

Pharmacokinetics

Pharmacokinetics

- Derived from two words: pharmakon meaning drug and kinesis meaning movement.
- Effect of body on the drug i.e. movement of the drug in, through and out of the body
- It means 'what the body does to the drug'

Pharmacokinetics

- Includes absorption (A), distribution (D), metabolism (M), and excretion (E).
- All these processes involve movement of the drug molecules through various biological membranes.
- All biological membranes are made up of a lipid bilayer.

Absorption

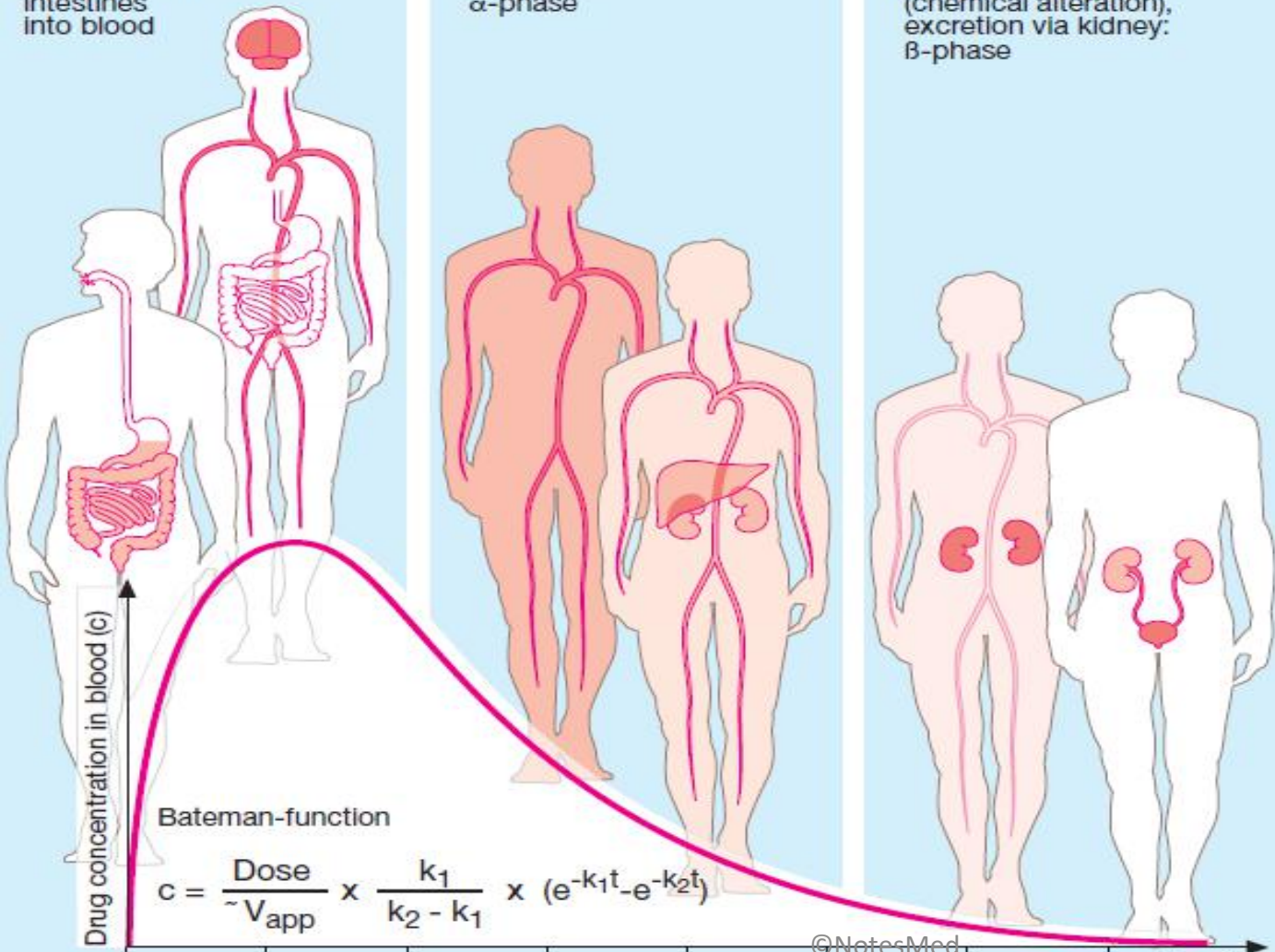
Uptake from stomach and intestines into blood

Distribution

into body tissues:
 α -phase

Elimination

from body by biotransformation (chemical alteration), excretion via kidney: β -phase



Drug concentration in blood (c)

Bateman-function

$$c = \frac{\text{Dose}}{V_{app}} \times \frac{k_1}{k_2 - k_1} \times (e^{-k_1 t} - e^{-k_2 t})$$

