DRUG DISTRIBUTION

Katzung’ s Basic & Clinical Pharmacology, 16th Edition

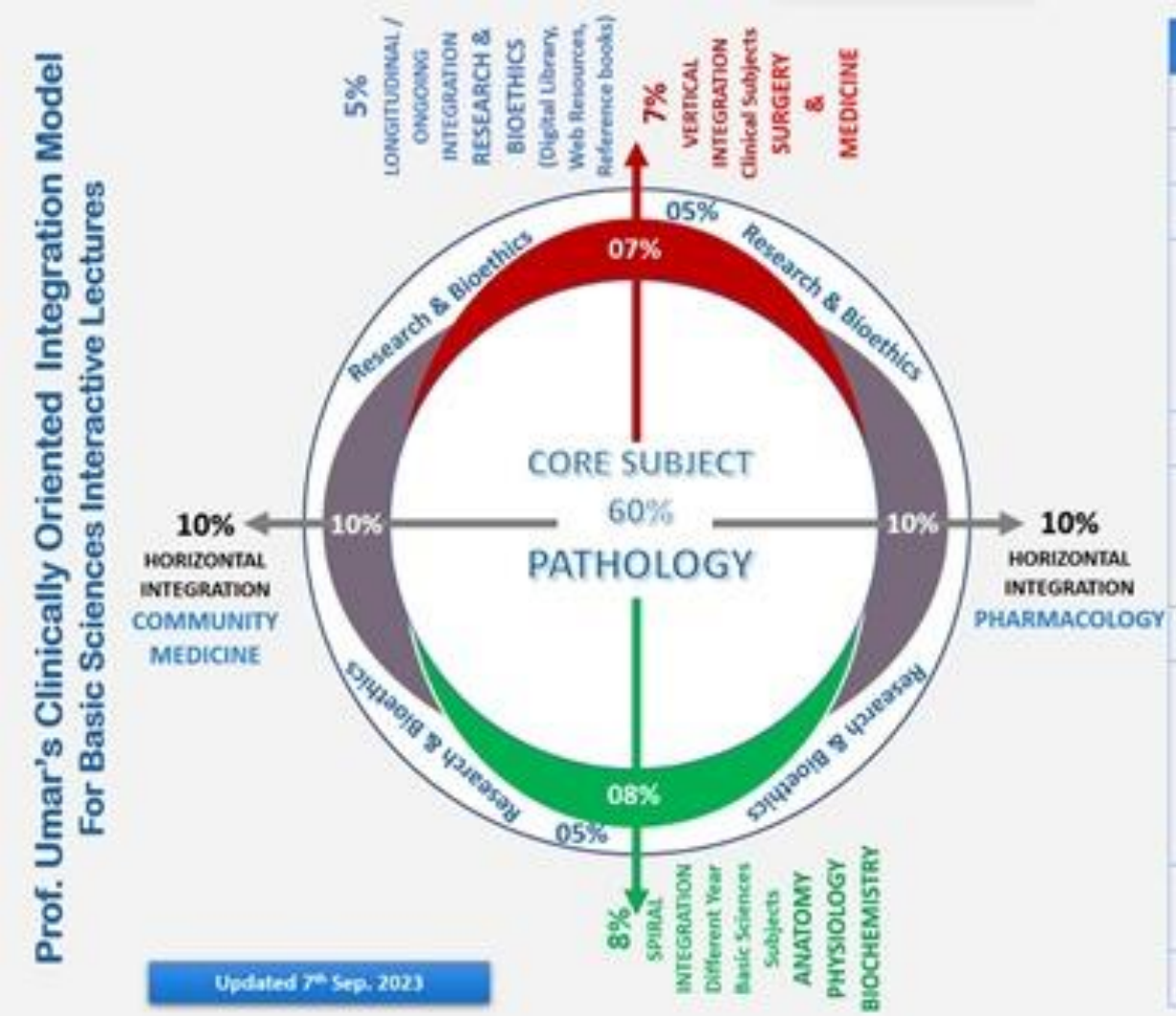
Goodman and Gilmans The Pharmacological Basis of Therapeutics, 13th Edition

Dr. Zunera Hakim

MOTO AND VISION

- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

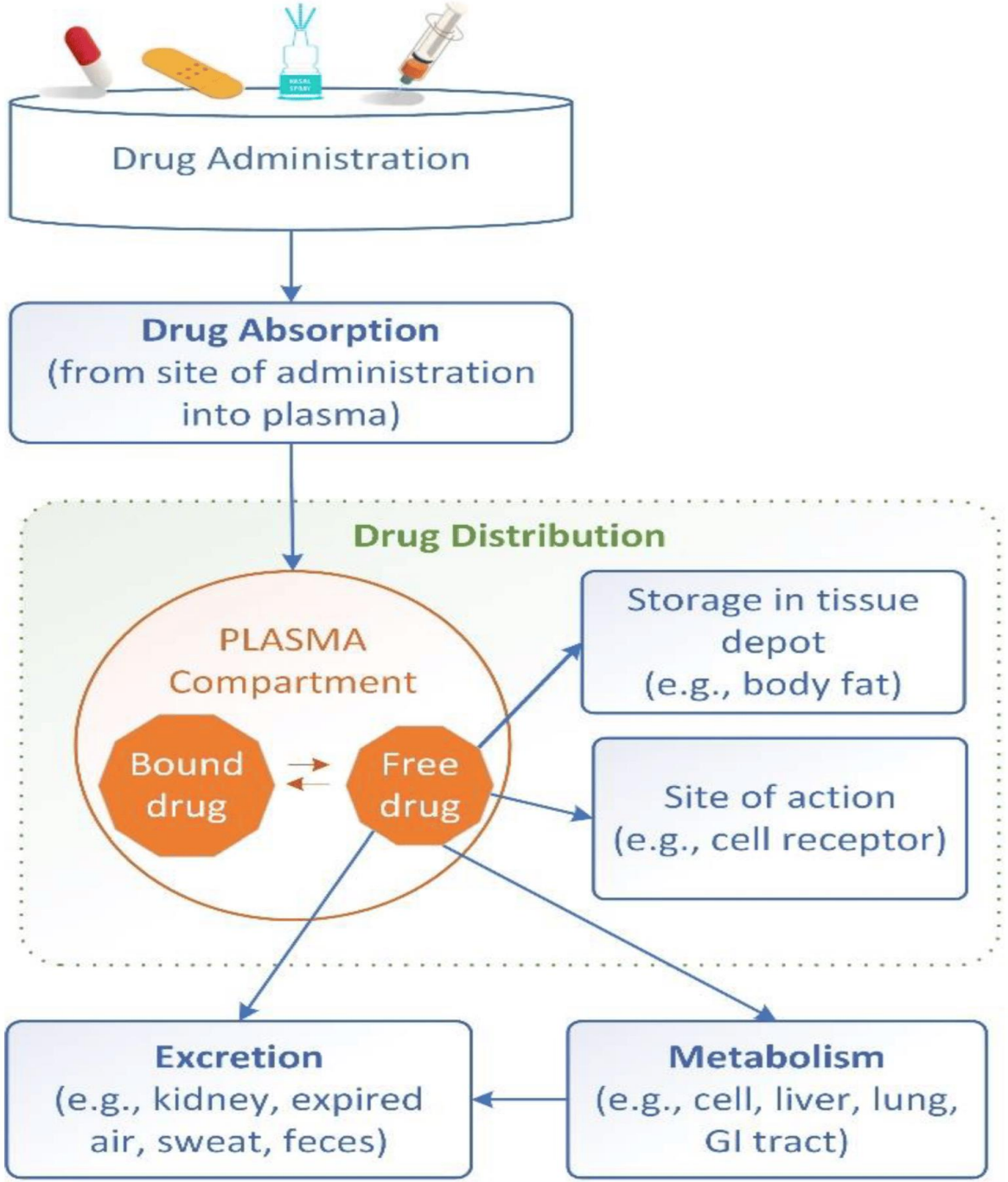
UMAR' S MODEL OF INTEGRATION



Model 3rd Year Pathology LGIS (≈30 slides)	
Core Subject – 60% (≈ 18-20 slides)	
Pathology (≈ 18-20 slides)	
Horizontal Integration – 20% (≈ 5-6 slides)	
Same Year Subjects	• Pharmacology (10%) (≈ 2-3 slides) • Community Medicine (10%) (≈ 2-3 slides)
Vertical Integration – 07% (≈ 2-3 slides)	
Clinical Subjects	• Medicine (3-5%) (≈ 1-2 slides) • Surgery (3-5%) (≈ 1-2 slides)
Spiral Integration – 08% (≈ 2-3 slides)	
Different Year Basic Sciences Subjects	• Anatomy (1-3%) (≈ 1-2 slides) • Physiology (1-3%) (≈ 1-2 slides) • Biochemistry (1-3%) (≈ 1-2 slides)
Longitudinal / Ongoing Integration – 05% (≈ 1-2 slides)	
Research & Bioethics (≈ 1-2 slides)	

