DRUG DISTRIBUTION

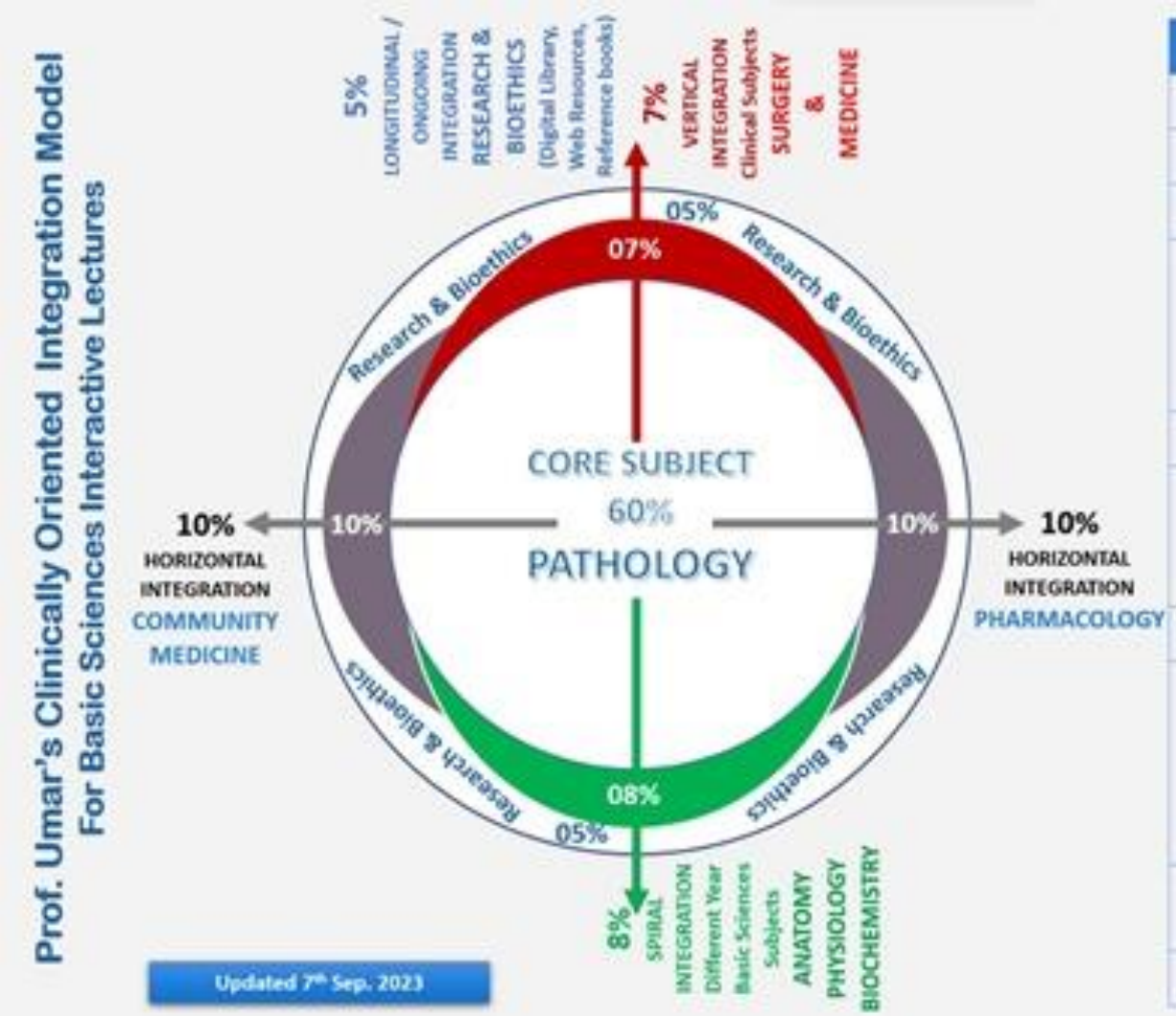
Katzung’ s Basic & Clinical Pharmacology, 16th Edition

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

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)	

Pre-Lecture Assessment

1. Drugs that dissolve in water (water-soluble drugs), such as such as the antihypertensive drug atenolol, tend to stay where in the body?

A. Ones
B. Blood
C. Muscle
D. Nerves
E. Fat

Pre-Lecture Assessment

2. Drugs that dissolve in fat (fat-soluble drugs), such as the antianxiety drug clorazepate, tend to concentrate in fatty tissues, which act as a reservoir of extra drug. How does this affect the distribution of a fat-soluble drug?

A. The drug's effects do not last long

B. It is more potent.

C. It must be taken more often.

D. Its effects are prolonged.

E. It has short t1/2

Pre-Lecture Assessment

3. Distribution of a drug may vary from person to person. Distribution of a fat soluble drug in older people may be similar to distribution in which other people?

A. Young people

B. Obese people

C. Thin people

D. Very thin people

E. Children

Pre-Lecture Assessment

4. The Initial distribution of drug into the tissue is determined chiefly by

A. Rate of blood flow to tissue

B. Plasma protein binding of drug

C. Affinity for tissue

D. Gastric emptying time

E. pH of the medium

Pre-Lecture Assessment

5. The distribution of drugs into the central nervous system (brain) usually depends on:

A. Aqueous diffusion
B. Lipid diffusion
C. Active transport
D. Facilitated transport
E. Endocytosis

Pre-Lecture Assessment

6. Which of the following is most likely to be associated with a high apparent volume of distribution

a. High hepatic extraction ratio

b. Penetration across the blood:brain and blood:testes barriers

c. Extensive binding to plasma protein

d. Extensive binding to tissue constituents

e. High clearance

Pre-Lecture Assessment

7. If the plasma concentration immediately after an IV bolus injection of 100 mg of drug is 8 ug/mL, what is the volume of distribution?

