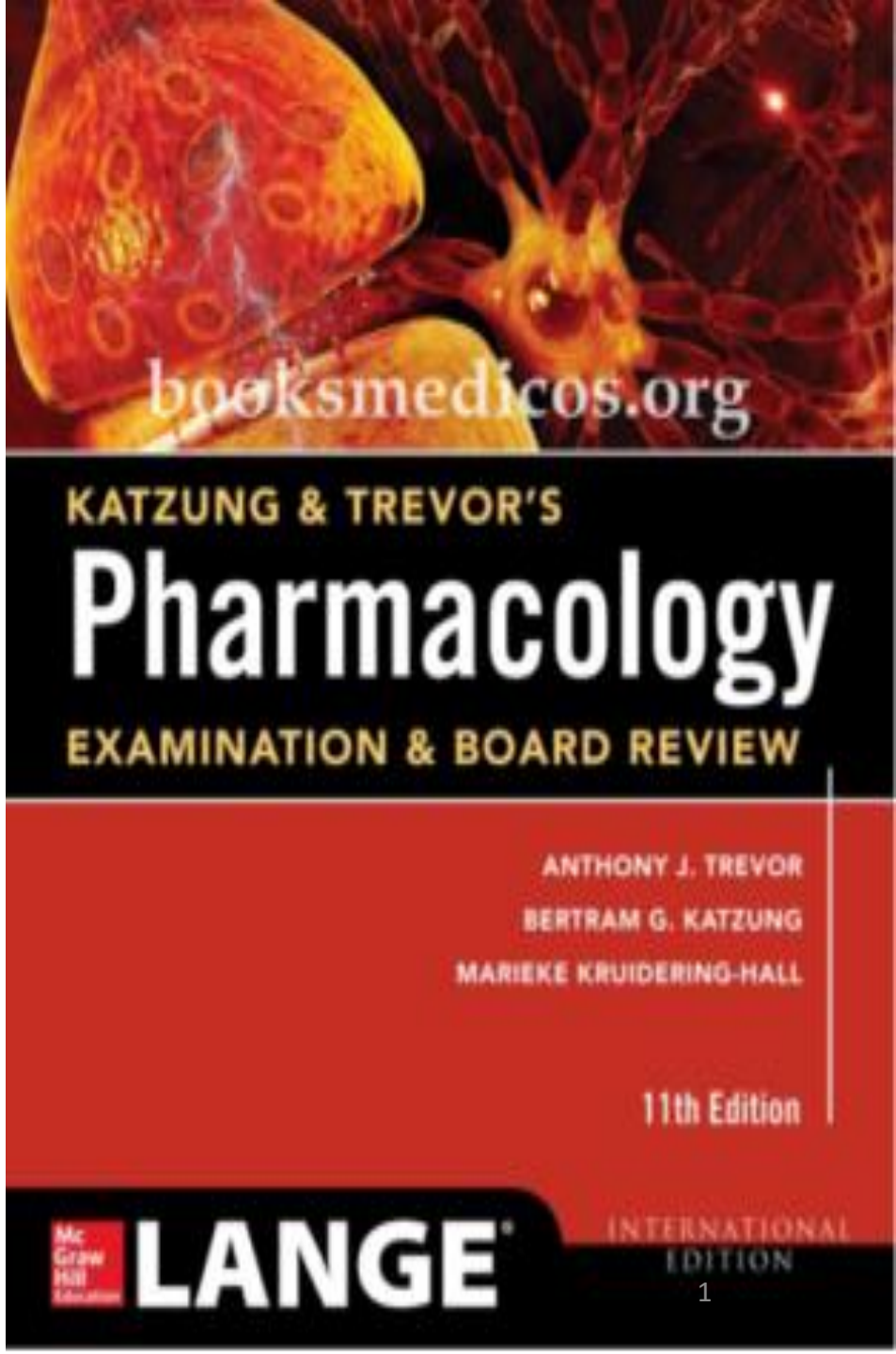
BASIC PRICIPLES OF PHARMACOLOGY



by Kabandize Balaam

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Learning outcomes

At the end of the course, you should:

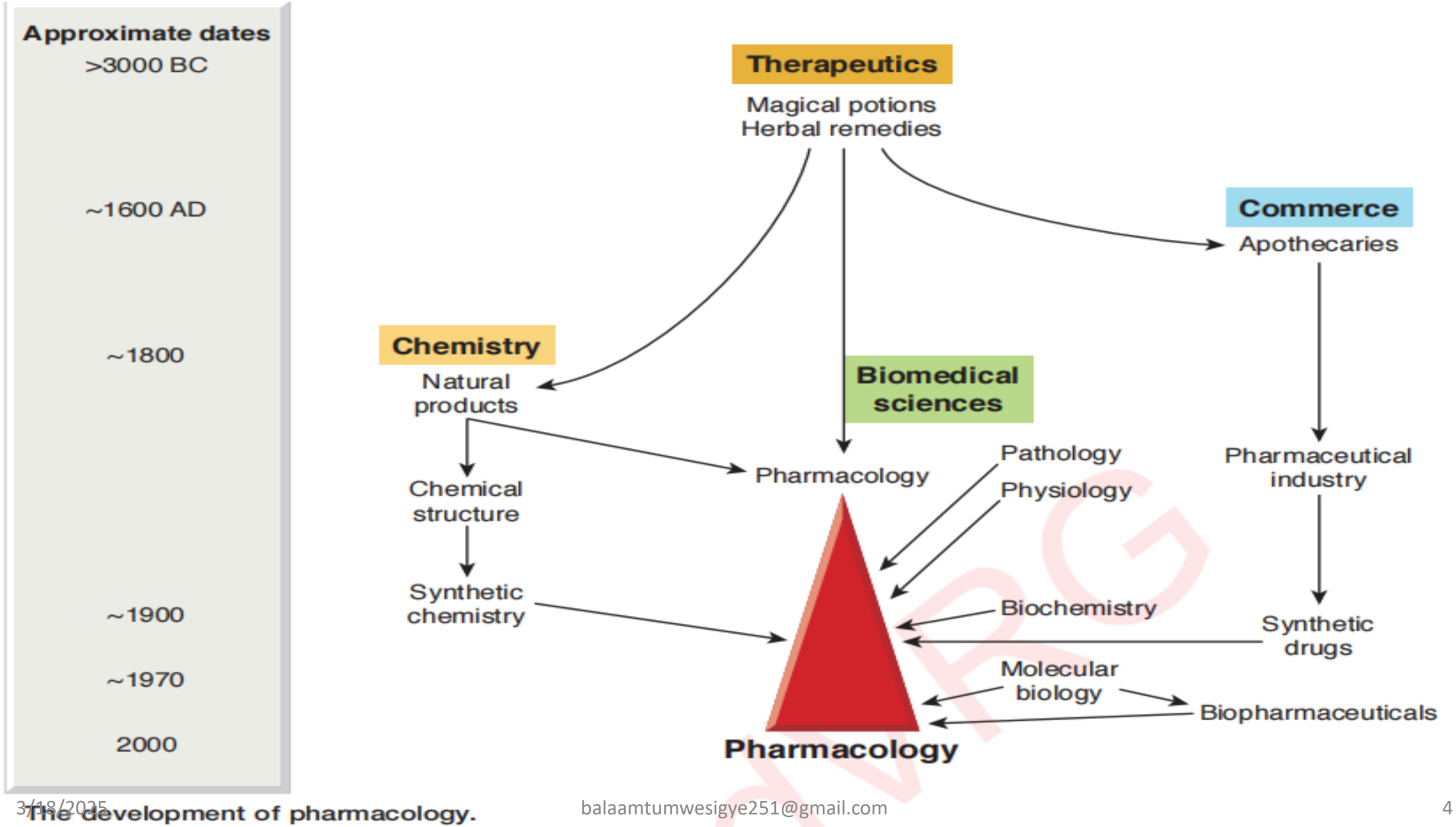
1. Explain the basic principles of pharmacology
2. Compare and contrast the common routes of drug administration
3. Analyze general factors governing drug action
4. Describe the actions of drugs in the body and how the body transforms given drugs

What is pharmacology??

- The term pharmacology comes from two Greek words:
  - pharmacon - drug or medicine
  - logos - meaning science
- Pharmacology can be defined as the study of the effects of drugs/chemicals on the function of living systems