LEARNING OBJECTIVES

- Define drug distribution
- Discuss the factors affecting drug distribution
- Describe plasma protein binding and its effect on drug distribution
- Recognize the importance of drug distribution
- Define volume of distribution
- Express volume of distribution mathematically


Drug Administration
Drug Absorption
(from site of administration into plasma)
Drug Distribution
PLASMA Compartment
Bound drug
Free drug
Storage in tissue depot
(e.g., body fat)
Site of action
(e.g., cell receptor)
Excretion
(e.g., kidney, expired air, sweat, feces)
Metabolism
(e.g., cell, liver, lung, GI tract)

DRUG DISTRIBUTION

Drug distribution refers to the reversible movement of a drug to and from the blood and various tissues of the body (for example, fat, muscle, and brain tissue)

The process by which a drug reversibly moves from blood stream to and enters the extracellular fluid and/or cells of tissues.

DRUG DISTRIBUTION

WHERE DO DRUGS GO?

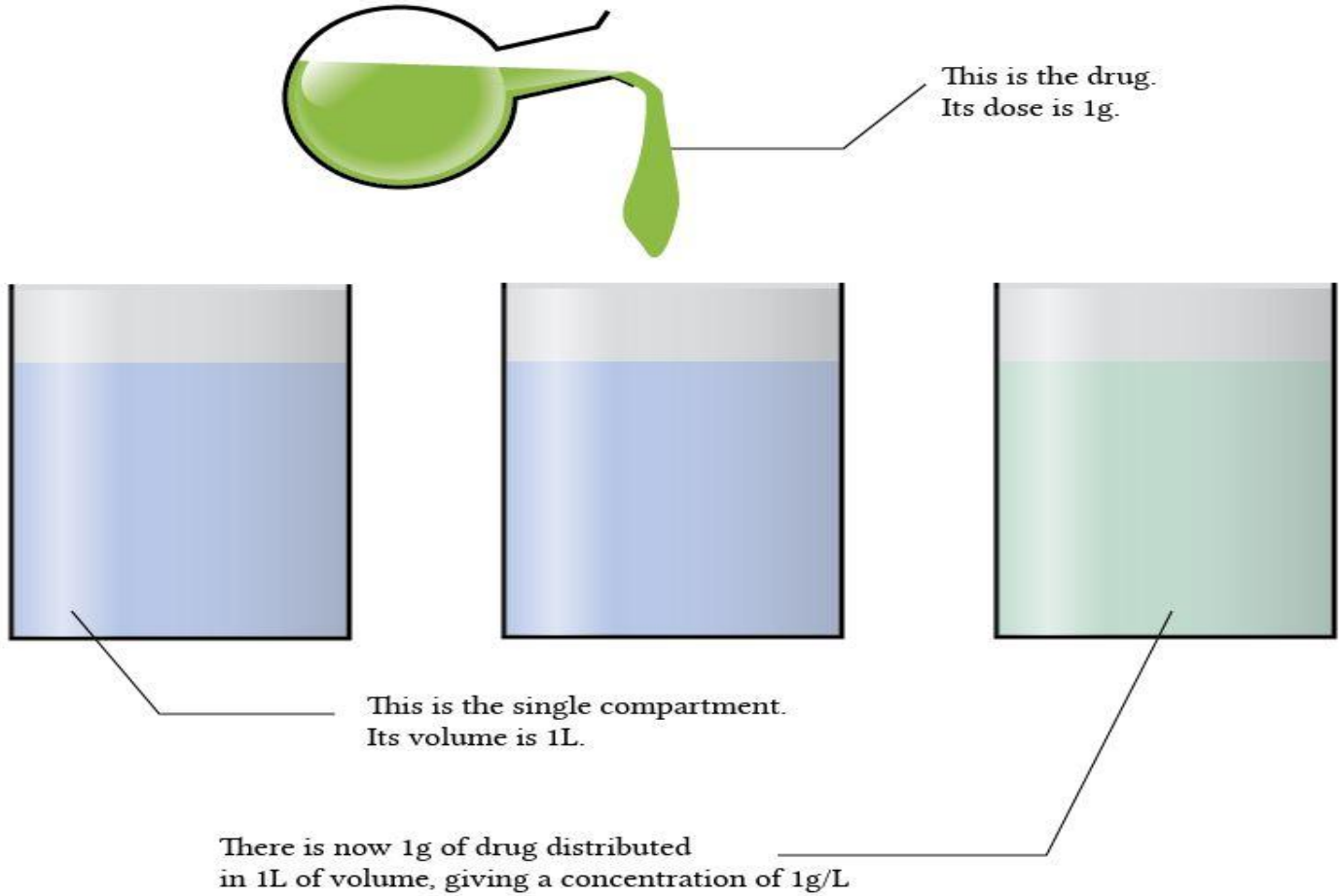
COMPARTMENT MODELS OF DRUG DISTRIBUTION

A pharmacokinetic compartment is a mathematical concept which describes a space in the body which a drug appears to occupy. It does not need to correspond to any specific anatomical space or physiological volume.