A) 12.5 mL

B) 800 mL

C) 80 L

D) 12.5 L

E) 125 L

Pre-Lecture Assessment

8. A 70 kg man with severe burns arrives in the Emergency Department and requires i.v. morphine to treat his pain. The Vd for morphine is 200 L. What i.v. loading dose do you need to give to rapidly achieve a therapeutic level of 60 ng/ml and relieve his pain?

A. 3 ug
B. 30 ug
C. 120 ug
D. 12 mg
E. 30 mg

Pre-Lecture Assessment

9. Which one of the following has very low perfusion rate?

a) Fat and bone

b) Muscle and skin

c) Lungs and kidney

d) Liver and Heart

e) Brain and kidney

Pre-Lecture Assessment

10. Following intravenous administration, drugs are distributed fastest to:

(a) the skin, kidney, and brain

(b) the liver, kidney, and brain

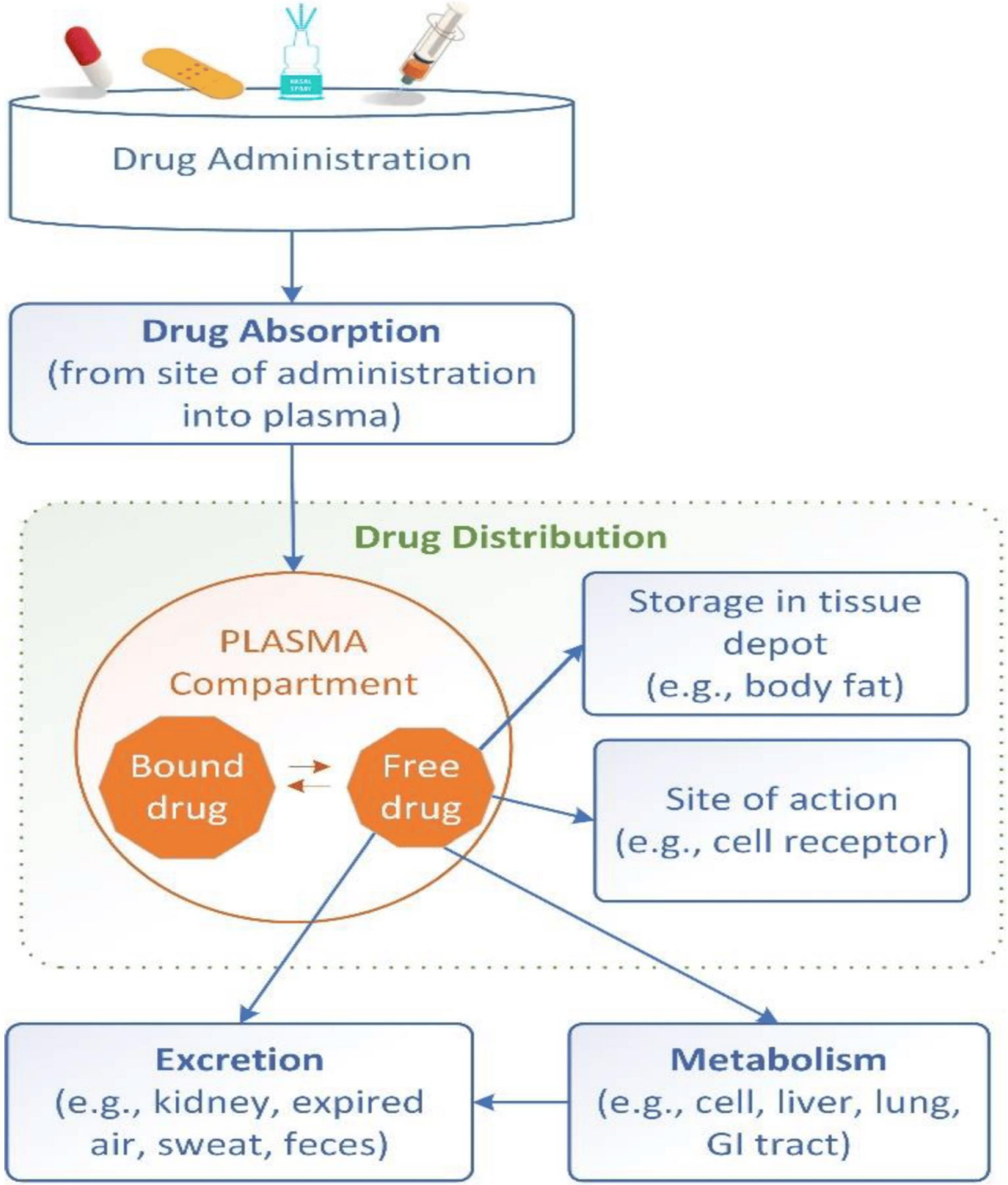
(c) the liver, adipose, and brain

(d) the liver, kidney, and adipose

(e) the lung , liver and bone

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

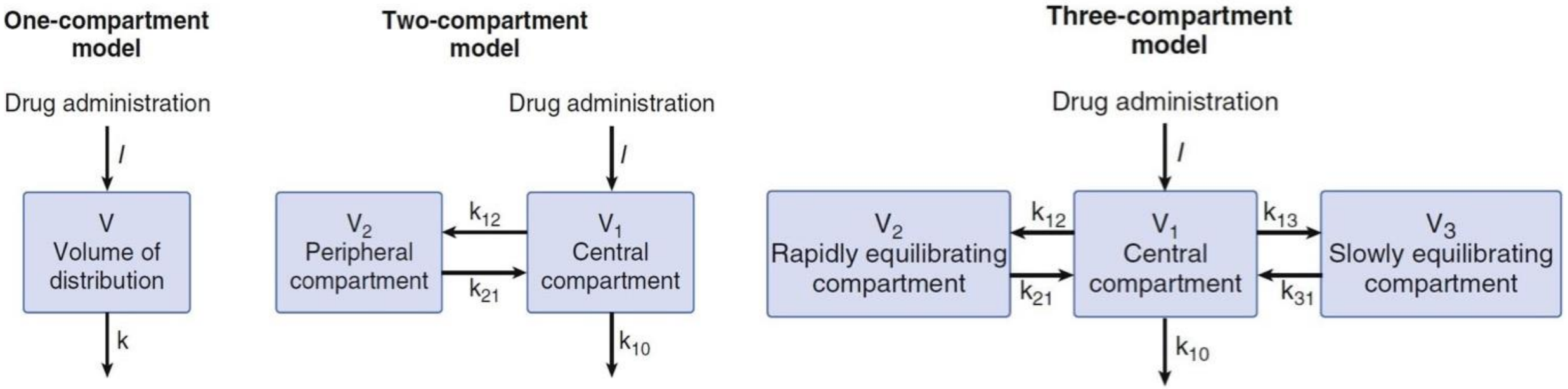
WHERE DO DRUGS GO?