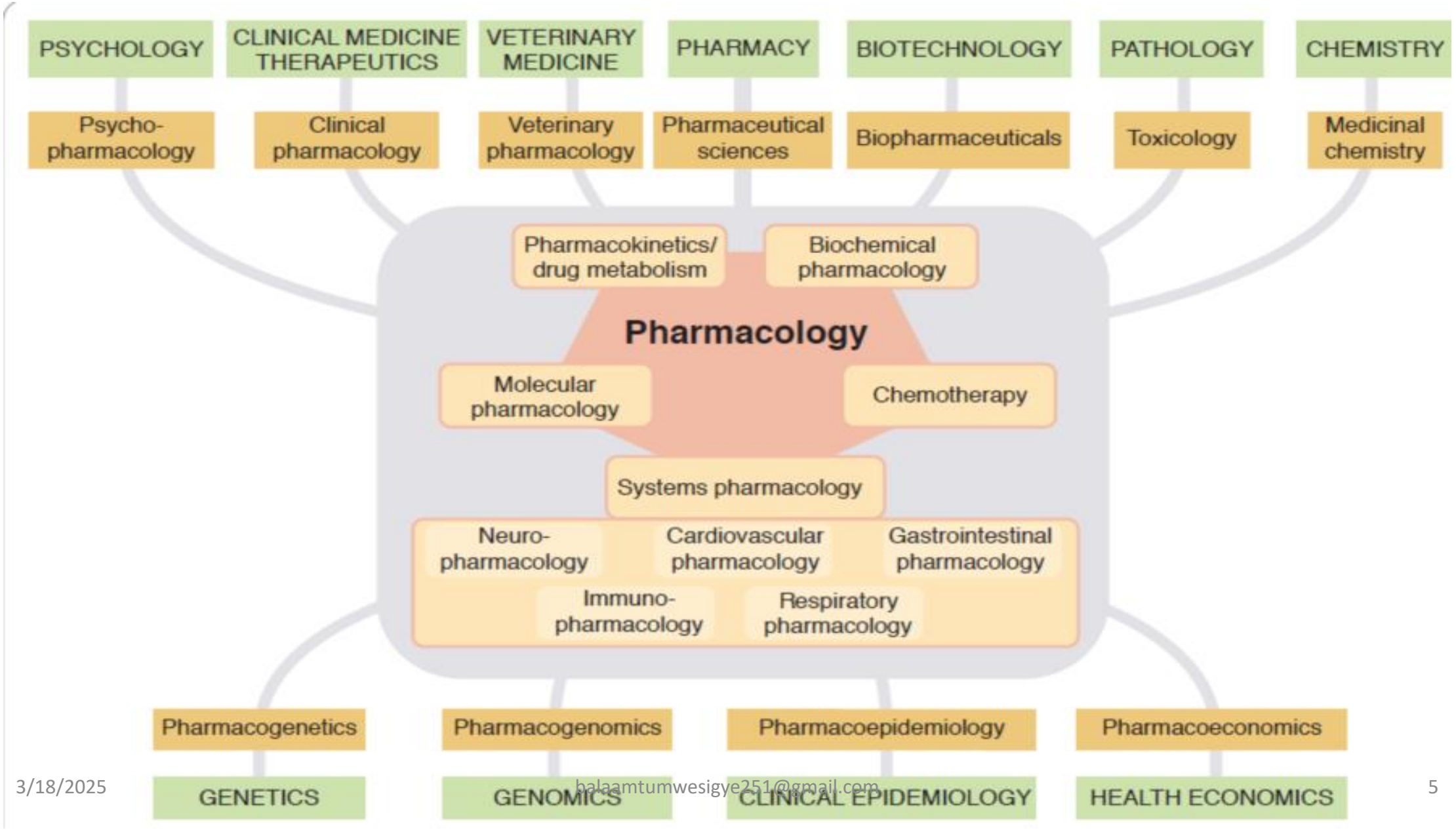
- medical pharmacology- focuses particularly on how drugs/ chemicals help to:
  - Prevent diseases
  - Correct physiology of living tissues
  - Cure or minimize diseases, etc

Evolution of pharmacology



The development of pharmacology.

Pharmacology with its various subdivisions



What is a drug?

- a chemical substance of known structure, other than a nutrient or an essential dietary ingredient, which, when administered to a living organism, produces a biological effect.

- Substances used to cure, control, prevent or diagnose a disease
- Drugs can be for therapeutic use (treatment), prophylactic use (prevention), or diagnostic use (diagnosis)

- Drugs may be synthetic chemicals, chemicals obtained from plants or animals, or products of genetic engineering

Explained

Targets for drug action

- A drug is a chemical applied to a physiological system that affects its function in a specific way.
- With few exceptions, drugs act on target proteins, namely:
  - receptors
  - enzymes
  - carriers
  - ion channels.
- The term *receptor* is used in different ways. In pharmacology, it describes protein molecules whose function is to recognise and respond to endogenous chemical signals. Other macromolecules with which drugs interact to produce their effects are known as *drug targets*.
- Specificity is reciprocal: individual classes of drug bind only to certain targets, and individual targets recognise only certain classes of drug.
- No drugs are completely specific in their actions. In many cases, increasing the dose of a drug will cause it to affect targets other than the principal one, and this can lead to side effects.

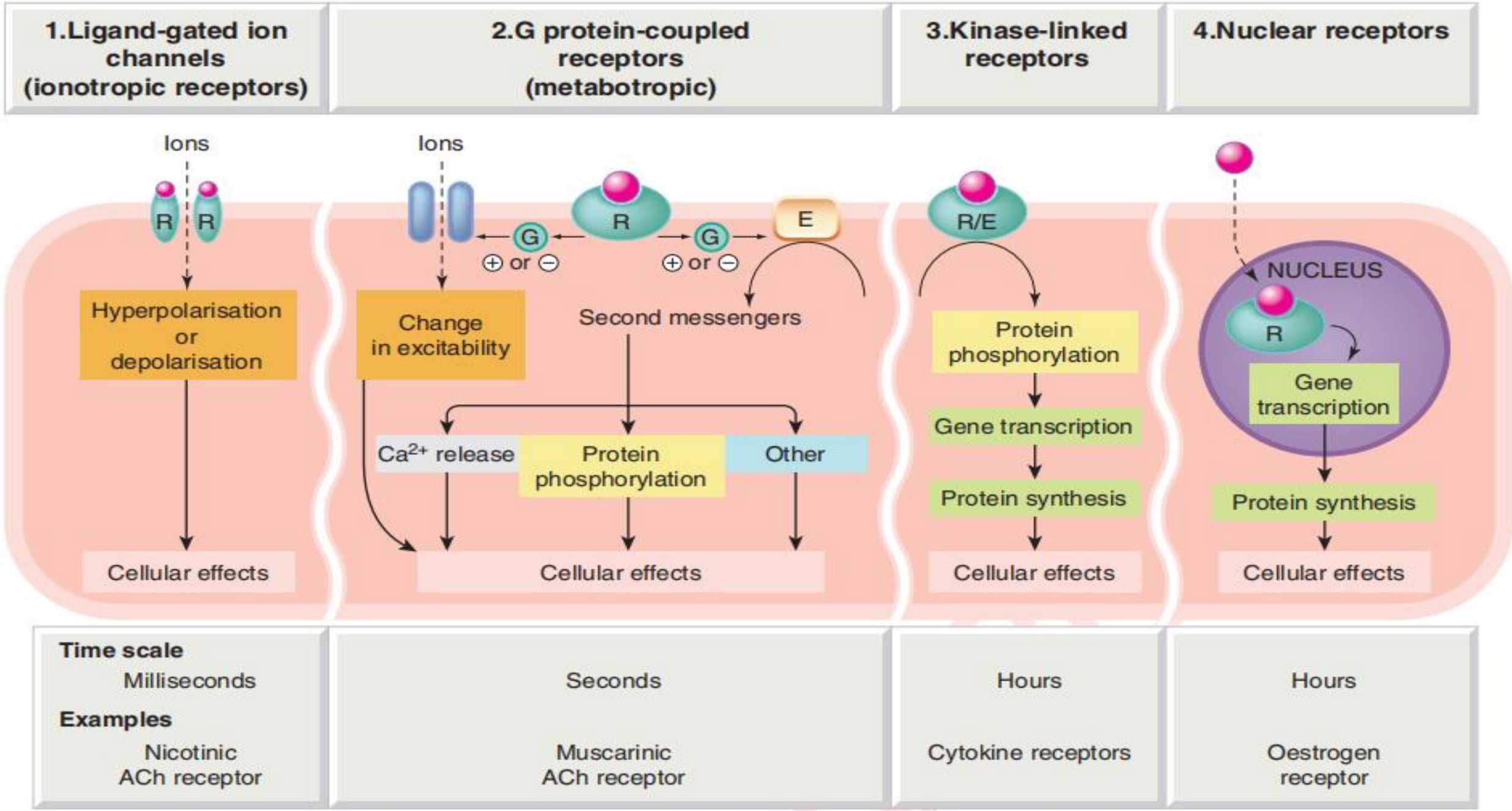


Fig. 3.2 Types of receptor–effector linkage. ACh, acetylcholine; E, enzyme; G, G protein; R, receptor.

Sources of Drugs

1) Plant Origin

- Opium: Morphine group.
- Cinchona bark: Quinine etc.
- Belladonna: Atropine group
- Vinca: Vincristine, vinblastine.
- Digitalis: Digoxin etc.

2) Animal Sources

- Pancreas of beef or pig: Insulin
- Thyroid gland: thyroxine
- Blood of horse: Anti-snake venom

Sources continued

3) From Human Being

- Immunoglobulins: From blood.
- Human Chorionic gonadotropin (HCG): From urine of pregnant women.
- Growth hormone: From pituitary gland.

4) From Microorganisms

- Penicillin: Penicillium chrysogenum and notatum (Fungus).
- Streptomycin: Streptomyces griseus (Actino-mycetes).
- Erythromycin: Streptomyces erythreus (Actinomycetes).
- Nystatin: Streptomyces nouresi.
- Griseofulvin: Penicillium griseofulvum.

Continued

- A drug generally has 3 categories of names:

(a) Chemical name: describes the substance chemically, e.g. **1-(Isopropylamino)-3-(1-naphthalloxy) propan-2-ol** for propranolol

(b) Non-proprietary (generic) name: name accepted by a competent scientific body authority, e. g. USAN(United states adopted Name), BAN and rINN(recommended international nonproprietary name) drug.

- Many older drugs still have more than one non-proprietary names, e.g. 'meperidine' and 'pethidine' or 'lidocaine' and 'lignocaine' for the same drugs

Continued

(c) Proprietary (Brand) name: **name assigned by the manufacturer(s) and is his property or trade mark.**

- **One drug may have multiple proprietary names, e.g. ALTOL, ATCARDIL, ATECO, ATEN, BETACARD, LONOL, TENOLOL,TENORMIN for atenolol from different manufacturers.**

- **Designed to be catchy, short, easy to remember and often suggestive, e.g. feverex drug for lowering fever**

Non-proprietary (generic) name vs *Proprietary (Brand) name*

- **Nonproprietary name sh'd be used in prescribing b'se of:**
  - **uniformity,**
  - **convenience,**
  - **economy and**
  - **better comprehension**

- **When it is important to ensure consistency of the product in terms of quality and bioavailability, *Proprietary (Brand) name* sh'd be used.**

For example for panadol

Panadal

Tylenol Trade name

Komadol

Paracetamol – Generic name

N-acetyl – P – amino phenol Chemical name

EXAMPLE	
Proprietary name:	Rapifen®, Alfenta®
Common name:	Alfentanil hydrochloride
Chemical name:	N-(1-(2-(4-ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl)ethyl)-4-(methoxymethyl)-4-piperidinyl)-N-phenylpropanamide hydrochloride

Classification of drugs

- There is an internationally accepted drug classification criterion.
- Its however important to classify drugs in order to reduce them into smaller manageable groups.
- There are several classifications used including the following:-
  - According to **the body system** e.g cardiovascular drugs, renal drugs.
  - According **to the effect of the drug**. This is mainly used by clinicians e.g diuretics, stimulants, Bacteriostatic e.t.c
  - Basing on **the chemical structure**. Its often used by chemists e.g steroids, Barbiturates e.t.c
  - **Physiological classification** e.g parasympathomimetic drugs, Adrenergic, Neuromuscular drugs e.t.c.
  - **Basing on the source of the drug**:- This is usually done by identification of the plant source of the drug e.g digitalis extract
- Of these classifications, **classification according to the body system is the commonly used**.