- Single compartment model
- Multiple compartment model

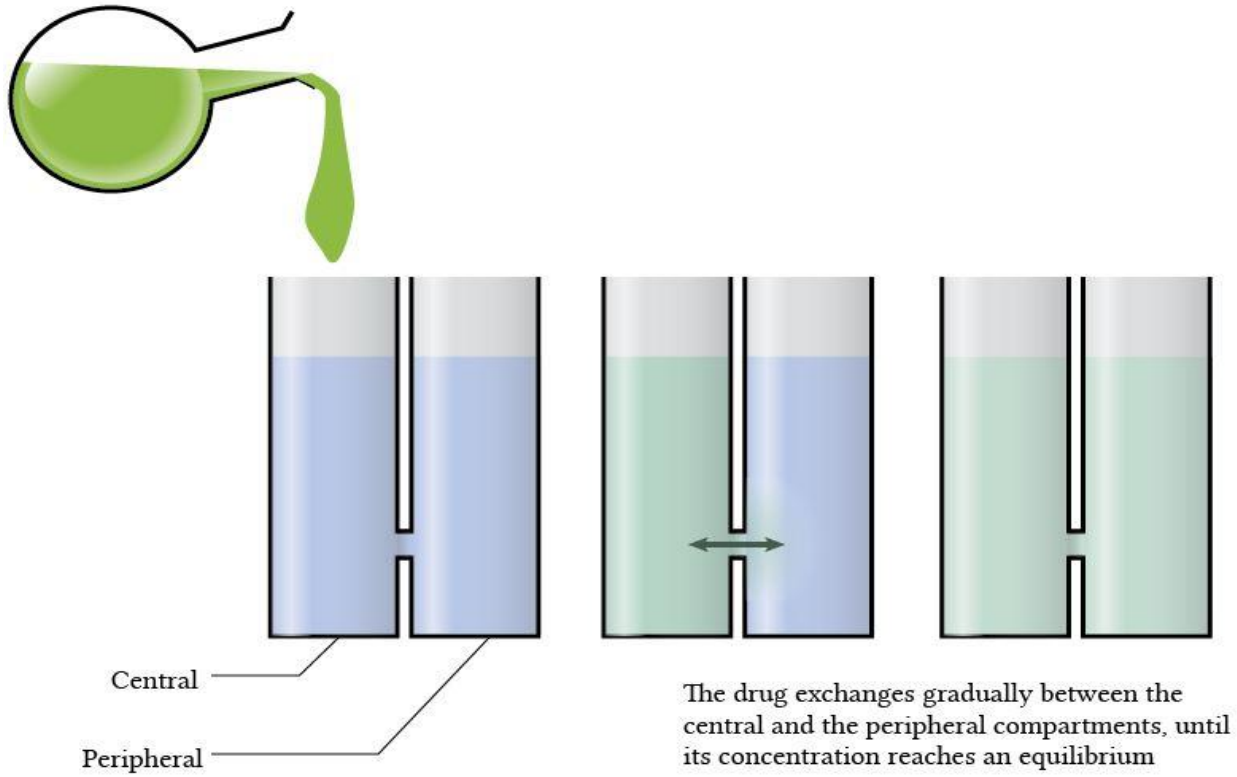
COMPARTMENT MODELS OF DRUG DISTRIBUTION

- **Single compartment model**



COMPARTMENT MODELS OF DRUG DISTRIBUTION

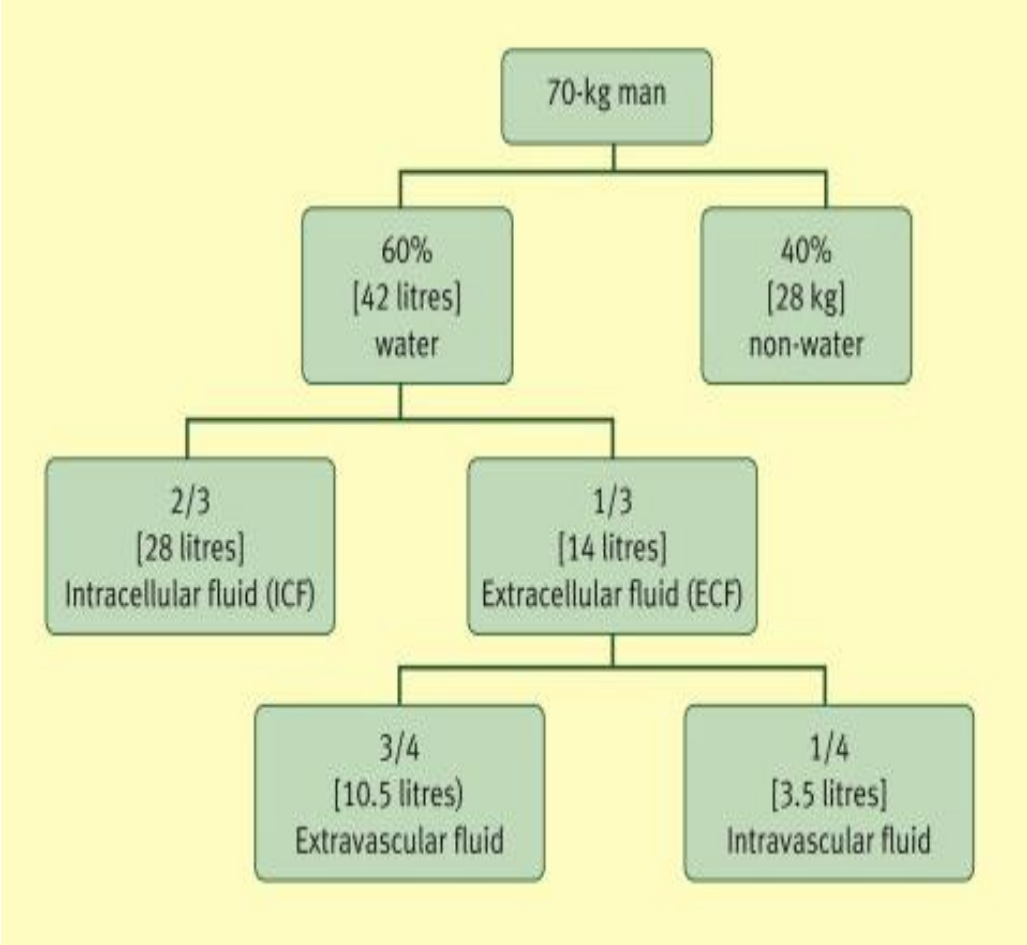
- **Two compartment model**

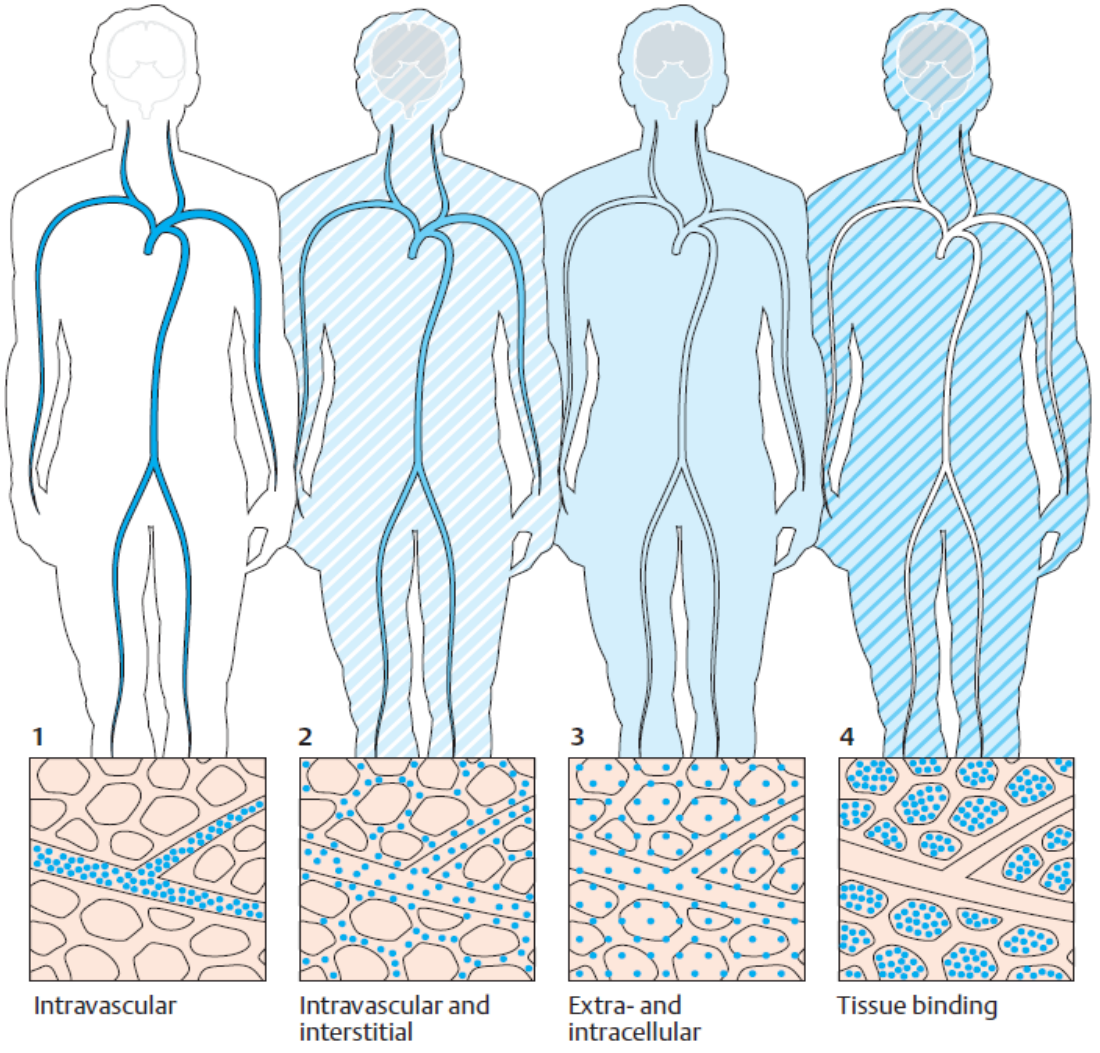


The drug exchanges gradually between the central and the peripheral compartments, until its concentration reaches an equilibrium