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.

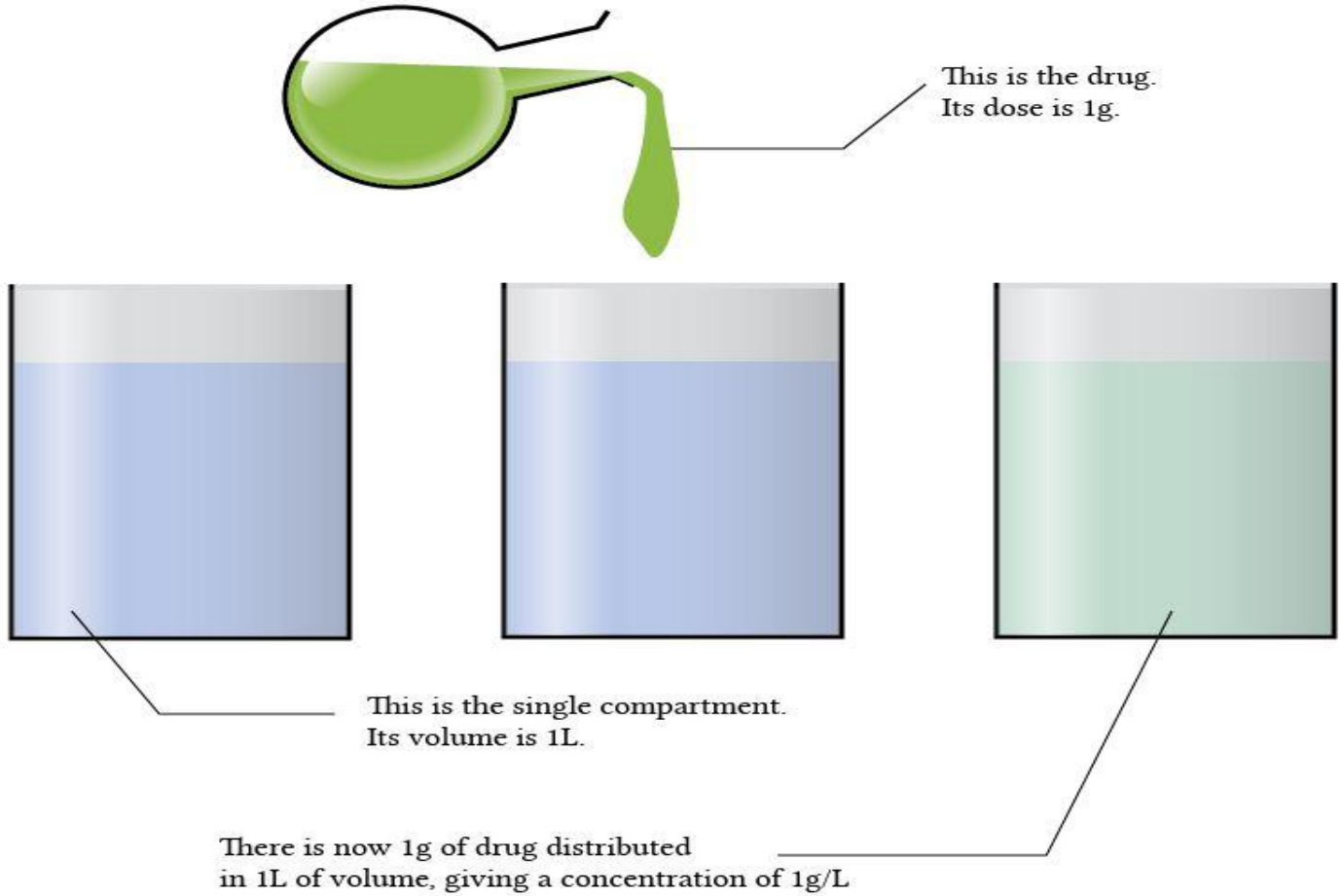
- Single compartment model
- Multiple compartment model