ASSIGNMENT

Read and write notes on the following;
The classification of routes of drug administration
The sub-routes, and their respective indications
The ‘Rights of medication administration’
Application of pregnancy category of drug classification in clinical pharmacology

Ref: Rang- Dale´s Pharmacology Text Book
pg 109

Think critically

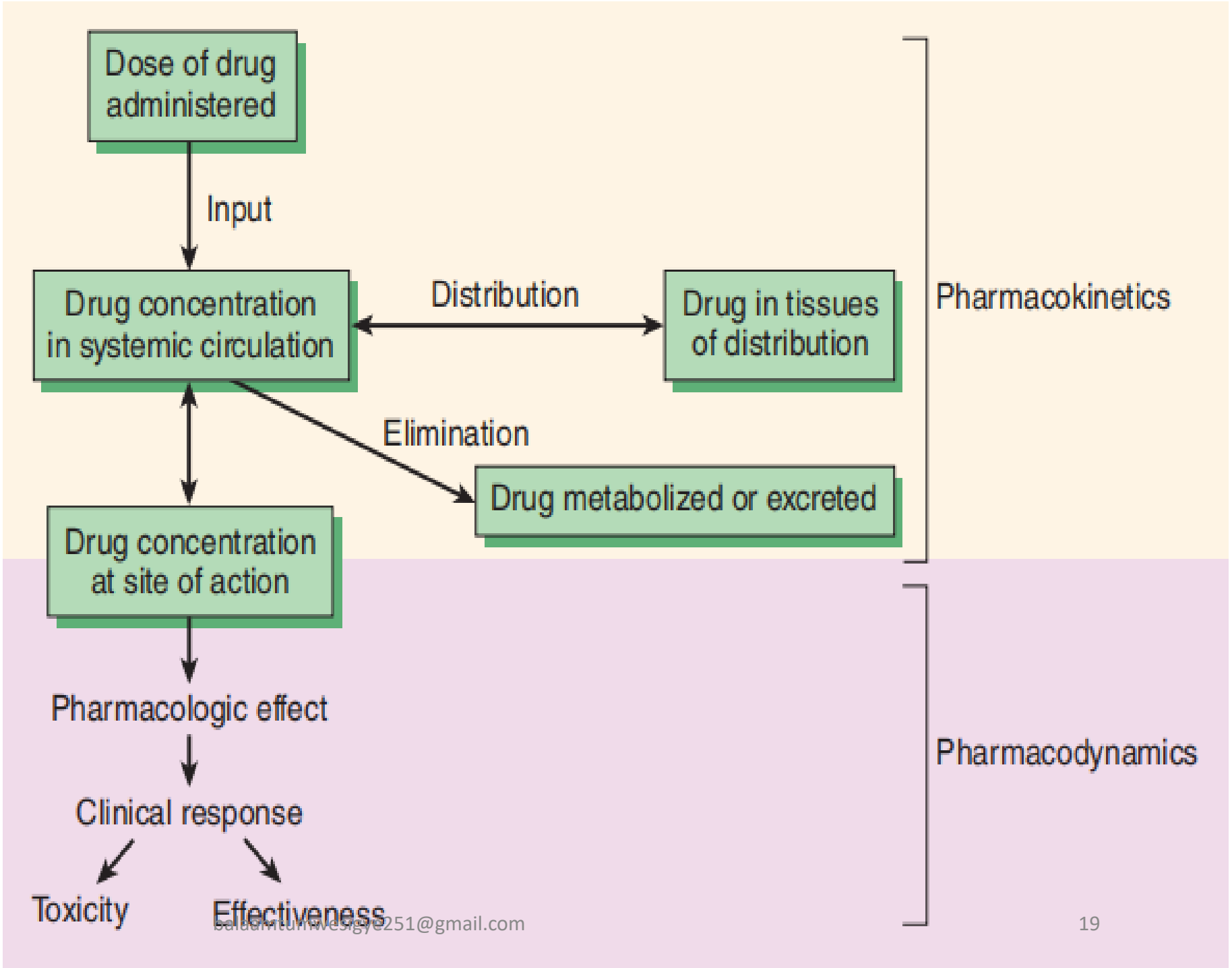
- **Four patients with angina are receiving a form of nitroglycerin, as follows:**
- Mrs. A., age 88, takes 9 mg twice a day to prevent angina.
- Mr. B., age 63, takes a form that delivers 0.2 mg/hr, also to prevent angina.
- Mrs. C., age 58, takes 0.4 mg only if needed for chest pain.
- Mr. D., age 62, is in the hospital with severe, unstable angina and is receiving 20 mcg/hr.

- State the route or form of nitroglycerin that each patient is receiving.
- 2. For each patient, state the rationale for the route or form of drug that was chosen. Which forms have immediate action? Why would this be important?
- 3. Which form or forms are most affected by the first-pass effect? Explain your answer.
- 4. What would happen if Mrs. A. chewed her nitroglycerin dose? If Mrs.C. chewed her nitroglycerin dose?

Session two

PHARMACOKINETICS
PHARMACODYNAMICS

Look at this



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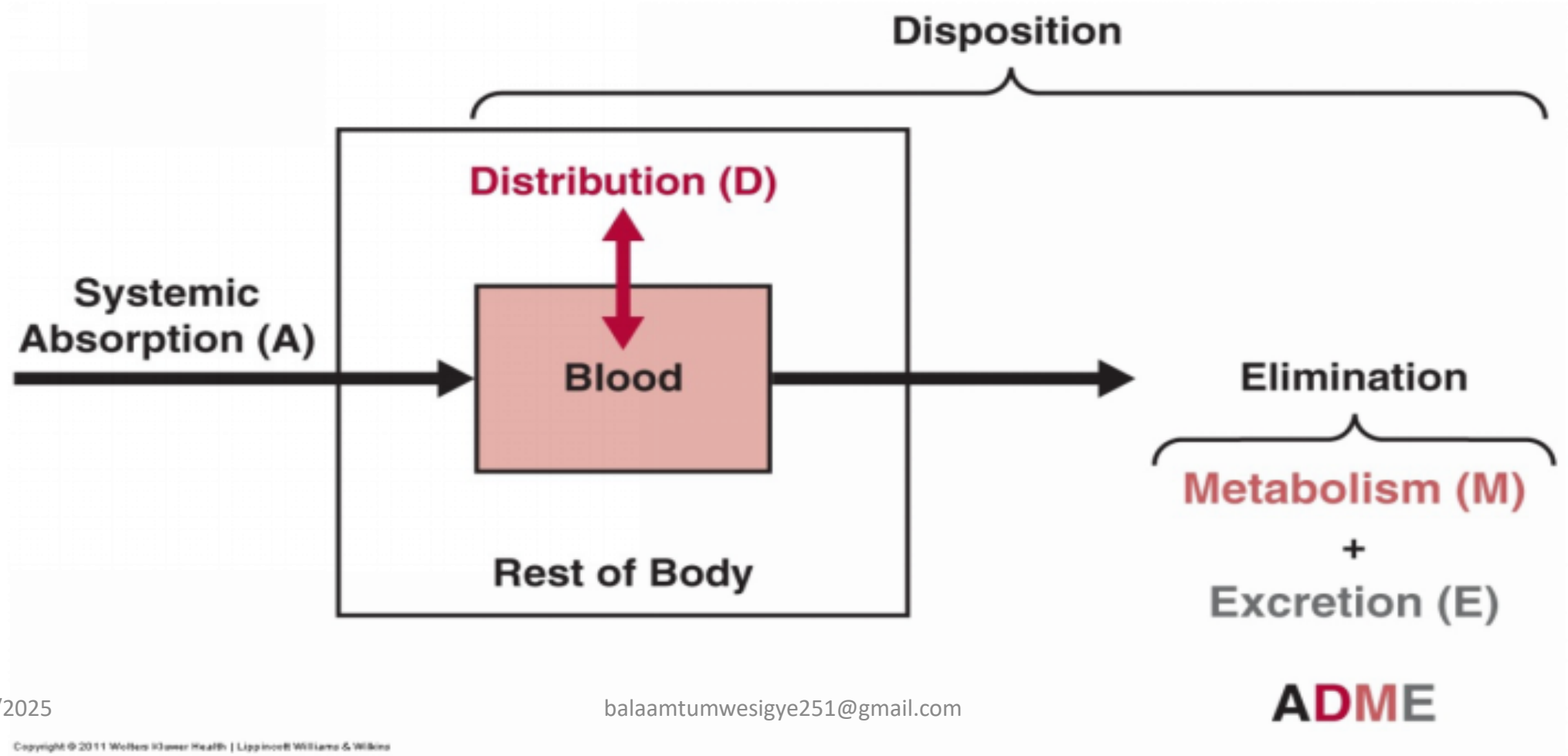
PHARMACOKINETICS

- **The time course of drug concentrations in the body as determined by the processes of absorption, distribution, metabolism and excretion (ADME)**