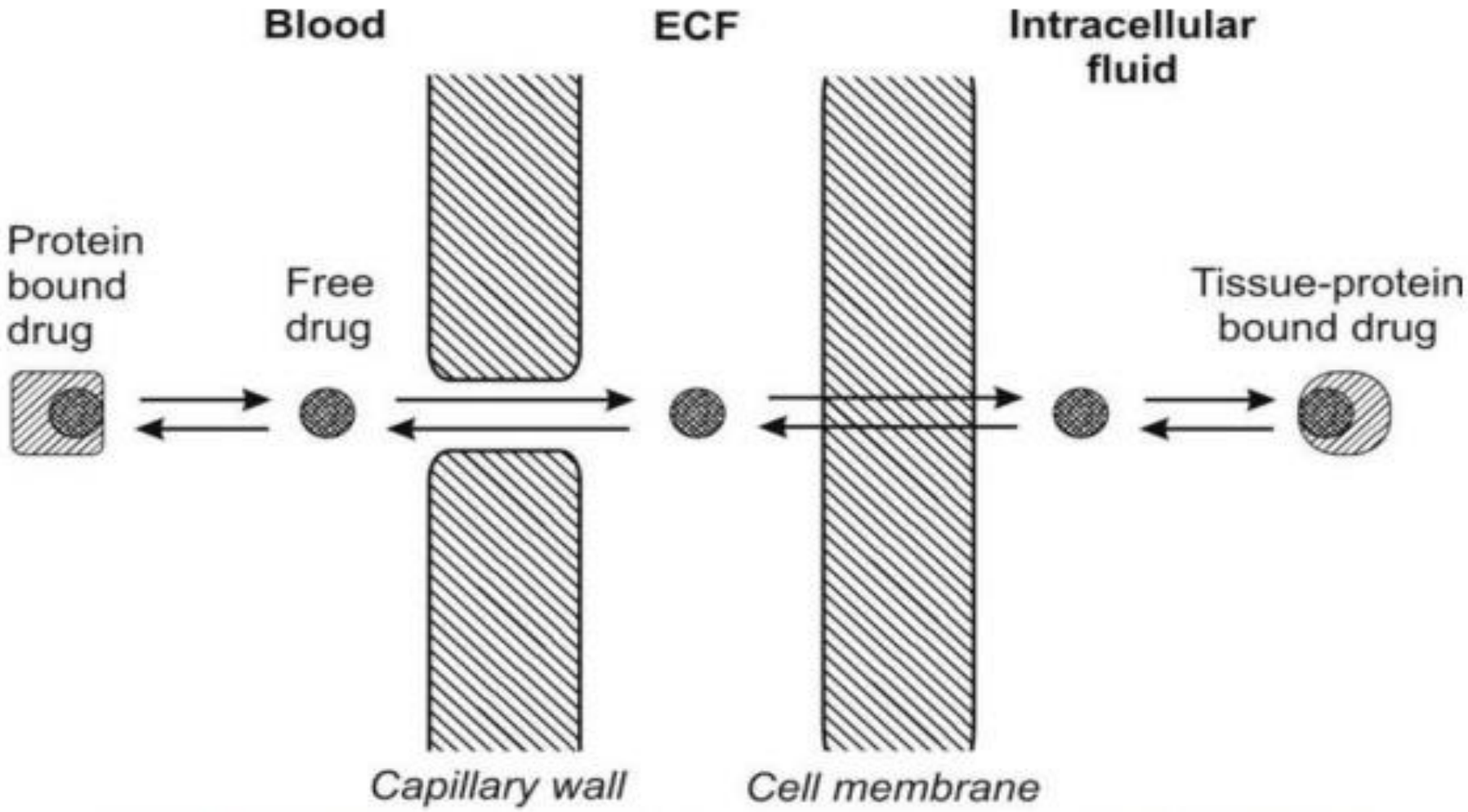
PHYSIOLOGICAL SPACES FOR DRUG DISTRIBUTION

DISTRIBUTION OF BODY VOLUMES





STEPS OF DRUG DISTRIBUTION



DRUG DISTRIBUTION

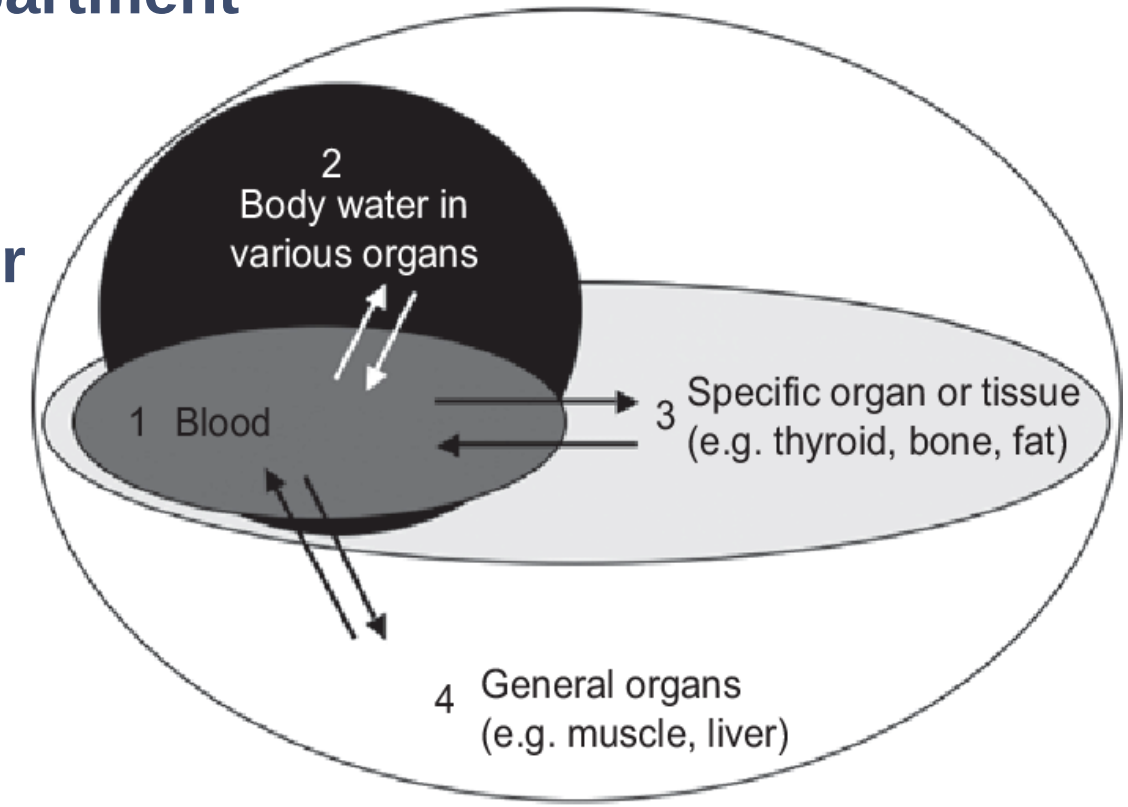
NOT ALL TISSUES ARE EQUAL

DISTRIBUTION PATTERN OF DRUGS

- **Drug confined to blood/intravascular compartment**
  (high molecular weight/ protein bound)
  Heparin, Warfarin

- **Uniform distribution throughout body water**
  (small molecular weight)
  Ethanol

- **Concentrated in specific and general tissues/organs**
  Chloroquine in liver
  Tetracycline in bone and teeth



FACTORS AFFECTING DISTRIBUTION

- Regional blood flow (perfusion rate)
- Capillary permeability
- Binding to plasma and tissue proteins
- Tissue permeability of drugs
- Miscellaneous factors