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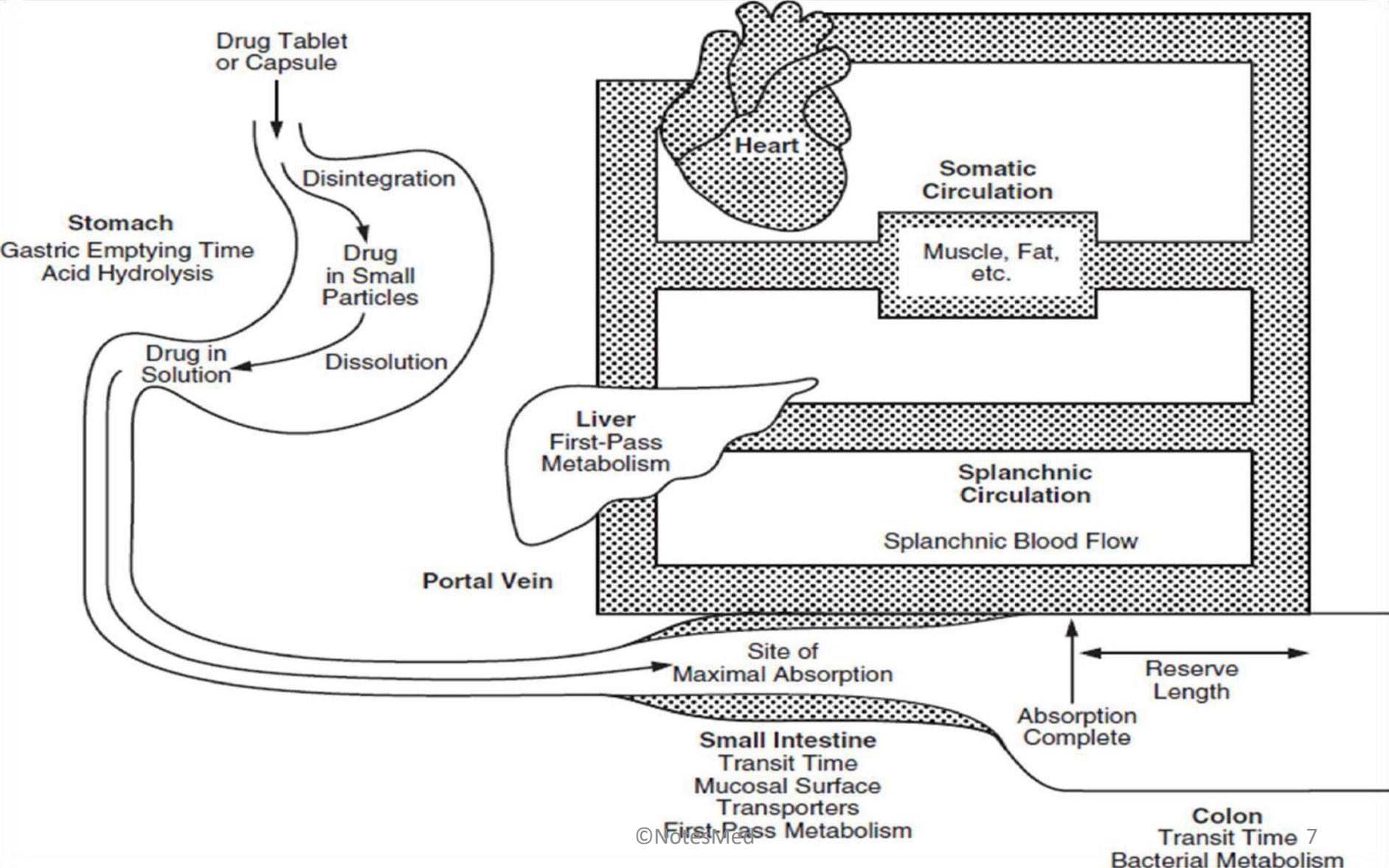
Time (t)

Variables in Pharmacokinetics

- Absorption, Distribution, Metabolism, Excretion
- Drug passage across cell membranes
- Bioavailability
- Plasma protein binding
- Time course of drug concentration
- Plasma half-life and steady-state concentration
- Therapeutic drug monitoring