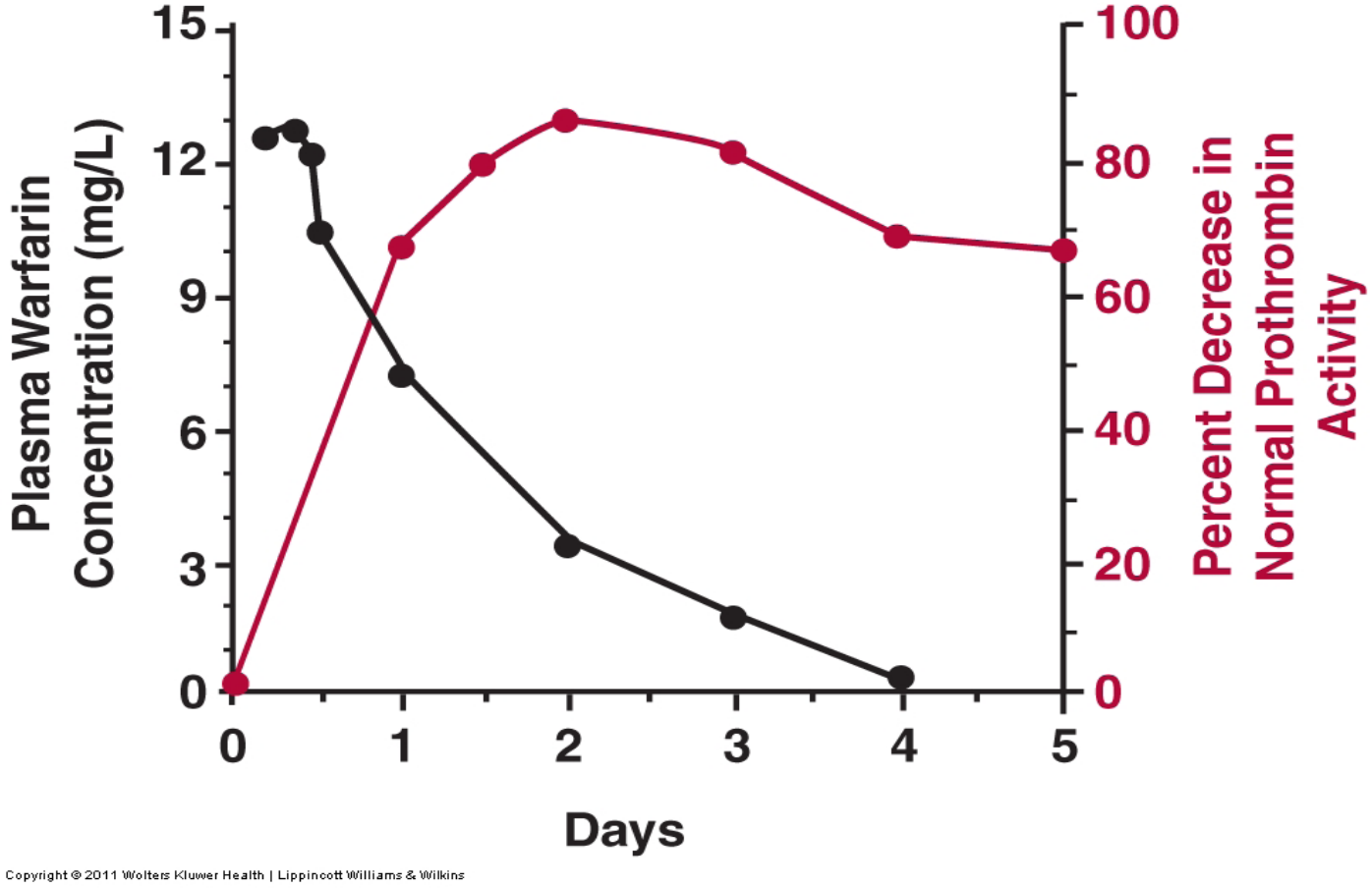
PHARMACODYNAMICS

- **Pharmacodynamics (PD): The time course of drug effects.**
  - **PD effects may influence responses of *efficacy or safety.***
  - **PD effects are dependent upon exposure to a drug (PK/PD).**
  - **PK and PD models can be combined to provide a representation of the time course of drug response referred to as PK/PD modelling-**
  - **Clinical PK – application of the principles of PK and PD to individual patient (prescribing the right dose)**

The two compared

- **“Pharmacokinetics may be simply defined as what the body does to the drug,**

- **Pharmacodynamics may be defined as what the drug does to the body**



The ADME approach

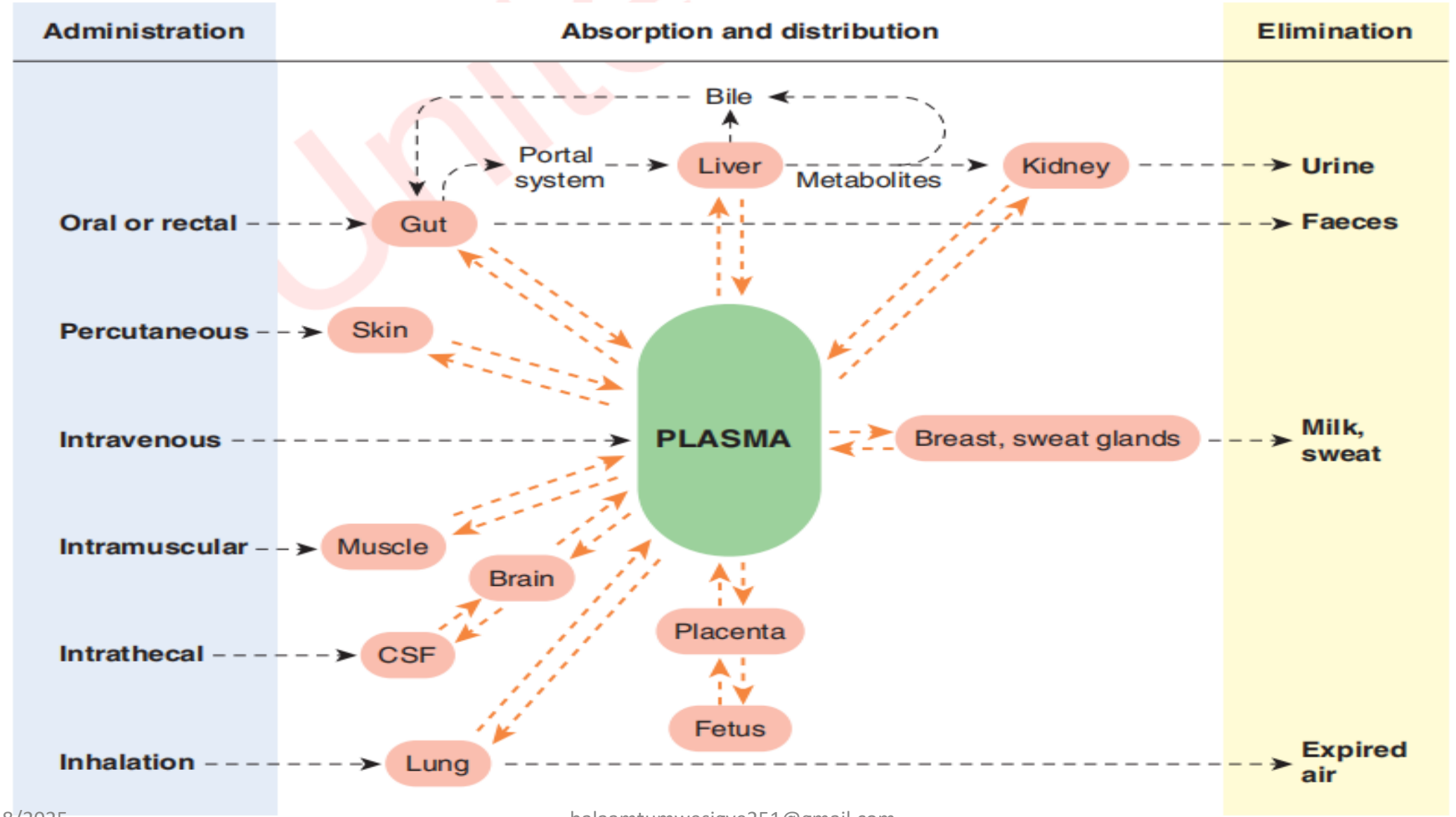
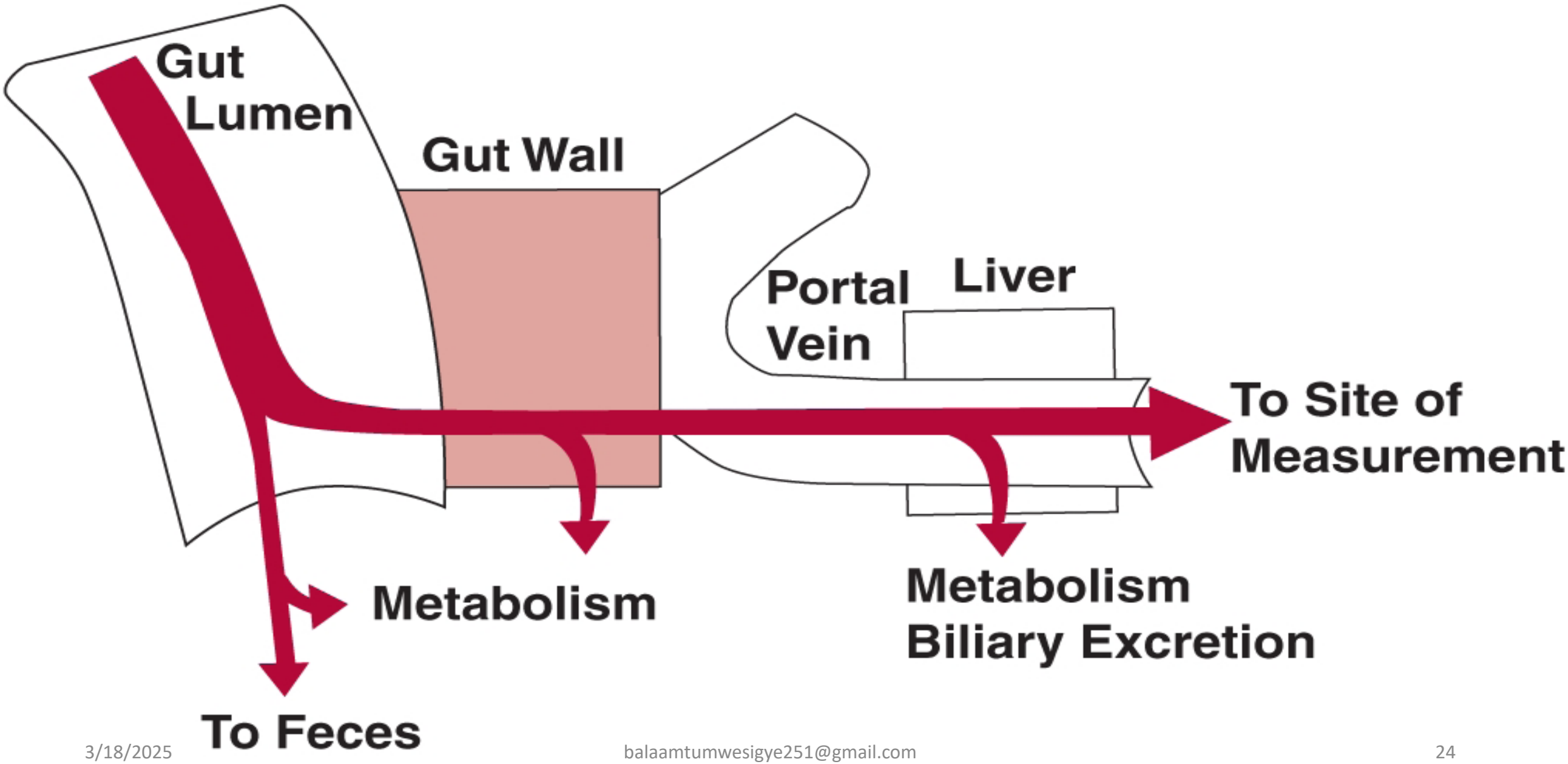


Fig. 8.8 The main routes of drug administration and elimination.