COMPARTMENT MODELS OF DRUG DISTRIBUTION



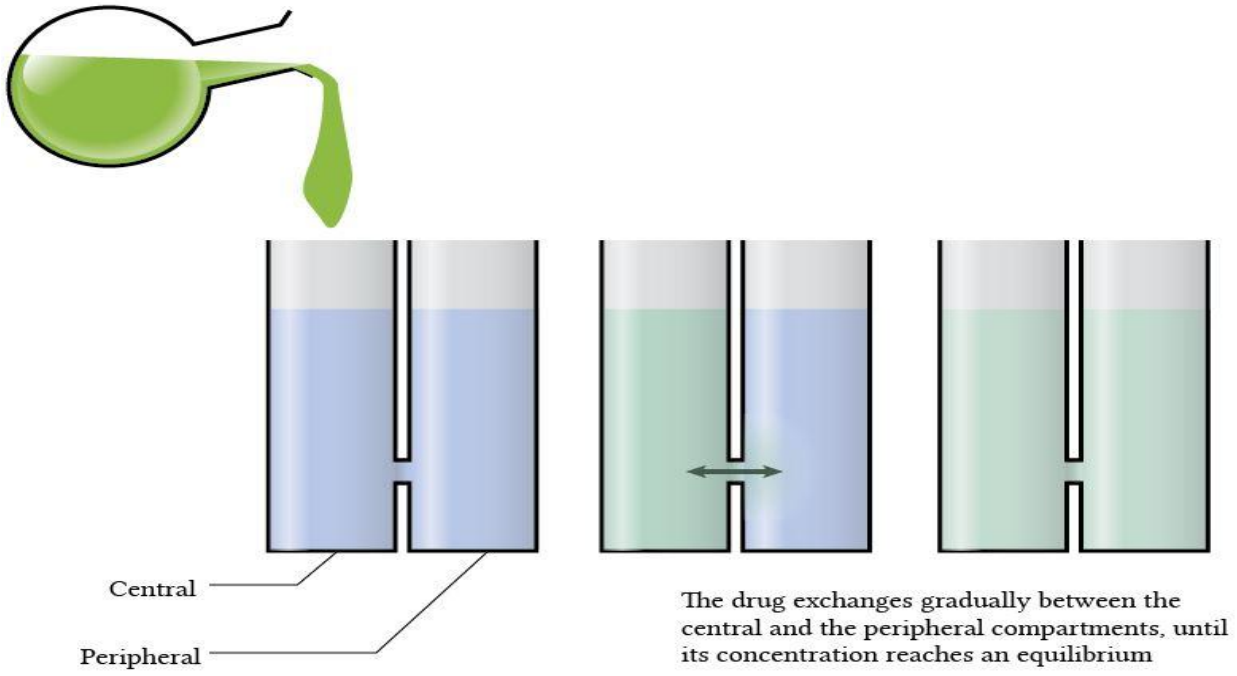
COMPARTMENT MODELS OF DRUG DISTRIBUTION

- **Single compartment model**

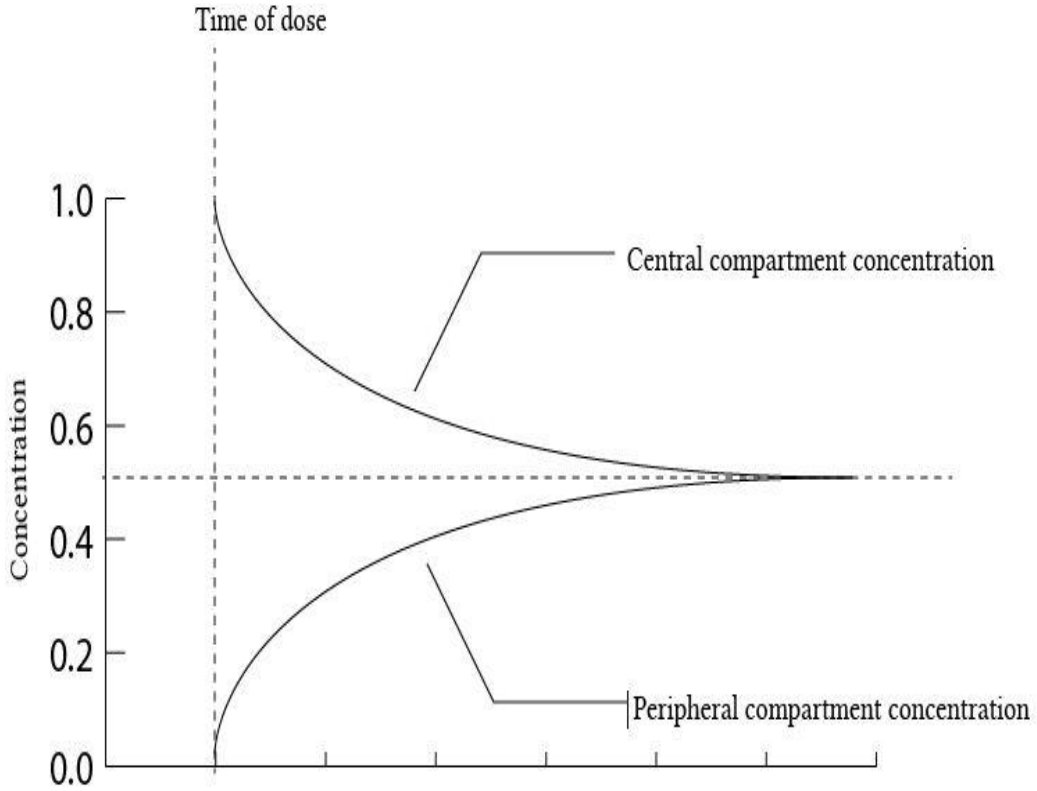


COMPARTMENT MODELS OF DRUG DISTRIBUTION