FACTORS AFFECTING DISTRIBUTION

Regional Blood Flow/ Perfusion Rate

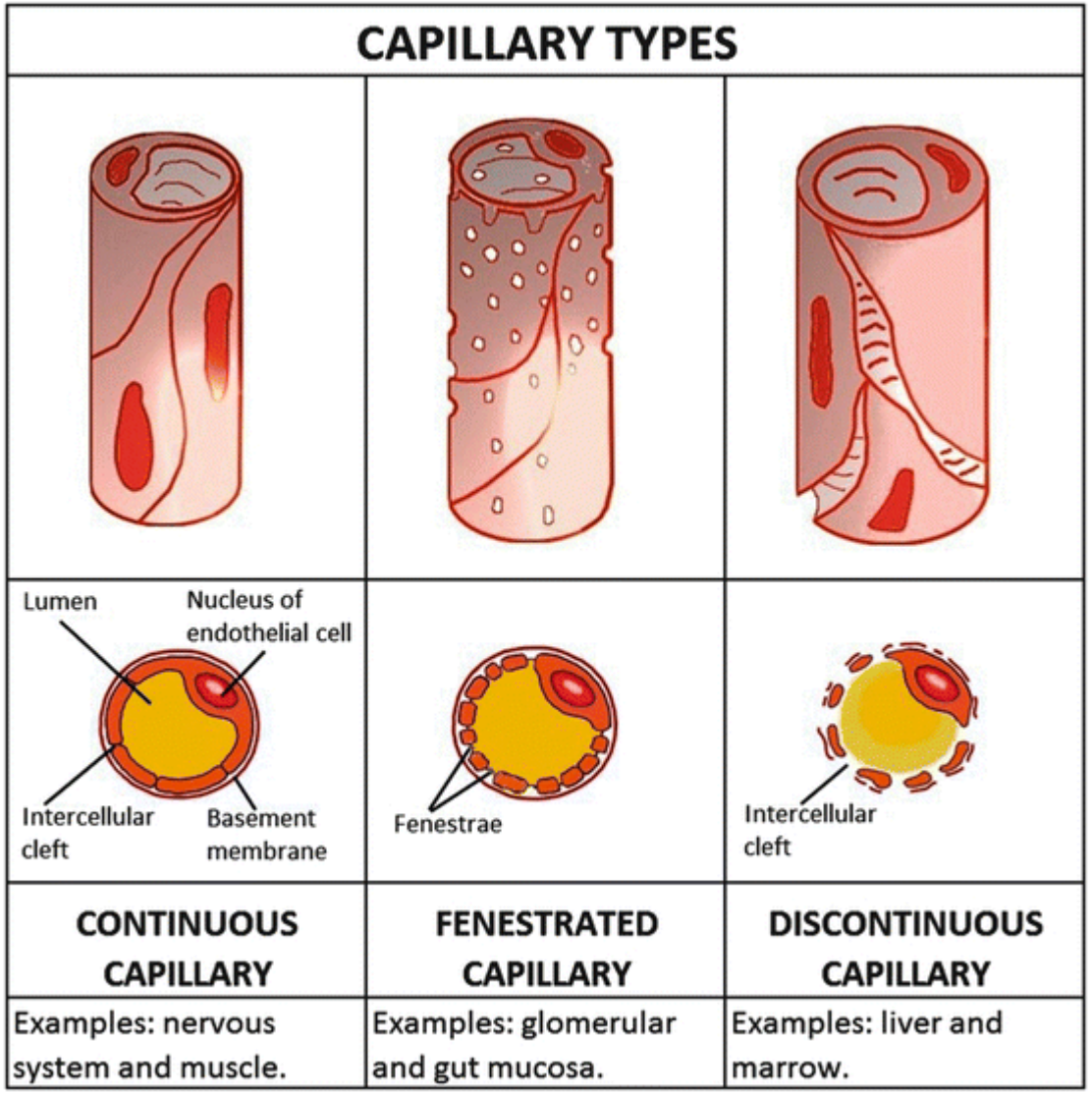
- Greater the blood flow, faster is the rate of distribution
- There are two phase of distribution based on perfusion rate:

❖ Rapid initial phase
❖ Slow second phase

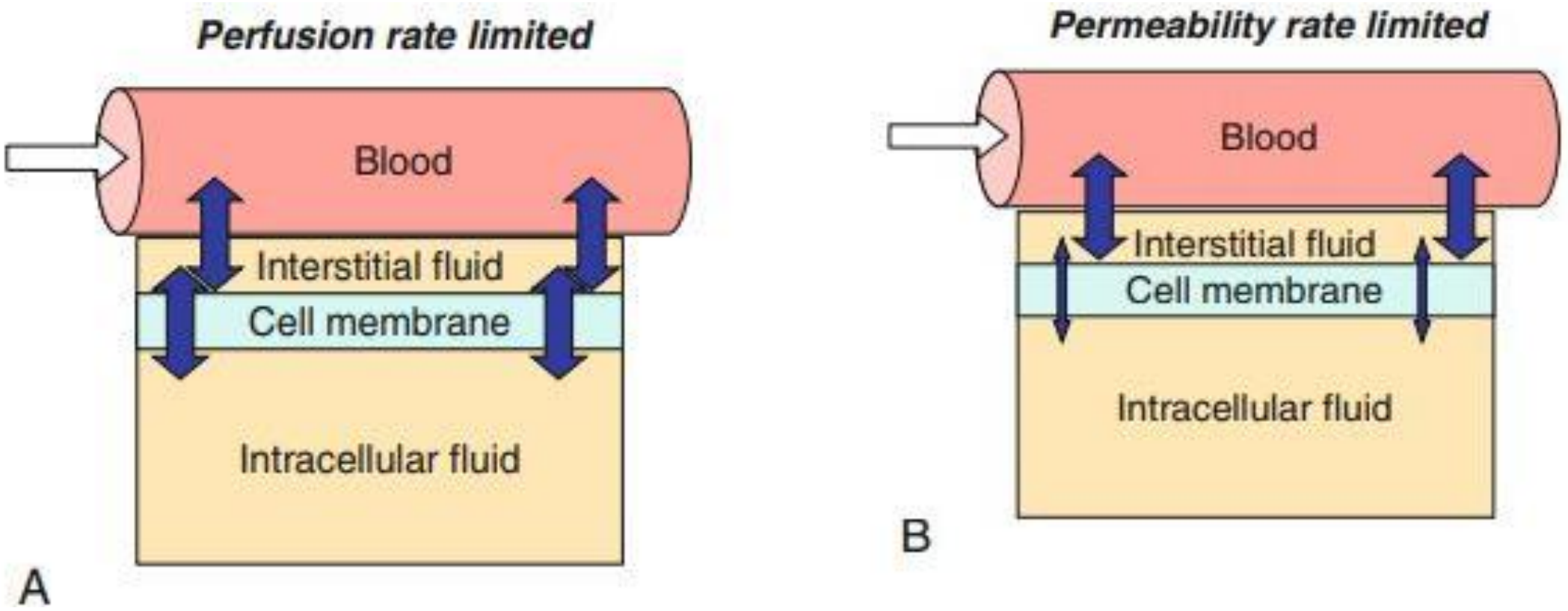
FACTORS AFFECTING DISTRIBUTION

Capillary permeability

- Capillary permeability is tissue dependent
- It determines the ease with which the drug crosses the blood tissue barrier



FACTORS AFFECTING DRUG DISTRIBUTION



FACTORS AFFECTING DISTRIBUTION

Protein Binding of Drugs

- Formation of reversible complexes between drugs and blood components and extravascular tissues
- Protein-binding data are frequently expressed in terms of per cent bound. (90% bound are called highly bound drugs)
- Binding of drugs to proteins falls into 2 categories:

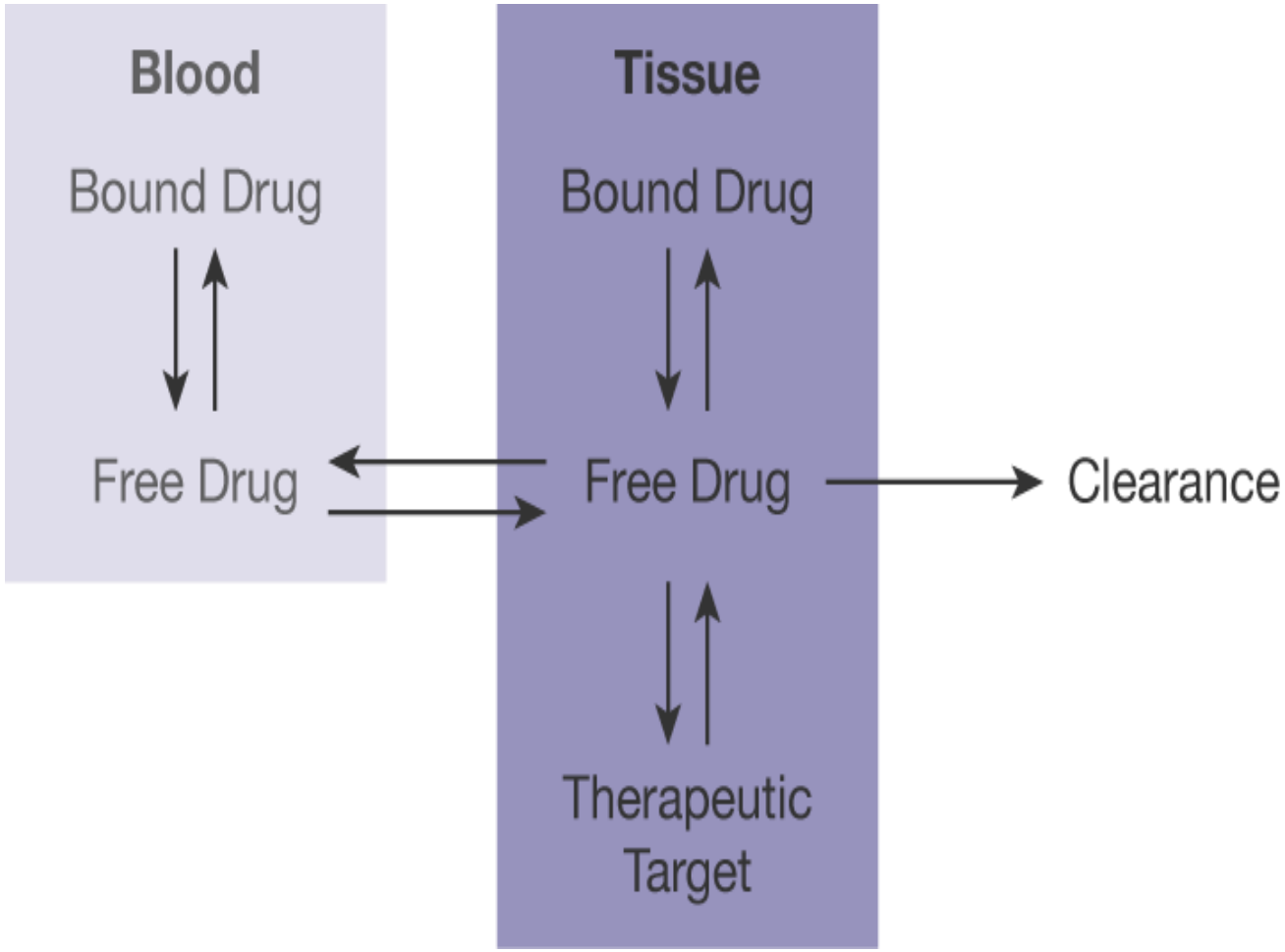
i. Blood components

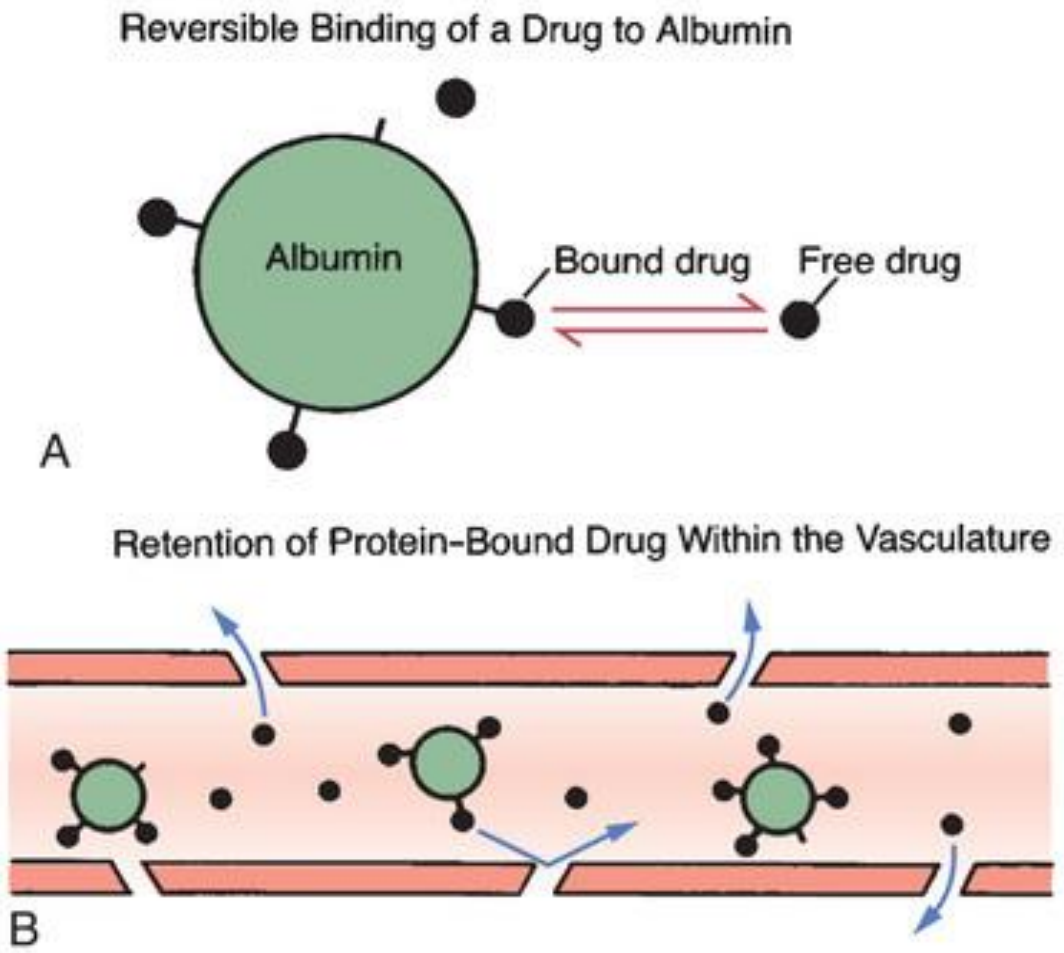
- ❖ Plasma proteins
- ❖ Blood cells (barbiturates, chlorpromazine, imipramine, and phenytoin)

ii. Extravascular tissue proteins

FACTORS AFFECTING DISTRIBUTION

Plasma Protein Binding





FACTORS AFFECTING DISTRIBUTION

Plasma Protein Binding

Protein	*Molecular Weight*	*Concentration (g%)*	*Drugs that bind*
Human Serum Albumin	65,000	3.5-5.0	Large variety of all types of drugs
α_1-Acid Glycoprotein	44,000	0.04-0.1	Basic drugs such as imipramine, lidocaine, quinidine, etc.
Lipoproteins	200,000 to 3,400,000	Variable	Basic, lipophilic drugs like chlorpromazine
α_1-Globulin	59,000	0.003-0.007	Steroids like corticosterone, and thyroxine and cyanocobalamin
α_2-Globulin	1,34,000	0.015-0.06	Vitamins A, D, E and K and cupric ions
Haemoglobin	64,500	11-16	Phenytoin, pentobarbital, and phenothiazines

FACTORS AFFECTING DISTRIBUTION

Plasma Protein Binding

- Binding between the drug and plasma proteins is reversible
- The unbound concentration of drug in plasma and tissues will the same at equilibrium
- Unbound fraction is pharmacological and toxicological active Endogenous substances and co-administered drugs compete for binding sites
- Bound drugs can act as drug reservoir
- Determinants of plasma protein binding are :

i. Concentration of the drug
ii. Number of available binding sites
iii. Affinity for binding sites (association constant)

FACTORS AFFECTING DISTRIBUTION

Extravascular/ Tissue Binding

- **Liver :** Paracetamol, chloroquine, digoxin
- **Skin** : Chloroquine
- **Eye** : Ephedrine, atropine
- **Bones & teeth** : Tetracycline, phenytoin
- **Fat :** DDT, thiopental, minocycline
- **Skeletal muscle**, **heart** : digoxin, emetine
- **Brain** : acetazolamide, chlorpromazine
- **Kidney, vestibular apparatus** : gentamicin