Gastrointestinal Absorption



Passage of drugs

Movement of drugs across cellular barriers

- To traverse cellular barriers (e.g. gastrointestinal mucosa, renal tubule, blood–brain barrier, placenta), drugs have to cross lipid membranes.
- Drugs cross lipid membranes mainly (a) by passive diffusional transfer and (b) by carrier-mediated transfer.
- The main factor that determines the rate of passive diffusional transfer across membranes is a drug's lipid solubility.
- Many drugs are weak acids or weak bases; their state of ionisation varies with pH according to the Henderson–Hasselbalch equation.
- With weak acids or bases, only the uncharged species (the protonated form for a weak acid, the unprotonated form for a weak base) can diffuse across lipid membranes; this gives rise to pH partition.
- pH partition means that weak acids tend to accumulate in compartments of relatively high pH, whereas weak bases do the reverse.
- Carrier-mediated transport is mediated by solute carriers (SLCs), which include organic cation transporters (OCTs) and organic anion transporters (OATs), and P-gps (ABC transporters) in the renal tubule, blood–brain barrier and gastrointestinal epithelium. These are important in determining the distribution of many drugs, are prone to genetic variation and are targets for drug interactions.

Passage through the gut

- There are four main ways by which small molecules
- cross cell membranes:
- by diffusing directly through the lipid
- by combination with a *solute carrier* (SLC) or other membrane transporter
- by diffusing through aqueous pores formed by
- special proteins (*aquaporins*) that traverse the lipid
- by *pinocytosis*.

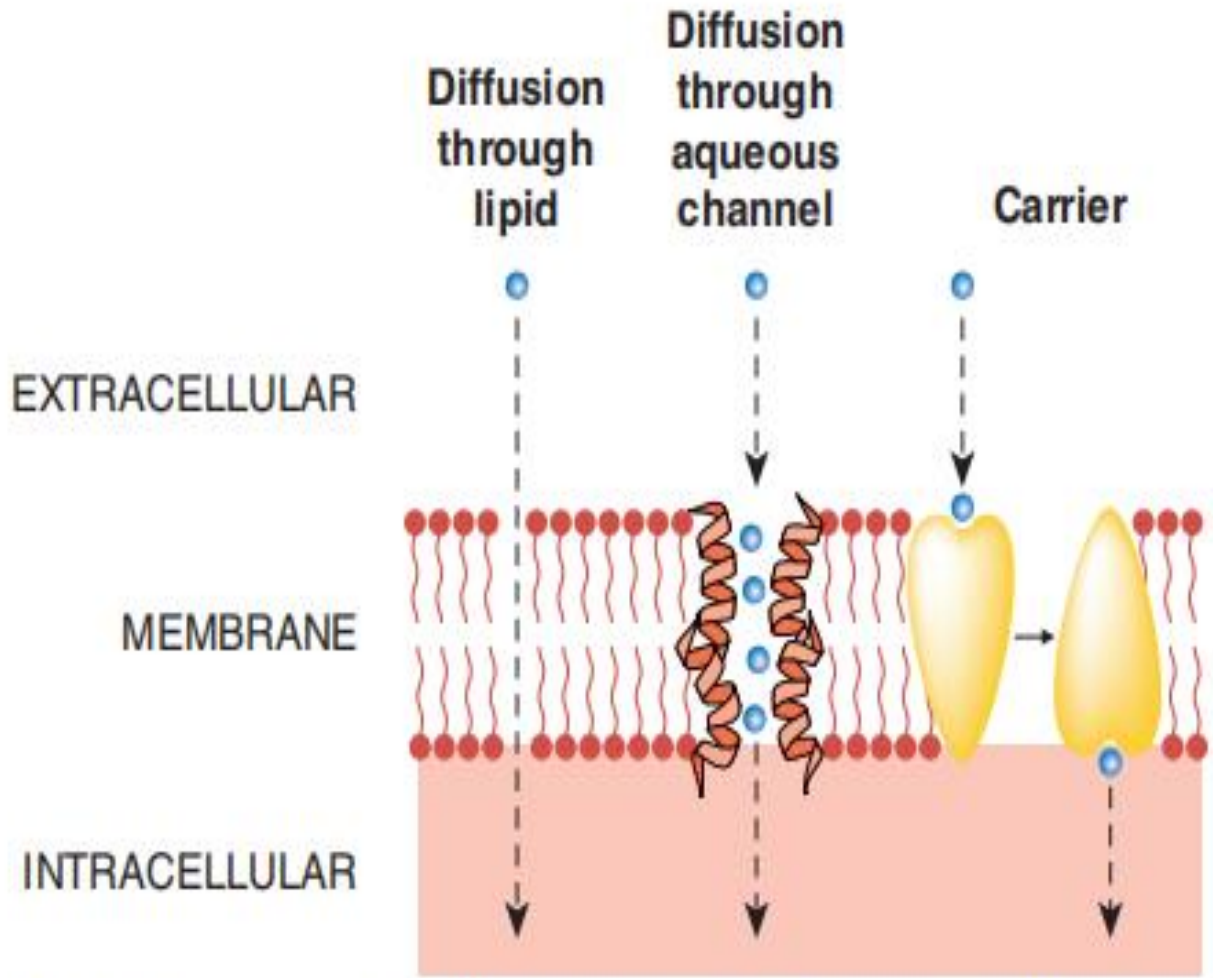
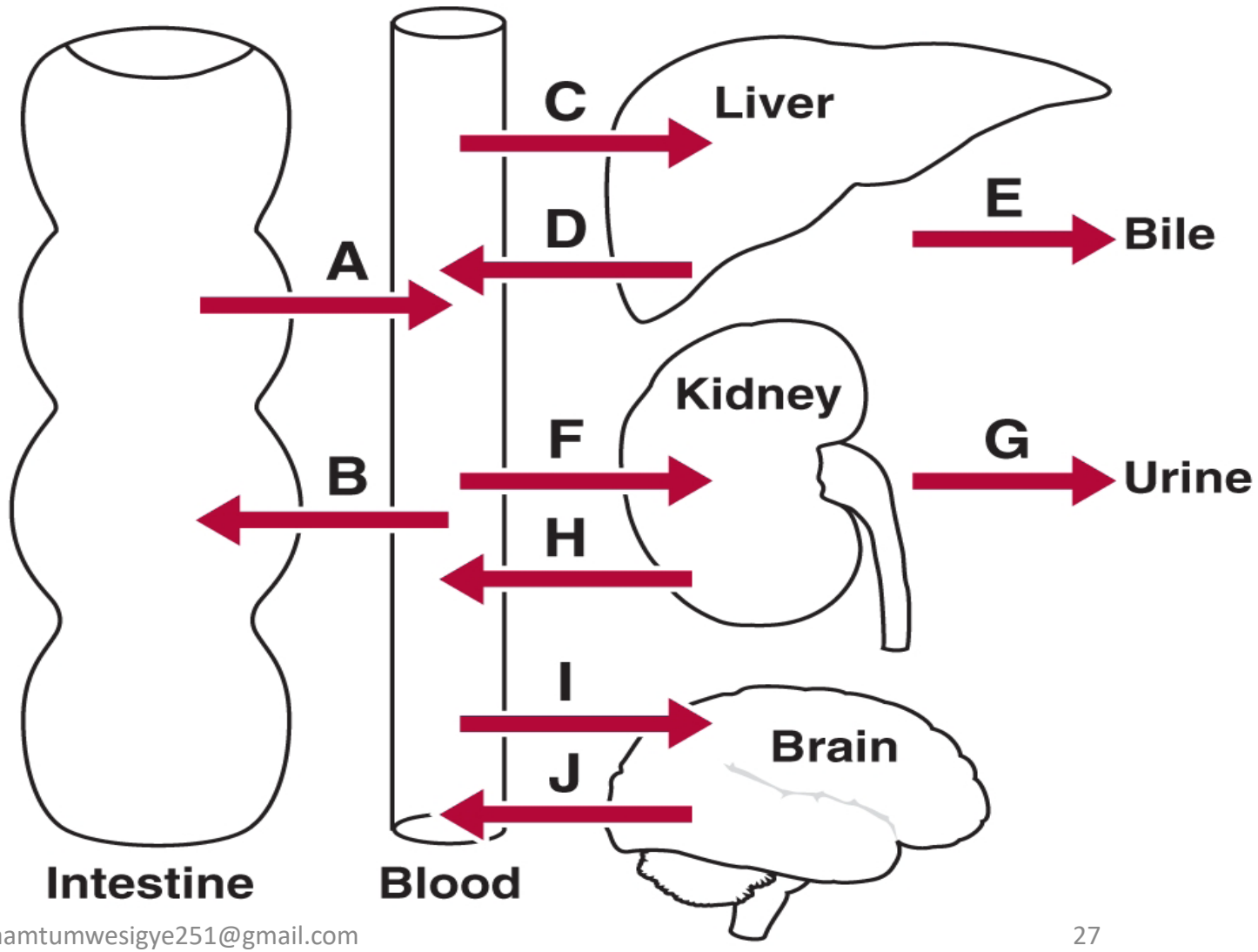


Fig. 8.1 Routes by which solutes can traverse cell membranes. (Molecules can also cross cellular barriers by pinocytosis.)