- **Two compartment model**

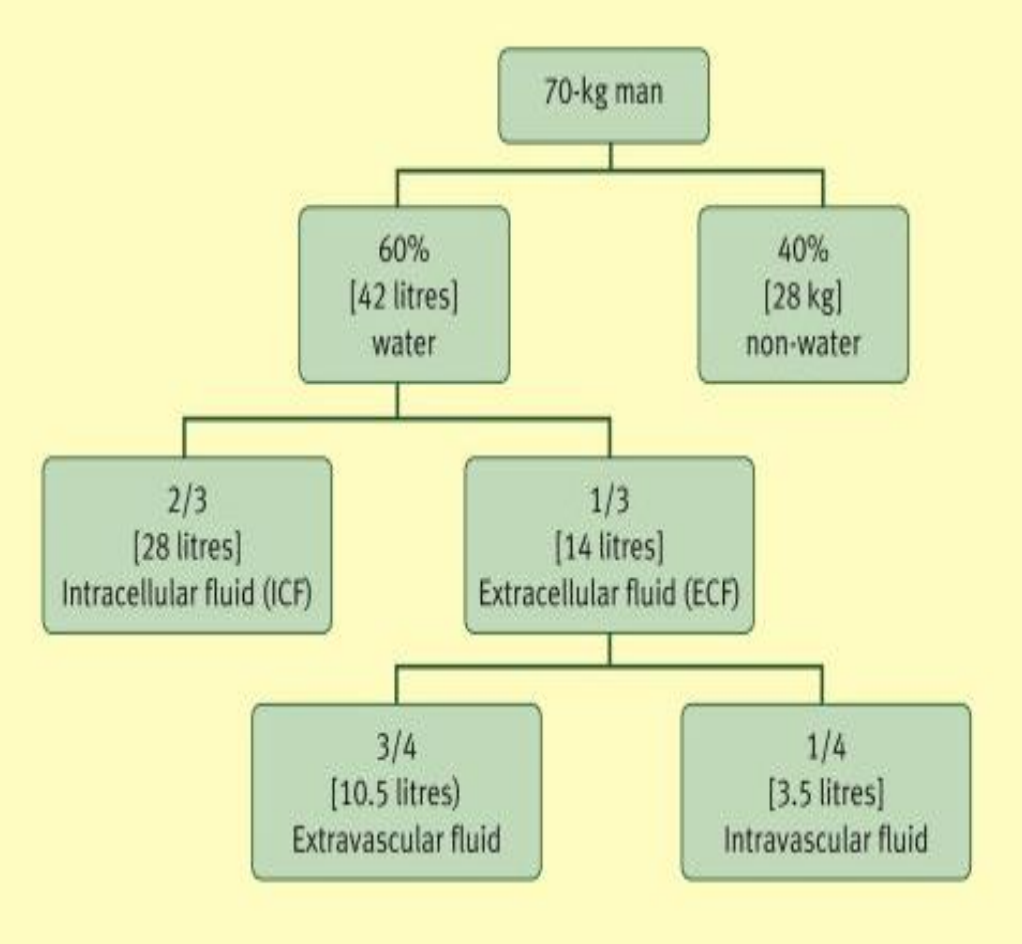


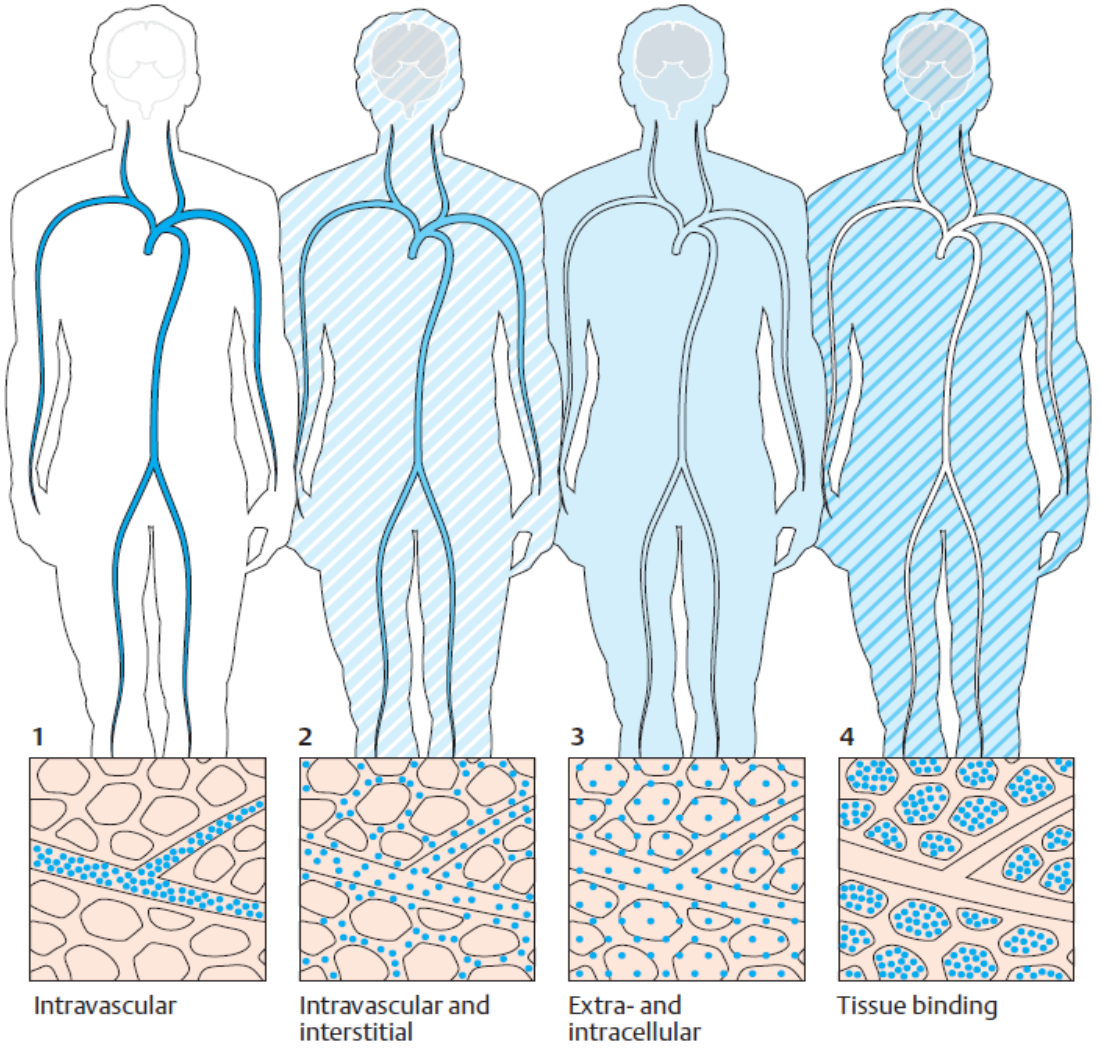
The drug exchanges gradually between the central and the peripheral compartments, until its concentration reaches an equilibrium



