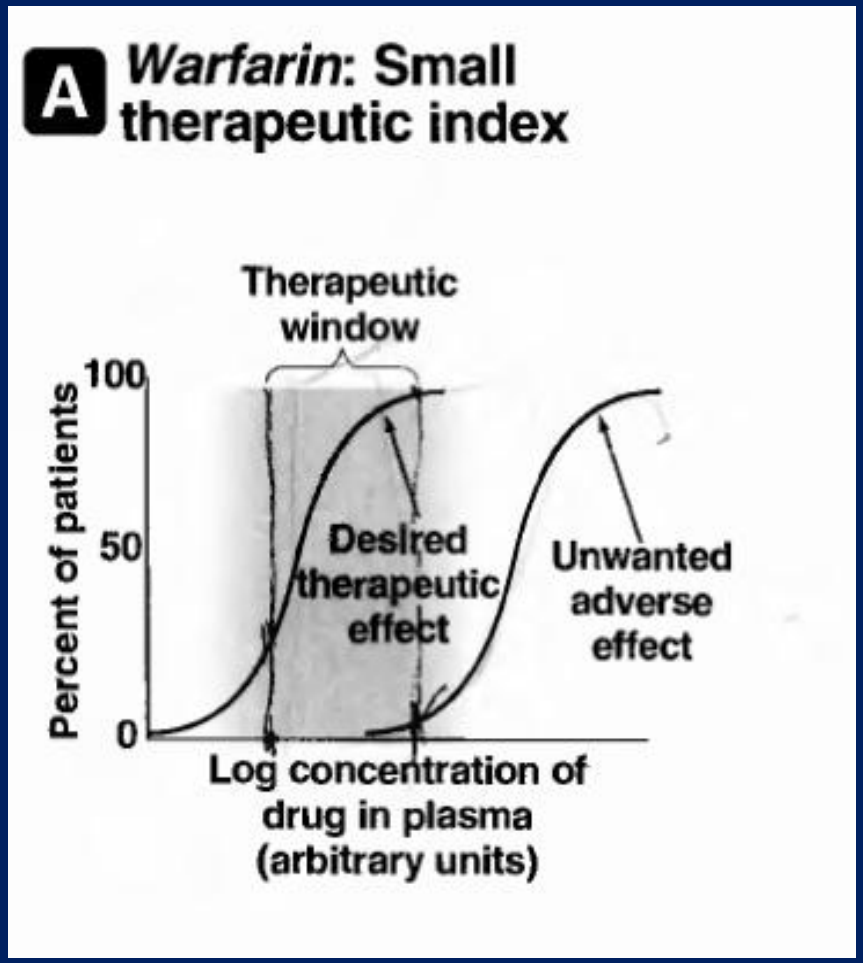
Pharmacodynamics:

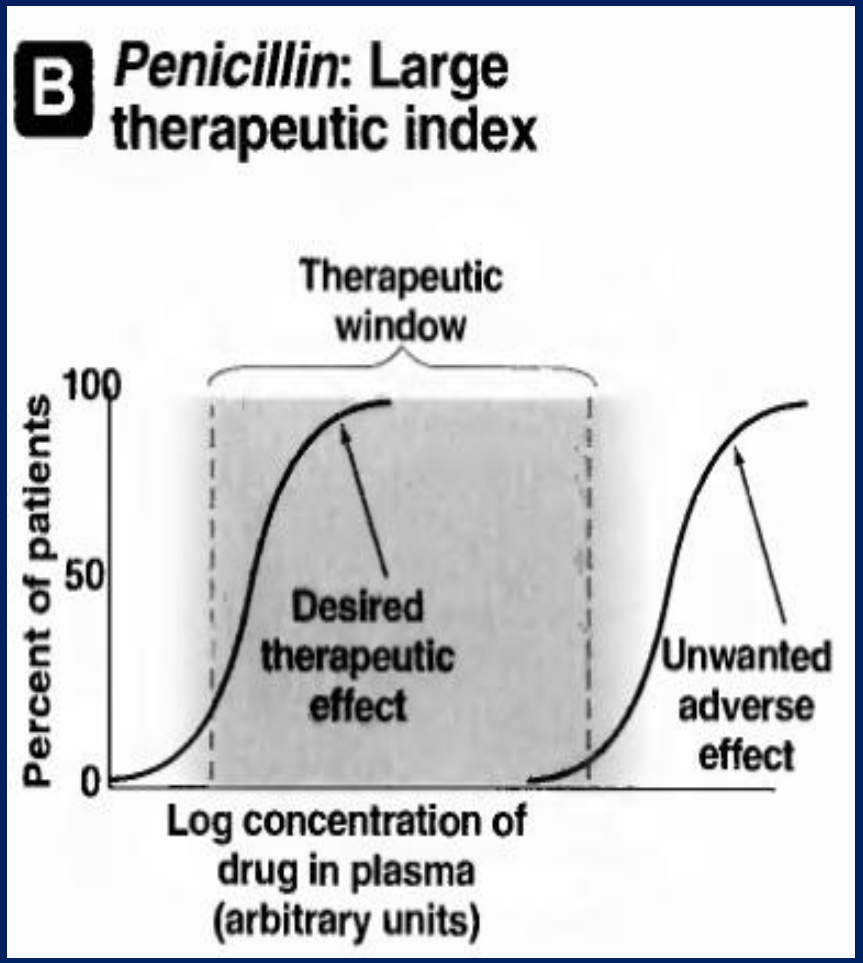


Effects of drug antagonists.

Reproduced from Lippicott's, 2007

Cumulative percent of patients responding to plasma levels of drugs





Reproduced from Lippicott's, 2007

Quantitative aspects of renal drug elimination

Excretion rate:

$$\underset{\text{mg/min}}{\text{Excretion rate}} = \underset{\text{ml/min}}{\text{(clearance)}} \; \underset{\text{mg/ml}}{\text{(plasma concentration)}}$$

$$t_{1/2} = \ln 0.5/k_e = 0.693\ V_d/CL$$

Total body clearance

$$CL_{total} = CL_{hepatic} + CL_{renal} + CL_{pulmonary} + CL_{other}$$

Influence of the rate of drug infusion on the steady-state

$$C_{ss} = R_0/k_e V_d = R_0/CL_t$$

where C_{ss} = the steady state concentration of drug

R_o = the infusion rate (for example, mg/min)

k_e = first-order rate constant for drug elimination from the total body

V_d = volume of distribution

CL_t = total body clearance

Volume of distribution and the half-life of a drug

$$CL_{total} = k_e V_d$$

$$t_{1/2} = 0.693\ V_d/CL_{total}$$

Pharmacotherapeutics: Monitoring

- Therapeutic index
- Drug concentration
- Patient's condition
- Tolerance and dependence
- Interactions
- Side effects/adverse drug effects

References:

- 1. Betram G. Katzung, Basic & Clinical Pharmacology, Ninth Edition, McGraw Hill

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