Transporters

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



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Drug Absorption: movement of a drug from its site of administration into the bloodstream

For solid dosage forms (tablet or capsule), dissolution precedes absorption

Sites of absorption

a) Stomach

Lipid-soluble drugs & weak acids are absorbed directly from the stomach

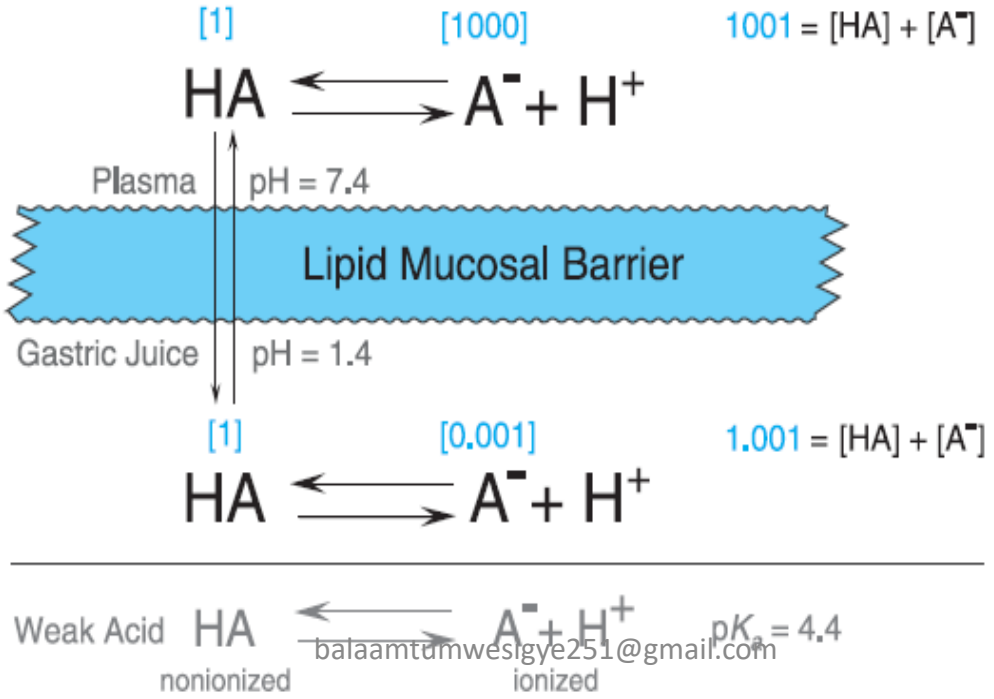
Weak bases & strong acids are not normally absorbed from this site b 'se they exist as ions

Sites of absorption cont'd

b) Small intestine

is the primary site of absorption of most drugs b'se of very large SA across which drugs, including partially ionized weak acids & bases, may diffuse

Acids are normally absorbed more extensively from the small intestine than from the stomach, even though the intestine has a higher pH



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Kinetics related to absorption

Fick's law: Simple (passive) diffusion of the molecules from the cell membrane depends on Fick's law.

first order kinetics

Rate of diffusion is proportional to the *concentration of the drug at the administered area. Drugs hv a characteristic & constat T ½*

Drug decreases by 50% with each T ½

zero order kinetics

If the absorption occurs independently from the concentration of the drug

Concentration has no effect on the diffusion rate of the drug, ***the absorption occurs in a constant speed***.

Common with ethanol and ASA & phenytoin at toxic concns

FACTORS AFFECTING DRUG ABSOPTION

1. Physicochemical properties of the drug:

a. ***Physical state***: Liquid form of the drug is better absorbed than solid formulations

b. ***Lipid-soluble and unionized form*** of the drug is better absorbed than the water-soluble and ionized form.

c. Particle size: Drugs with smaller particle size are absorbed better than larger ones.

d. ***Disintegration time***: It is the time taken for the formulation (tablet or capsule) to break up into small particles and its variation may affect the bioavailability

continuation

e. ***Dissolution time***: It is the time taken for the particles to go into solution. Shorter the time, better is the absorption.
f. ***Formulations***: Pharmacologically inert substances like lactose, starch, calcium sulphate, gum, etc. are added to formulations as binding agents. These are may affect the absorption of drugs, e.g. calcium reduces the absorption of tetracycline's.

Factors influencincing drug absorption continued

2. Route of drug administration: A drug administered by intravenous route bypasses the process of absorption, as it directly enters the circulation.

3.pH and ionization: Strongly acidic (heparin) and strongly basic (aminoglycosides) drugs usually remain ionized at all pH; hence they are poorly absorbed.

4. Food: Presence of food in the stomach can affect the absorption of some of the drugs. Food decreases the absorption of rifampicin, levodopa, etc

5.Presence of other drugs: Concurrent administration of two or more drugs may affect their absorption, e.g. ascorbic acid increases the absorption of oral iron. Antacids reduce the absorption of tetracyclines

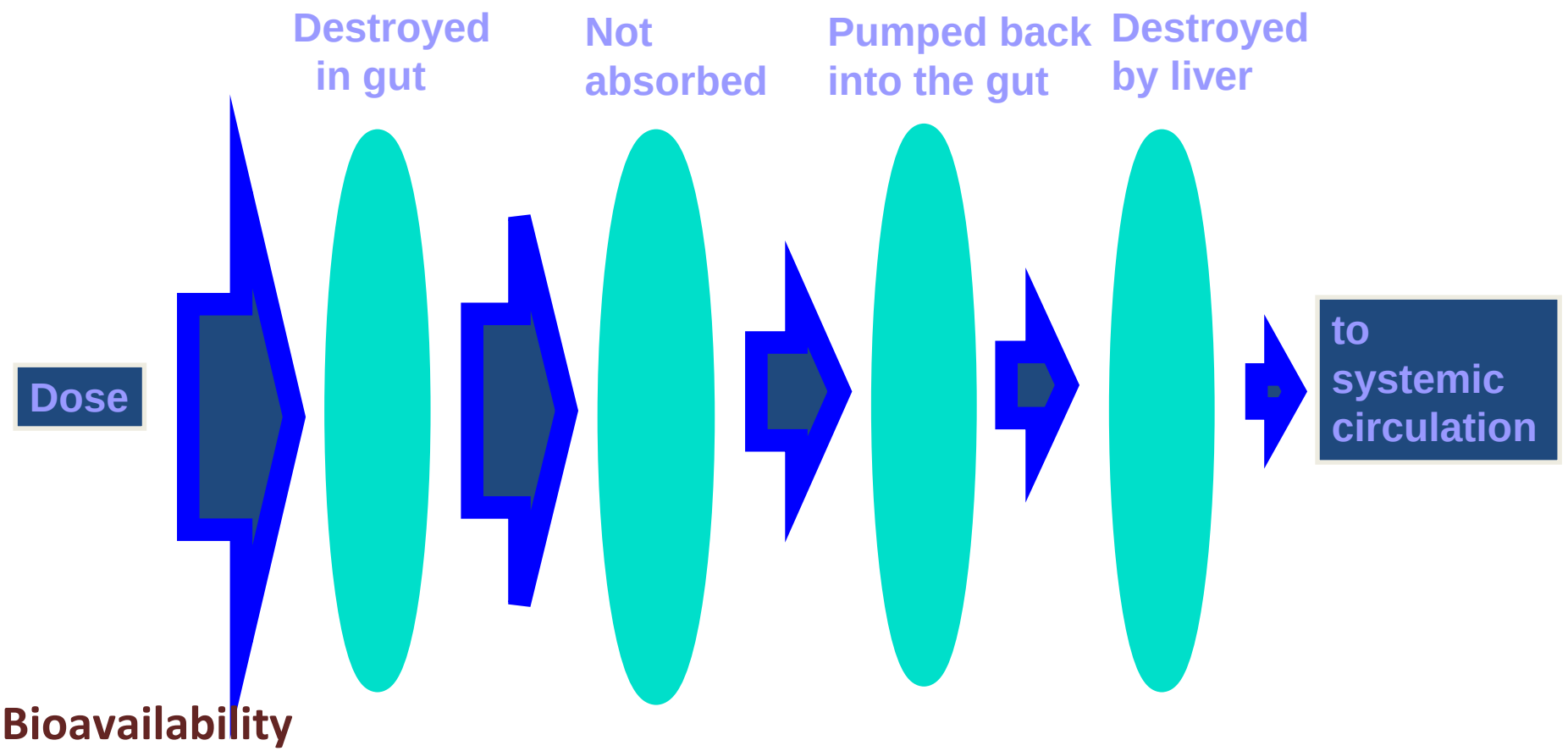
6. Pharmacogenetic factors: Genetic factors may influence drug absorption. In pernicious anaemia, vitamin B_{12} is not absorbed from the gut due to lack of intrinsic factor.

7. Area of the absorbing surface: Normally, drugs are better absorbed in the small intestine because of a larger surface area. Resection of the gut decreases absorption of drugs due to a reduced surface area.

8. Gastrointestinal and other diseases:

In gastroenteritis, there is increased peristaltic movement that reduces the drug absorption. In achlorhydria, absorption of iron from the gut is reduced. In congestive cardiac failure (CCF), there is GI mucosal oedema that reduces the absorption of drugs.

Concept of Bioavailability



Bioavailability

Fraction of the administered dose reaching the systemic circulation

Session 3
pharmacokinetics
drug distribution

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Body Fluid Compartments & Drug Distribution

Total Body Water (50-70% of Body Weight)

Higher in men than women.

Main Fluid Compartments:

1. **Extracellular Fluid (ECF):**

Blood Plasma (4.5%) – Drug transport via circulation.

Interstitial Fluid (16%) – Surrounds tissue cells; site of drug diffusion.