PHYSIOLOGICAL SPACES FOR DRUG DISTRIBUTION

DISTRIBUTION OF BODY VOLUMES

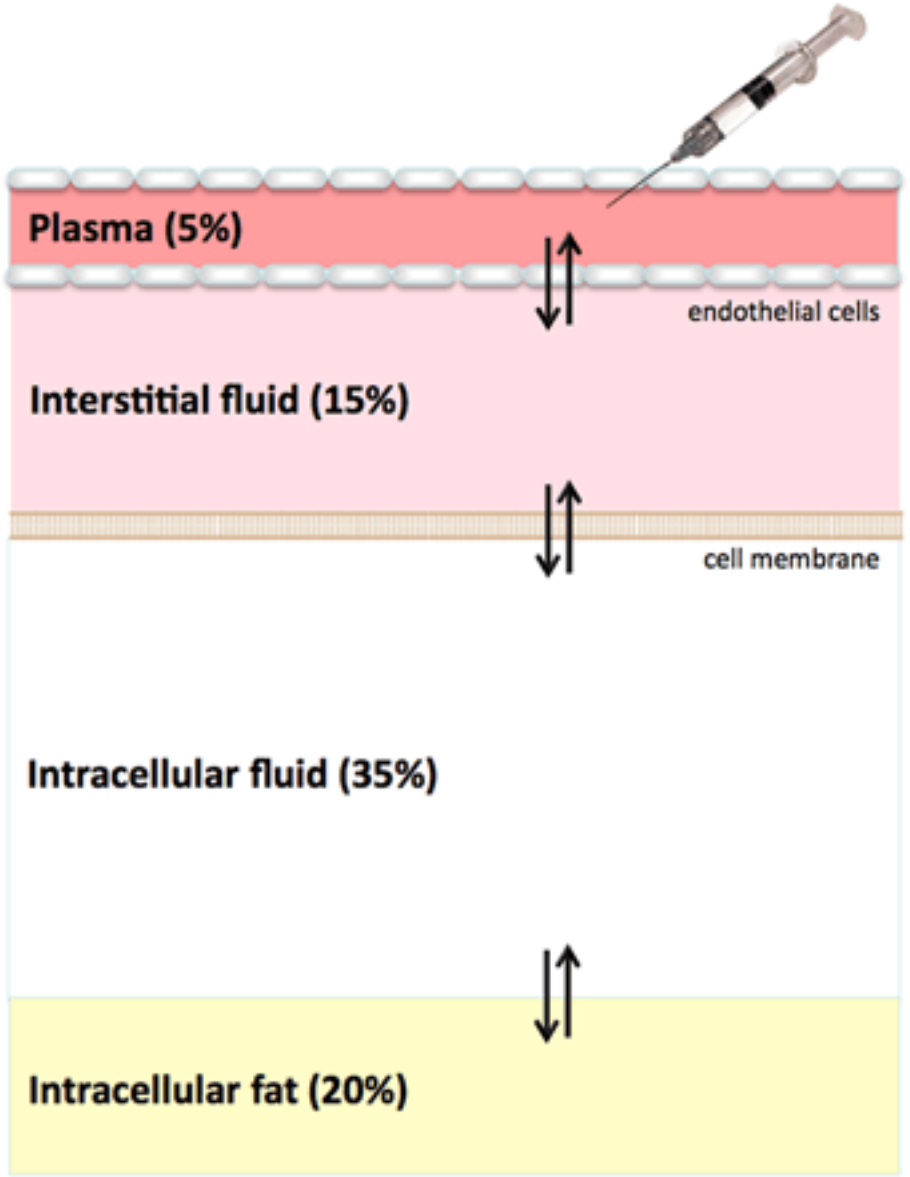




Spiral Integration- Physiology

PHYSIOLOGICAL SPACES FOR DRUG DISTRIBUTION

DISTRIBUTION OF BODY VOLUMES



STEPS OF DRUG DISTRIBUTION

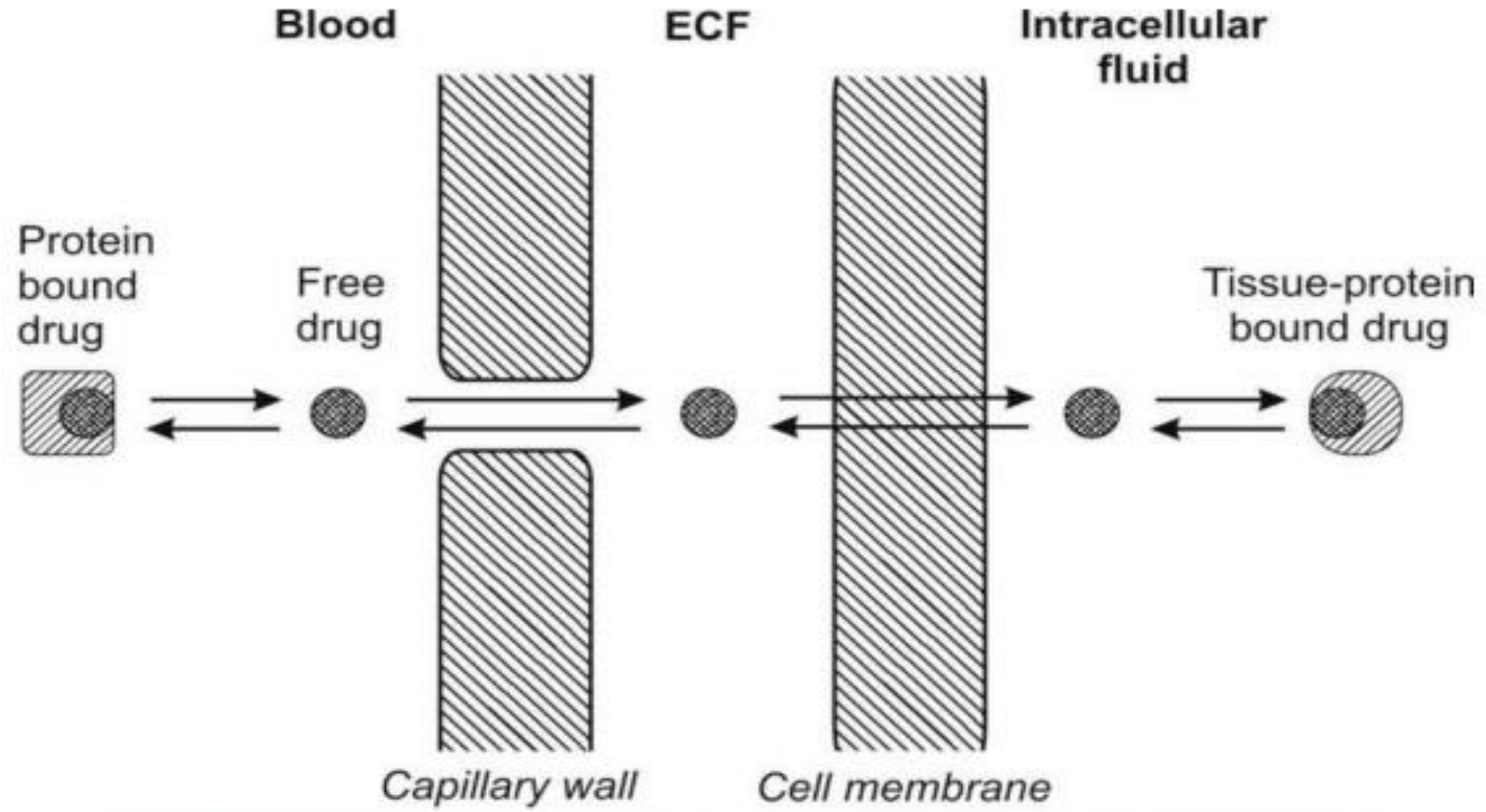
- Permeation of free or unbound drug present in the blood through the capillary wall (occurs rapidly) and entry into the interstitial/extracellular fluid (ECF).