FACTORS AFFECTING DISTRIBUTION

Tissue Permeability of Drugs

- Physiochemical properties of drugs
  - Molecular size
  - Molecular charge
  - pKa-Degree of ionization
  - Lipid/ water solubility
- Physiological barriers to drug distribution
  - Blood brain barrier
  - Placental barrier
  - Blood testis barrier

FACTORS AFFECTING DISTRIBUTION

Miscellaneous

- Age
- Gender
- Pregnancy
- Obesity
- Oedema
- Ascites

VOLUME OF DISTRIBUTION

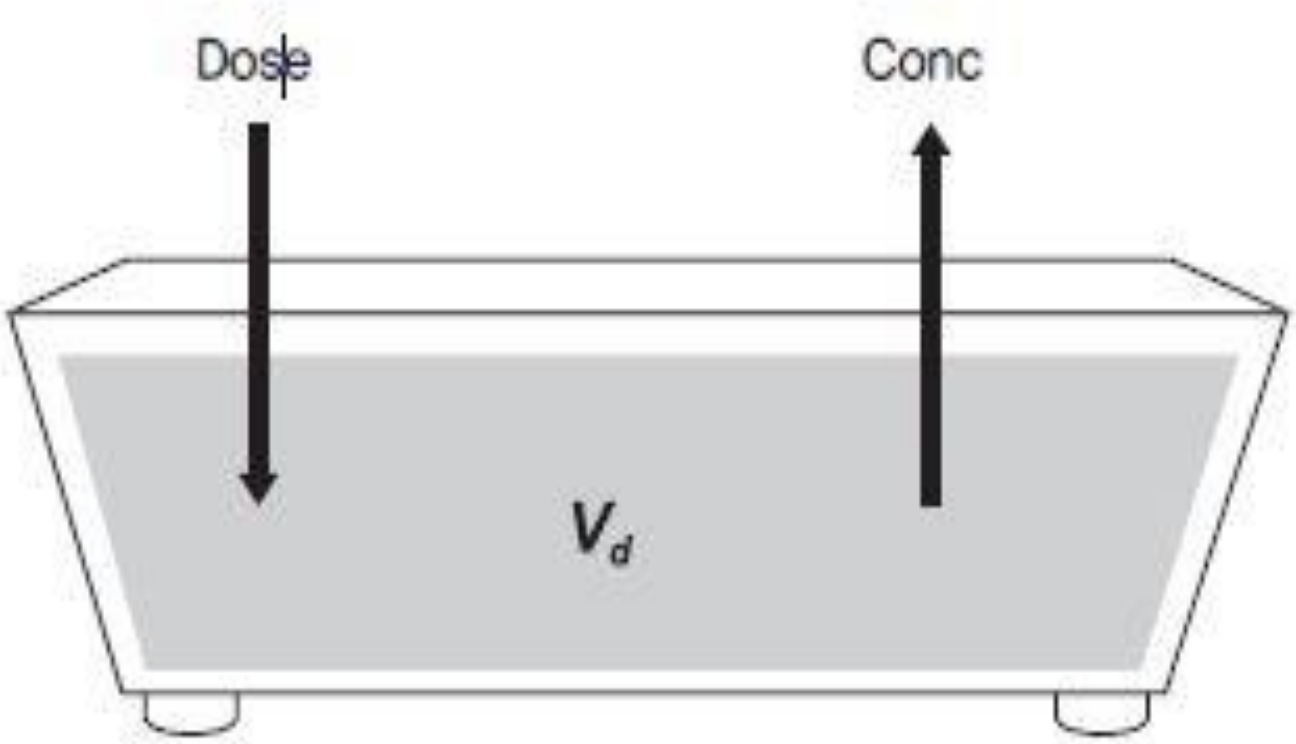
- Volume of distribution is the volume of fluid “apparently” required to contain the total-body amount of drug homogeneously at a concentration equal to that in plasma (or blood)

- Vd is a *proportionality constant* that relates the total amount of drug in the body to the plasma concentration of the drug at a given time.

$$Vd = \frac{\text{Amount of drug administered (D)}}{\text{Plasma concentration ©}}$$

Assessment of the Extent of Drug Distribution

The Bathtub Model of Volume of Distribution



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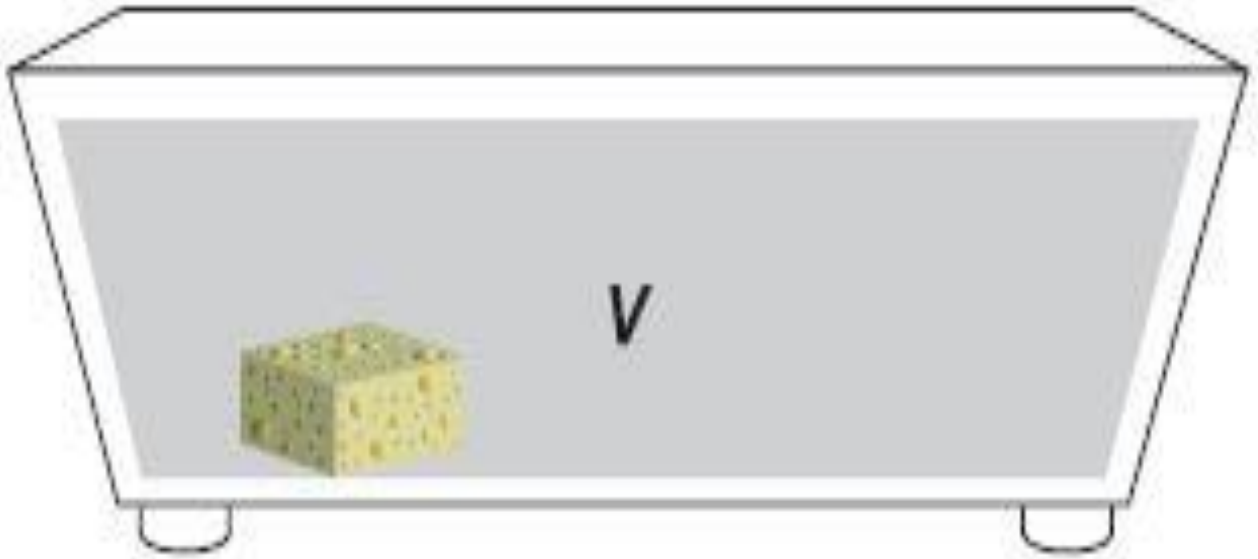


$$500\ L = 500\ \mu g / (1\ \mu g/L)$$

VOLUME OF DISTRIBUTION

Table 1: Examples of volume of distribution estimates

Drug	% plasma protein binding	Lipid solubility/ tissue binding	Volume of distribution (L/kg)
Warfarin	99	low	0.14
Gentamicin	<10	low	0.25
Amoxicillin	18	low	0.30
Theophylline	40	low/medium	0.48
Phenytoin	90	medium	0.70
Diazepam	99	high	1.10
Digoxin	25	high	7.00
Amitriptyline	95	high	15.00
Chloroquine	61	high	115.00

VOLUME OF DISTRIBUTION

- Volume of distribution provides a reference for the plasma concentration expected for a given dose
- Vd is a pharmacokinetic parameter representing an individual drug's propensity to either remain in the plasma or redistribute to other tissue compartments
- Vd is a characteristic property of the drug rather than the patient, although disease states may influence Vd

VOLUME OF DISTRIBUTION

Clinical Significance

- Vd is used to determine the loading dose needed to achieve a certain target concentration.

Loading dose= Vd x desired concentration

- Predict effectiveness of dialysis in removal of drugs in overdose

RESEARCH

Wang Y, Chen L. Lung tissue distribution of drugs as a key factor for COVID-19 treatment. British Journal of Pharmacology. 2020 Nov;177(21):4995.