Lymph (1.2%) – Can transport drugs to different tissues.

2. **Intracellular Fluid (ICF)** (30-40%)

Inside cells; drugs must cross membranes to reach this compartment.

Transcellular Fluid (2.5%)

Includes cerebrospinal, intraocular, peritoneal, pleural, synovial fluids, digestive secretions, and fetal compartment.

Important for drugs targeting specific organs (e.g., brain, eyes, joints).

Body compartments

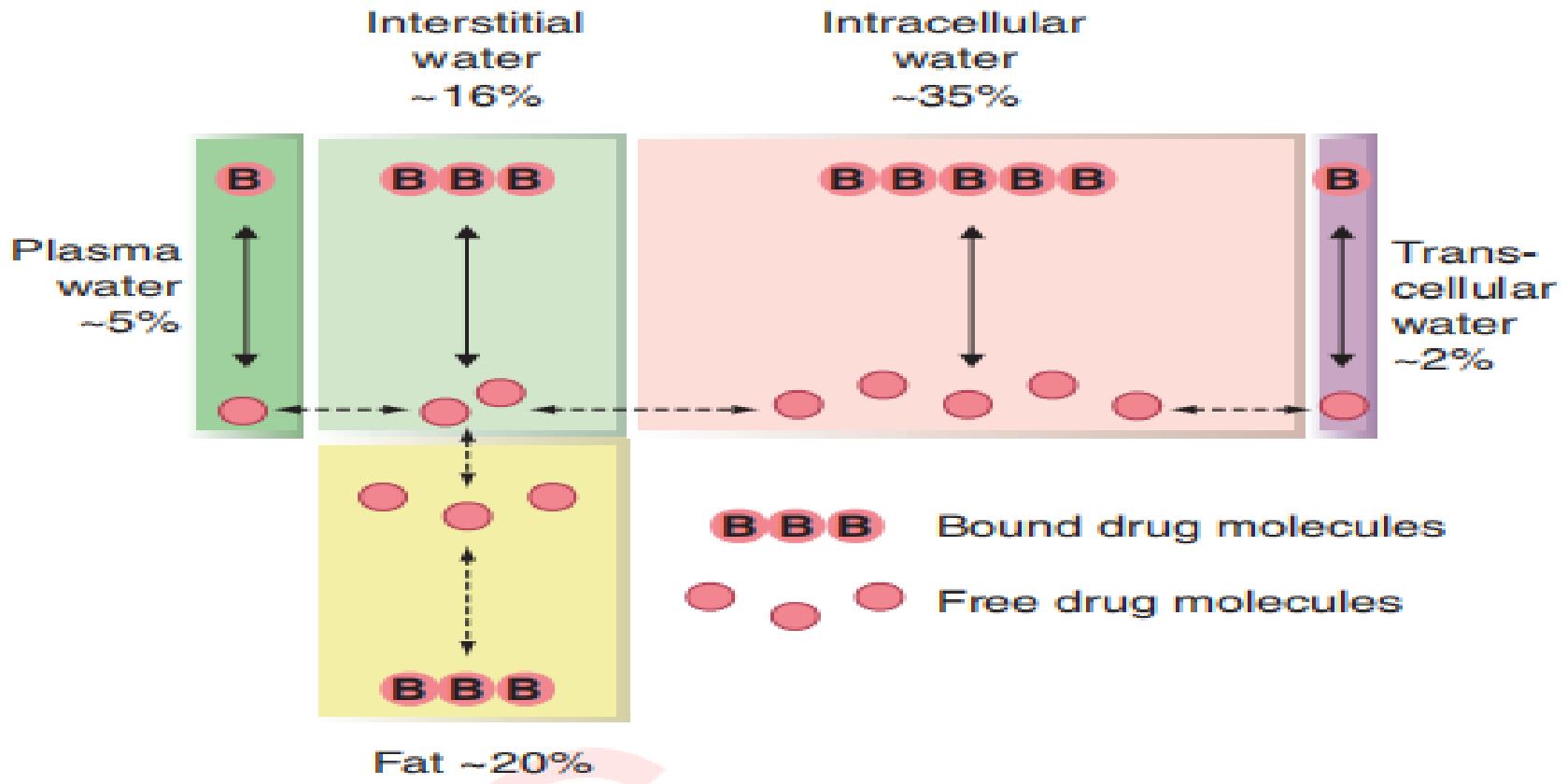
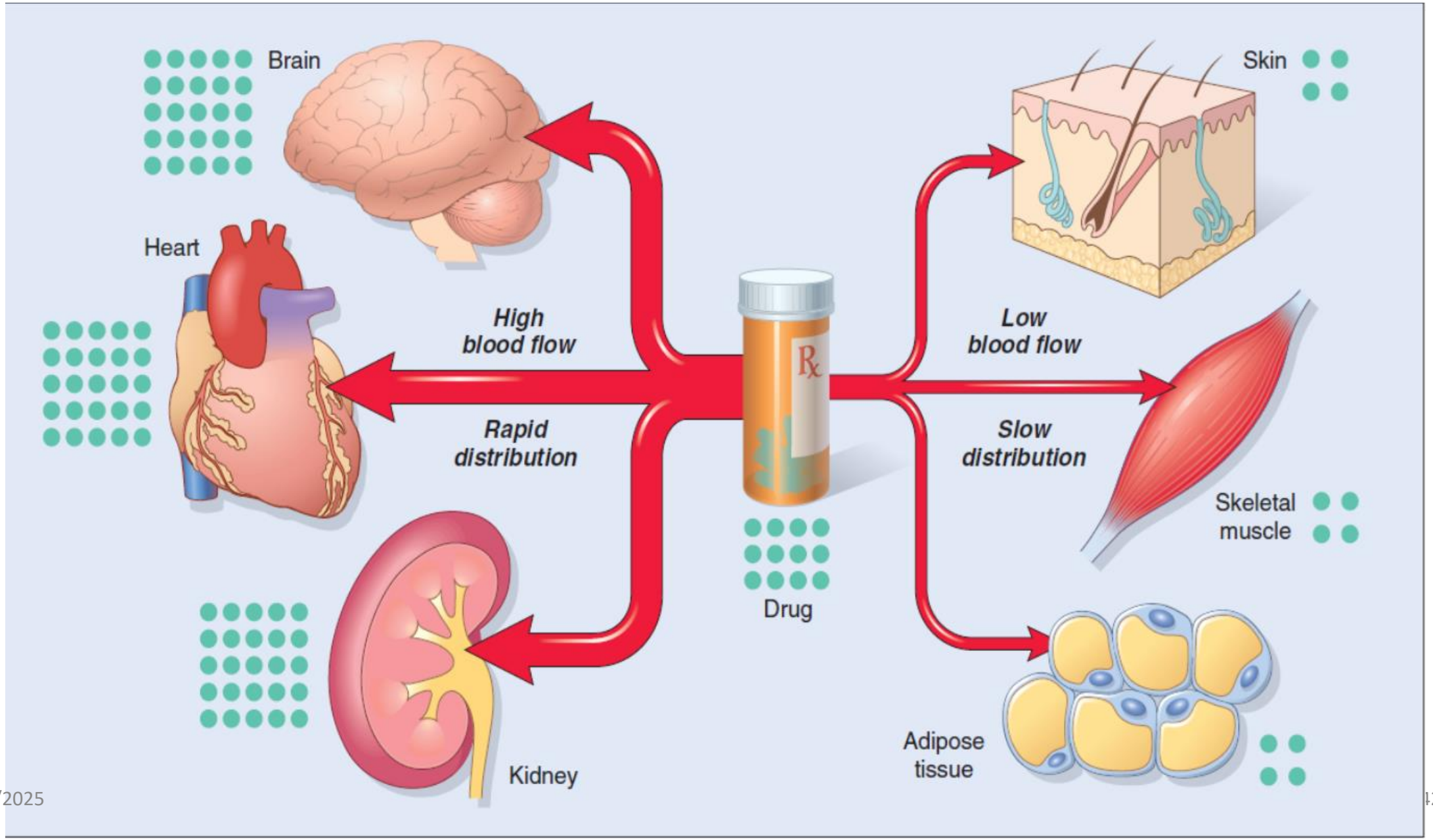


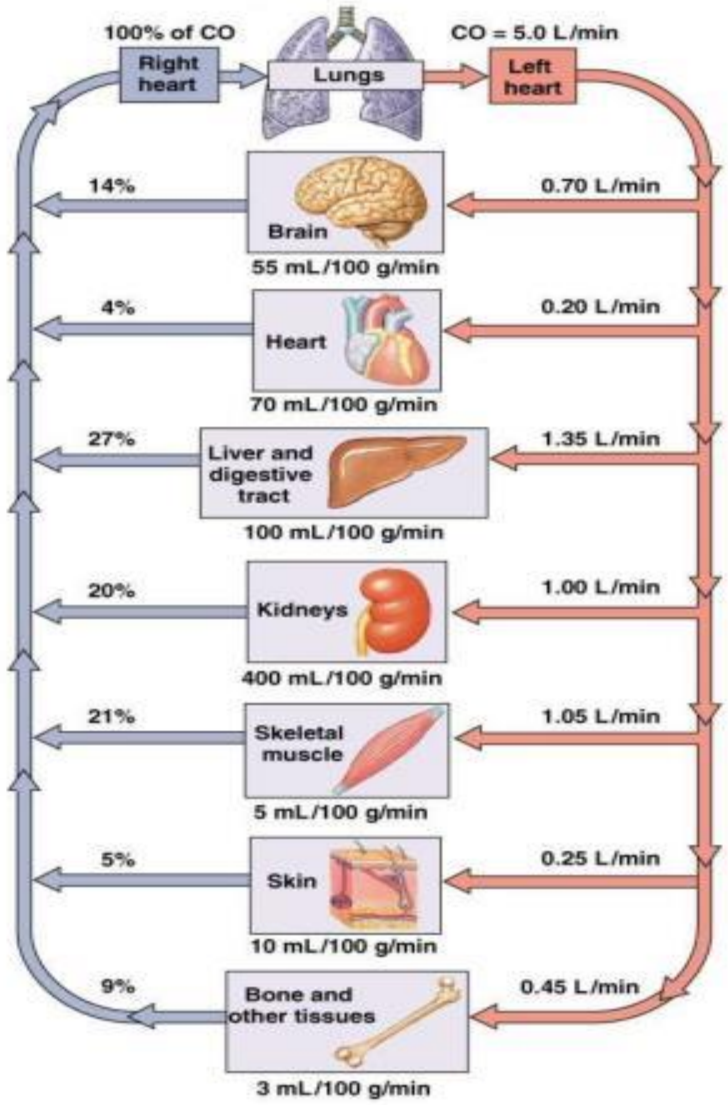
Fig. 8.11 The main body fluid compartments, expressed as a percentage of body weight. Drug molecules exist in bound or free form in each compartment, but only the free drug is able to move between the compartments.