- Permeation of drug present in the ECF through the membrane of tissue cells into the intracellular fluid. This step is rate-limiting and depends upon two major factors

❖ Rate of perfusion to the extracellular tissue

❖ Membrane permeability of the drug

STEPS OF DRUG DISTRIBUTION



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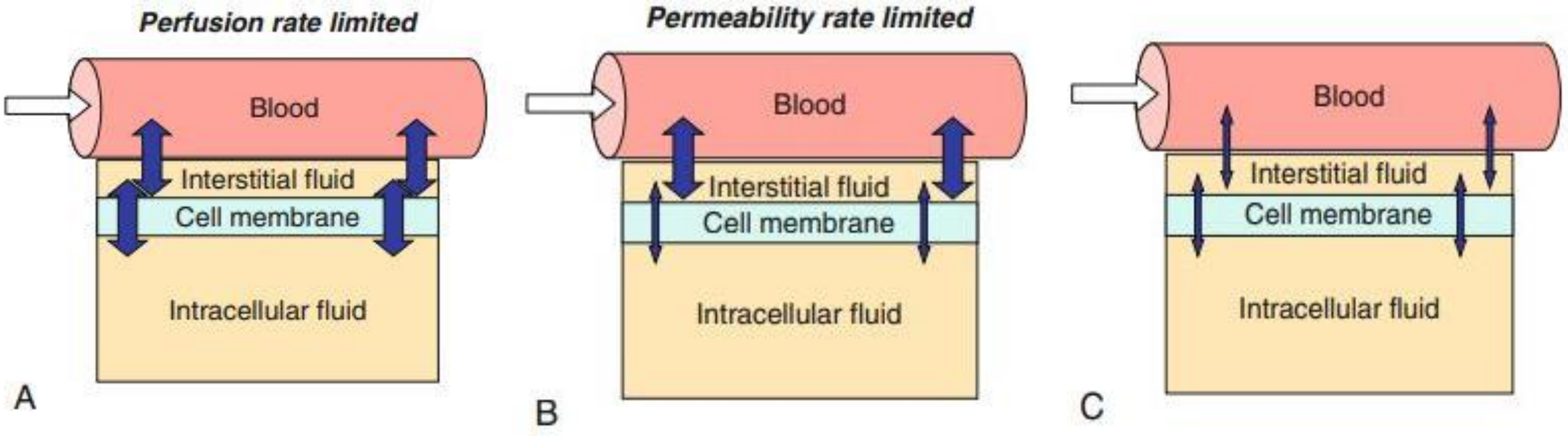
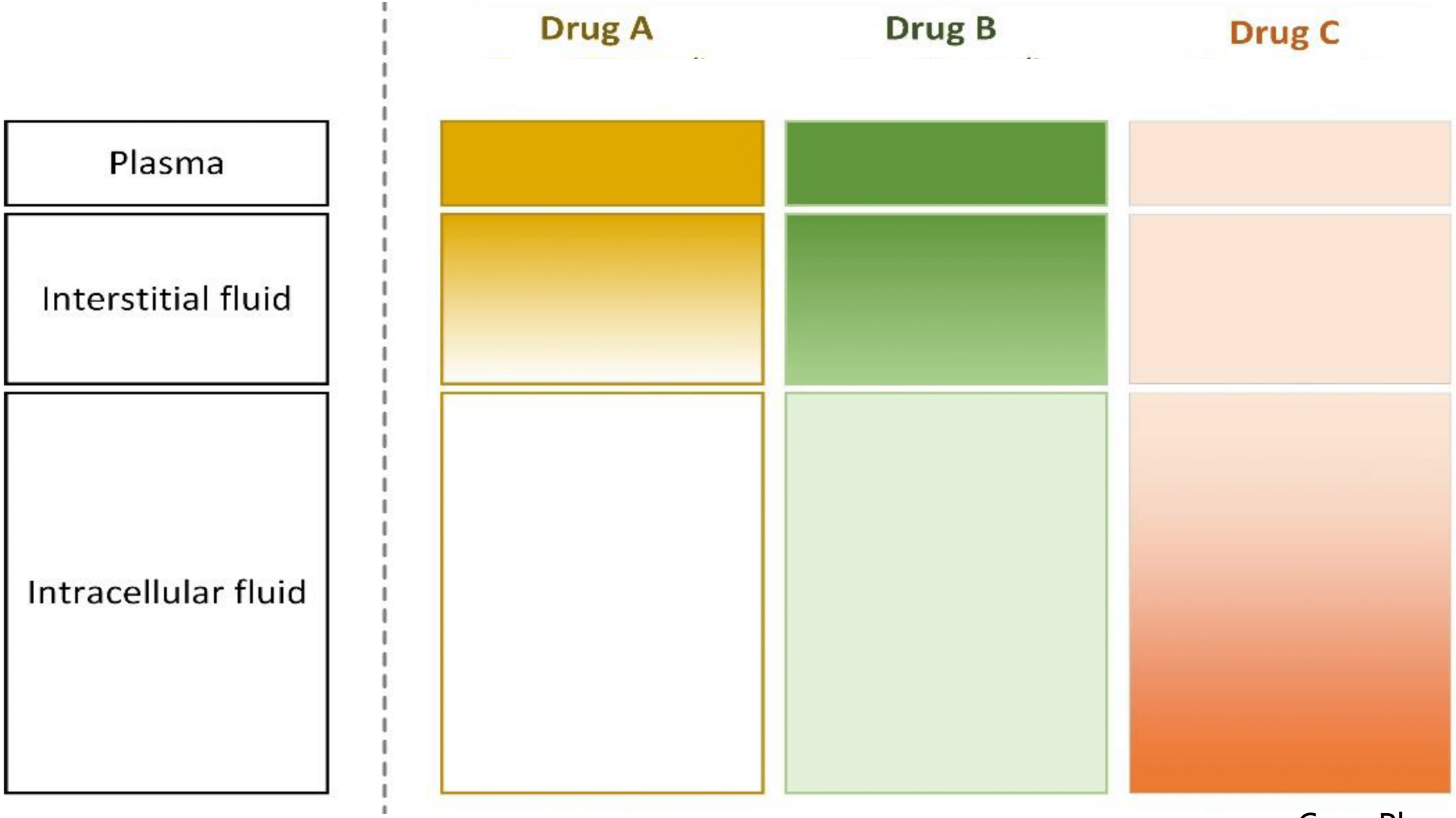