BIOETHICS

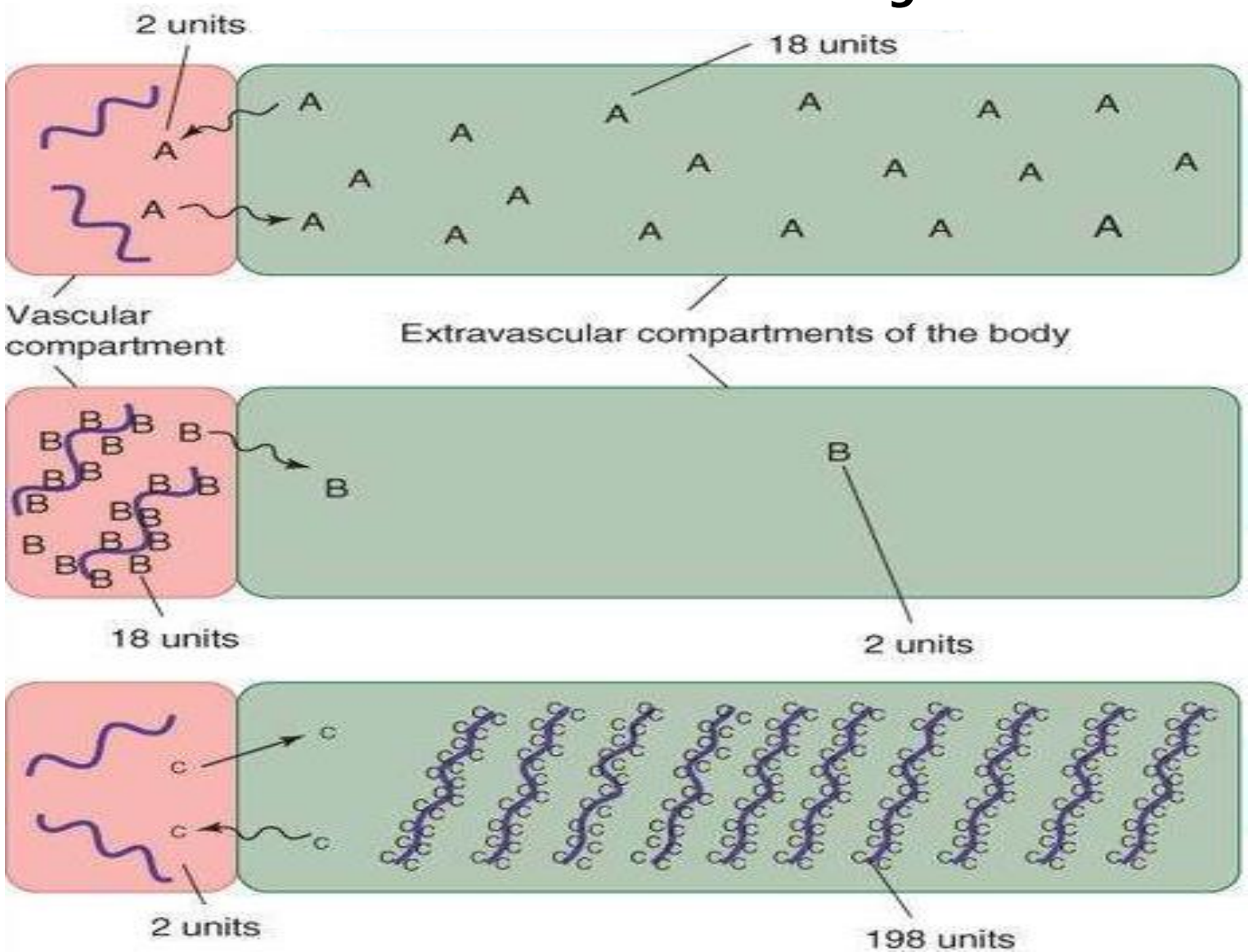
- Extensively bound drugs (phenytoin, diazepam etc) should be prescribed cautiously in patients with co –morbidities (chronic renal failure, chronic liver disease)

ARTIFICIAL INTELLIGENCE

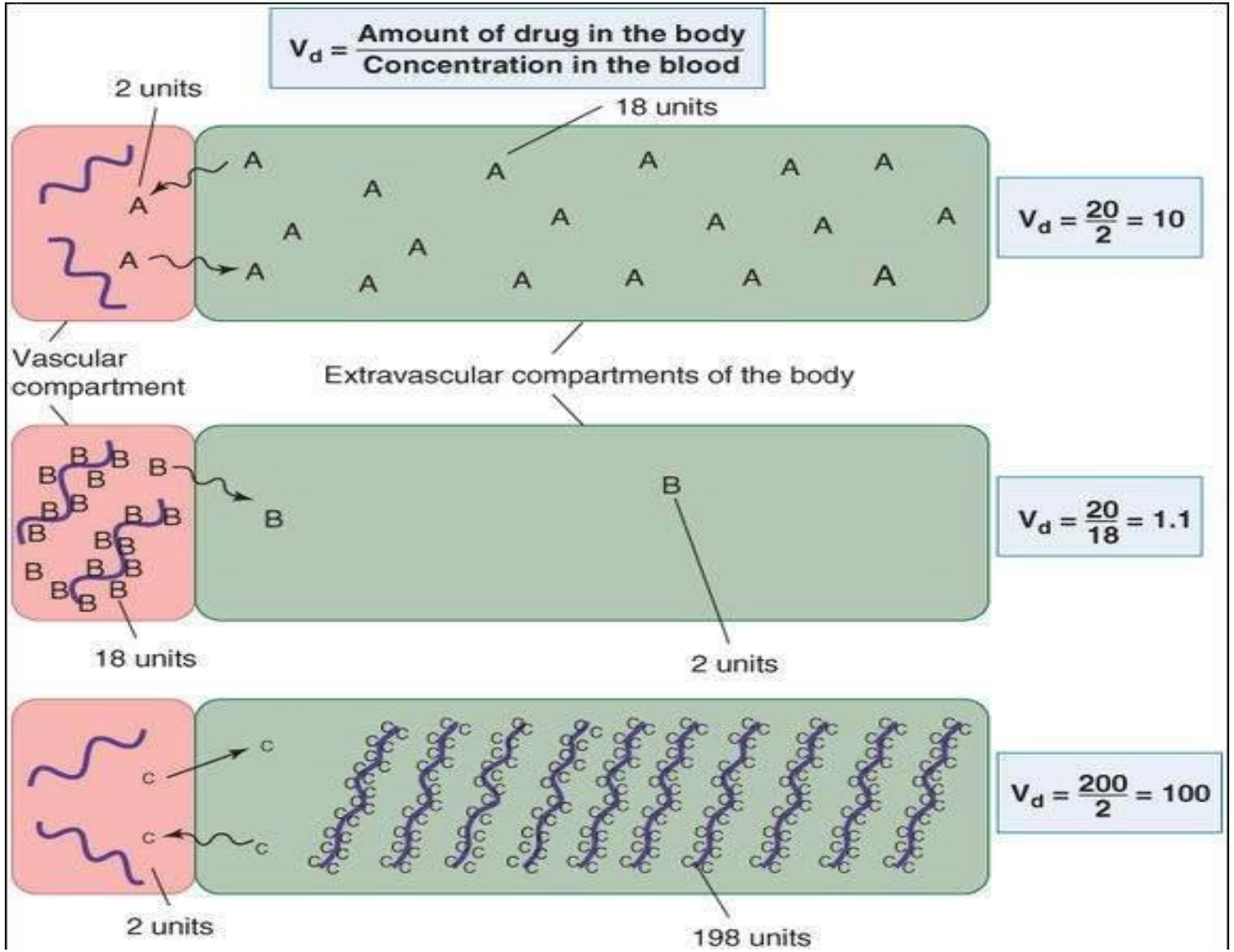
Yuan Y, Chang S, Zhang Z, Li Z, Li S, Xie P, Yau WP, Lin H, Cai W, Zhang Y, Xiang X. A novel strategy for prediction of human plasma protein binding using machine learning techniques. Chemometrics and Intelligent Laboratory Systems. 2020 Apr 15;199:103962.

END OF LECTURE ASSESSMENT

Calculate Vd in the following cases



END OF LECTURE ASSESSMENT



TAKE HOME MESSAGE

1. Drug molecules can bind to plasma protein and tissue protein.
2. Drugs diffuse into peripheral tissues by capillary filtration.
3. Lipophilicity of nonionized drug molecules affects diffusion; more lipophilic drugs diffuse faster and are retained for longer in fat-containing tissues.
4. Depending on a drug's potential for ionization, protein binding and lipophilicity, drugs distribute into various anatomical/ physiological spaces.