Drug distribution



Distribution of Blood

Distribution of blood in the body at rest



Drug distribution explained

- Distribution of drugs is the process by which a drug leaves the bloodstream and enters the extracellular fluids & tissues

- The extent of distribution of a drug depends on:
- Its lipid solubility,
- Its ionization at physiological pH,
- Its extent of binding to plasma and tissue proteins,
- Presence of tissue-specific transporters and
- Differences in regional blood flow (brain, liver, kidney > muscle, skin > fat, bone)

Drug Distribution Factors:

Free vs. Bound Drugs:

In each compartment, drugs exist in **free solution** (active form) and **bound to proteins or tissues** (inactive).

Drug Properties:

Lipid-soluble drugs diffuse easily across membranes.

Water-soluble drugs remain in the extracellular space.

Blood Flow & Tissue Permeability:

Organs with high blood flow (liver, kidney, brain) receive drugs faster.

Protein Binding:

Drugs bound to **albumin or globulins** remain in plasma, reducing free drug availability.

Factors affecting drug distribution

1. Equilibrium of Acids & Bases

Drugs exist in both **charged and uncharged forms**, depending on **pH**.

pH-dependent equilibrium influences drug distribution across compartments.

2. Factors Determining Drug Distribution

a. **Permeability across tissue barriers** – Affects drug entry into different compartments.

b. **Binding within compartments** – Drugs bind to proteins or tissues, limiting free drug availability.

c. **pH partition** – Ionization affects drug movement across membranes.

d. **Fat:Water partition** – Lipophilic drugs accumulate in fat, while hydrophilic drugs stay in aqueous compartments.

continued

3. Blood–Brain Barrier (BBB)

- **Structure:**
  - Composed of **endothelial cells with tight junctions**, surrounded by **pericytes**.
  - Limits entry of many drugs **unless they are highly lipid-soluble**.
- **Impact on Drug Penetration:**
  - **Inflammation disrupts the BBB**, allowing normally restricted drugs (e.g., **penicillin** for meningitis) to enter.
  - **Certain CNS regions (chemoreceptor trigger zone)** have a **leaky barrier**, permitting drug access.

Volume of distribution (Vd)

Relates amount of drug in the body to the concentration of drug (C) in the blood

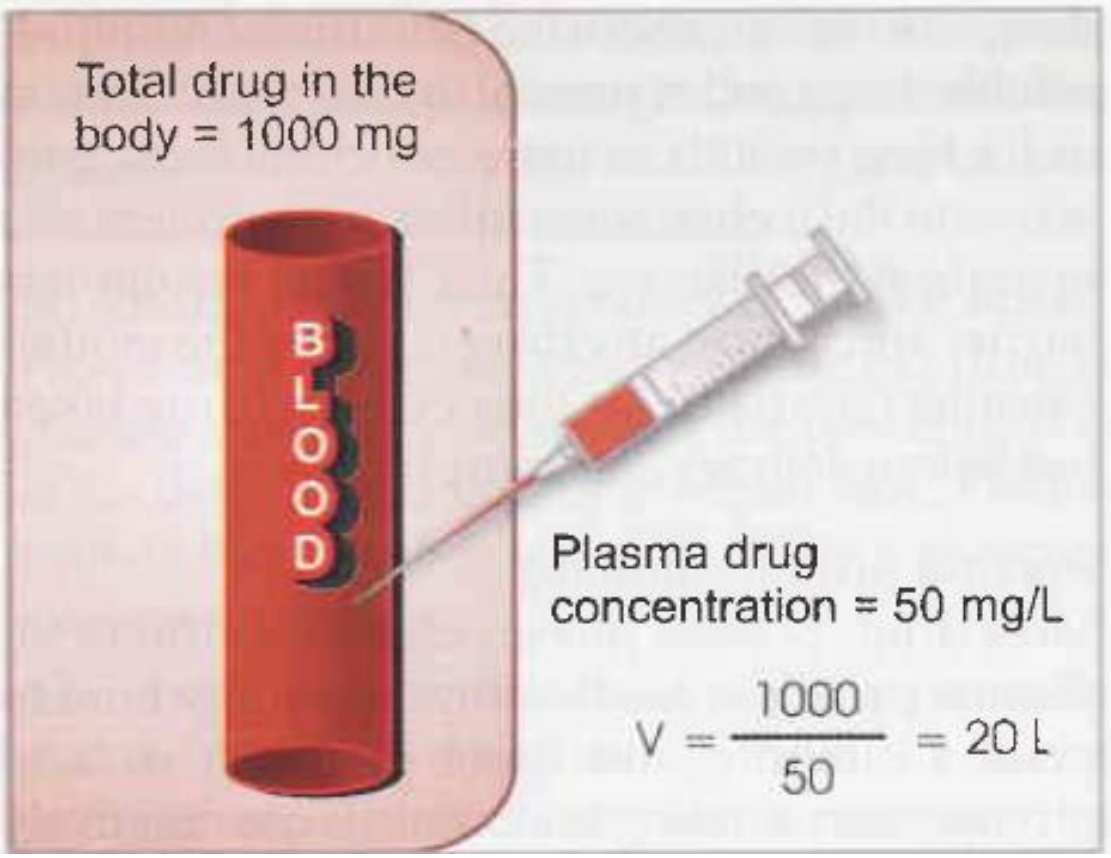
- **This volume does not necessarily refer to an identifiable physiological volume but rather to fluid volume that would be required to contain all the drug in the body at the same concentration measured in the blood**
- **Vd = amount of drug administered (m/g)/C (mg/L)**

- **A drug's Vd there4 reflects the extent to which it is present in extravascular tissues & not in the plasma**

- Fluid compartments in an average 70-kg adult
  - Plasma volume: 3 L
  - blood volume: about 5.5 L
  - extracellular fluid volume: 12 L
  - volume of total-body water is approximately 42

$$V = \frac{\text{dose administered i.v.}}{\text{plasma concentration}}$$

LOOK



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Take home points

Drug distribution

- The major compartments are:
  - plasma (5% of body weight)
  - interstitial fluid (16%)
  - intracellular fluid (35%)
  - transcellular fluid (2%)
  - fat (20%).
- Volume of distribution (V_d) is defined as the volume that would contain the total body content of the drug at a concentration equal to that in the plasma.
- Lipid-insoluble drugs are mainly confined to plasma and interstitial fluids; most do not enter the brain following acute dosing.
- Lipid-soluble drugs reach all compartments and may accumulate in fat.
- For drugs that accumulate outside the plasma compartment (e.g. in fat or by being bound to tissues), V_d may exceed total body volume.

Drug Metabolism and Excretion

Drug elimination refers to the **irreversible removal of drugs** from the body and occurs via **two key processes**:

- **Metabolism** (biotransformation) – chemical modification of drugs.
- **Excretion** – physical removal of drugs or their metabolites.

- ❑ Metabolism: Phase 1 and Phase 2 Reactions
- ❑ Metabolism occurs mainly in the liver and converts drugs into more polar, water-soluble compounds to facilitate elimination.

Phase 1

Phase 1 Reactions (Functionalization Reactions)

- Introduce or expose functional groups (e.g., –OH, –NH_2, –SH).
- Primarily mediated by the **cytochrome P450 (CYP) enzyme system**.
- Includes **oxidation, reduction, and hydrolysis**.
- Example: **Codeine → Morphine (by CYP2D6 oxidation).**

Phase 2

Phase 2 Reactions (Conjugation Reactions)

- Involve the attachment of large, **polar molecules** to the drug or its Phase 1 metabolite.
- Facilitates **renal or biliary excretion**.
- Includes **glucuronidation, sulfation, acetylation, methylation**.
- Example: **Morphine → Morphine glucuronide (by glucuronidation).**

Cytochrome P450(CYP) System

- The CYP system consists of a **superfamily of enzymes** found mainly in the **liver**.
- Functions in **drug oxidation** and plays a critical role in metabolism.
- CYP enzymes can be **induced or inhibited**, leading to **drug interactions**:
  - **Induction** (e.g., rifampicin, carbamazepine) increases drug metabolism → reduced drug effect.
  - **Inhibition** (e.g., ketoconazole, erythromycin) decreases metabolism → increased drug levels → toxicity risk.

Excretion

Drugs and their metabolites are eliminated via:

1. **Renal Excretion (Kidneys) – Major Route**
    1. Most drugs are excreted in **urine**, either **unchanged** or as **polar metabolites**.
    2. Lipophilic drugs require metabolism before renal elimination.
2. **Biliary Excretion and Enterohepatic Recirculation**
    1. Some drugs/metabolites are excreted into **bile** and enter the intestines.
    2. They may be **reabsorbed** into circulation (**enterohepatic recycling**), prolonging drug action.
    3. Example: **Digoxin, rifampicin**.

3. Pulmonary Excretion (Lungs)

Important for volatile drugs like anesthetics (e.g., halothane, isoflurane).

4. Other Minor Routes

Drugs may also be eliminated through sweat, saliva, and breast milk (concern for infants).

Clinical Significance of Drug Metabolism and Excretion

- **Renal Impairment:** Drugs normally excreted in urine (e.g., **digoxin**) may **accumulate** → toxicity.
- **Hepatic Impairment:** Metabolism-dependent drugs (e.g., **benzodiazepines**) may have **prolonged effects**.
- **Drug Interactions:** CYP **inducers** or **inhibitors** can **alter drug levels**, leading to treatment failure or toxicity.