DRUG DISTRIBUTION

NOT ALL TISSUES ARE EQUAL

DISTRIBUTION PATTERN OF DRUGS

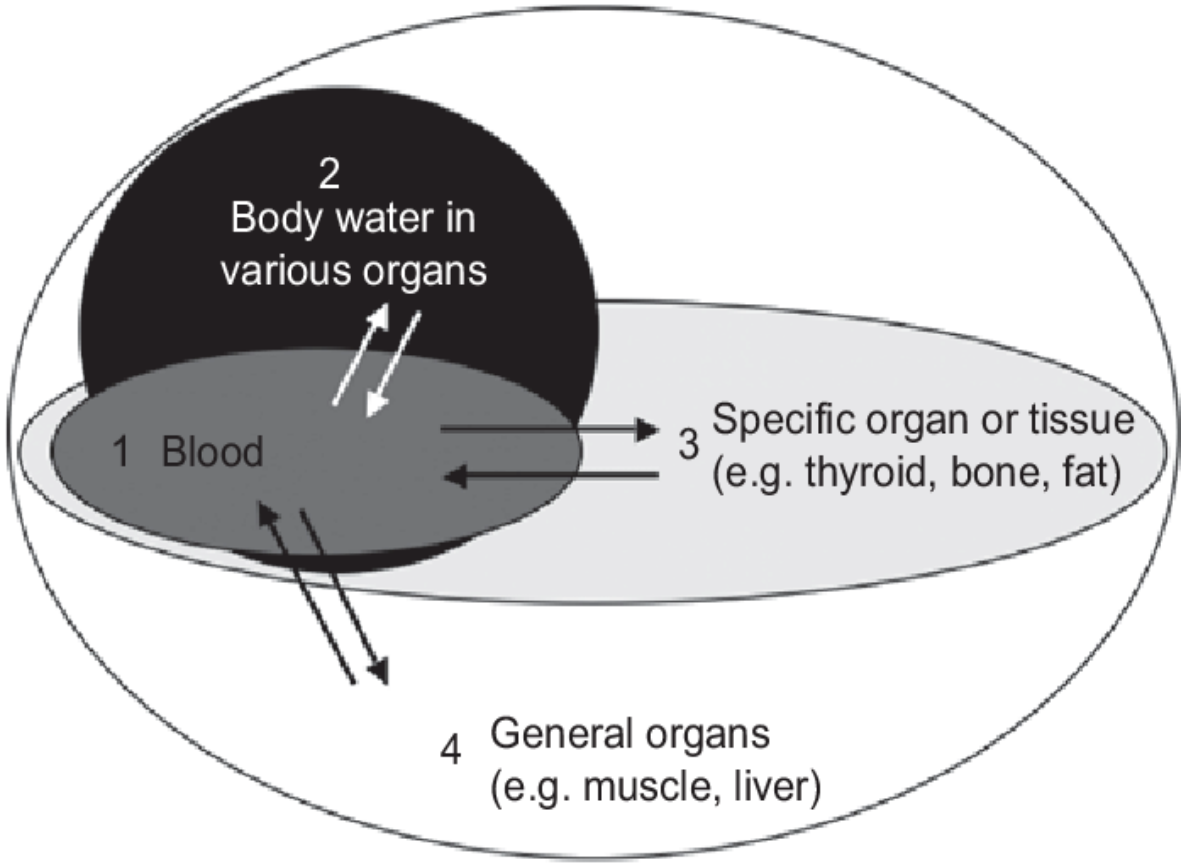


DISTRIBUTION PATTERN OF DRUGS

- 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



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.

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.