definitions in Pharmacokinetics

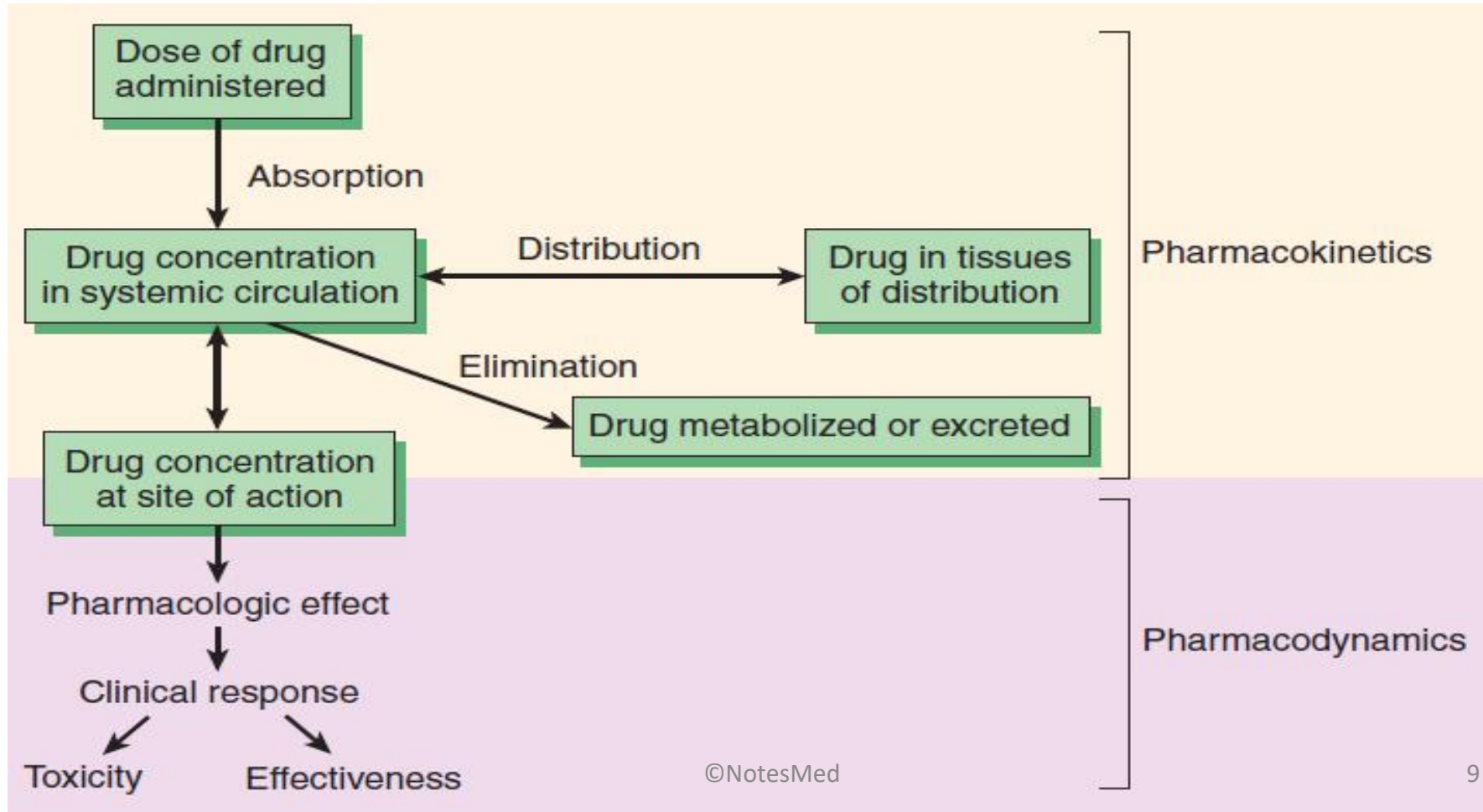
- Absorption: Movement of drug from administered site to systemic circulation
- Apparent volume of distribution: Volume that would accommodate all the drug in the body, if the concentration throughout was the same as in plasma
- Bioavailability: Fraction (F) of administered dose of a drug that reaches the systemic circulation in the unchanged form
- Metabolism/Biotransformation: Chemical alteration of the drug in the body that leads to inactivation or active metabolite from an active drug or activation of inactive drug
- Clearance: Theoretical volume of plasma from which the drug is completely removed in unit time
- Plasma half life: Time taken for its plasma concentration to be reduced to half of its original value.



Passage of drugs

- Drugs crosses the biological membranes by the following mechanisms:
 - Passive diffusion
 - Filtration
 - Specialized transport
 - Active transport (Uphill transport)
 - Primary
 - Secondary (symport and antiport)
 - Facilitated diffusion (Downhill transport)
 - Pinocytosis & Phagocytosis (Endocytosis/Exocytosis)

Relationship between dose and effect



- Passive diffusion:
 - Bidirectional process
 - Drug molecules move from a region of higher to lower concentration until equilibrium is attained.
 - Rate of diffusion is directly proportional to the concentration gradient across the membrane.
 - Lipid-soluble drugs are transported across the membrane by passive diffusion and does not require energy.
- Filtration
 - It is depends on the molecular size and weight of the drug.
 - If the drug molecules are smaller than the pores, they are filtered easily through the membrane.

Passive Diffusion

- Transfer process in which drug molecules pass through a biological barrier
- Bidirectional process
- Without any expenditure of energy
- Direction: higher concentration to lower concentration (**along concentration gradient**)
- No active role of membrane
- Lipid diffusion
 - Lipid soluble drugs diffuse by dissolving in the lipoidal matrix of the membrane
- Aqueous diffusion
 - Occurs within larger aqueous compartments (interstitial space, cytosol) and through aqueous pores
 - Permit passage of molecules as large as MW 20,000-30,000
- Rate of transport is proportional to lipid: water partition coefficient of the drug
- Passive flux of molecules down a concentration gradient is given by Fick's law

Filtration

- Passage of drugs through aqueous pores in cell membrane or paracellular spaces
- Size of pores : 4 Angstrom
- Paracellular spaces : 40 Angstrom
- Depends upon hydrostatic / osmotic pressure
- Diffusion of drugs across capillaries is dependent on rate of blood flow

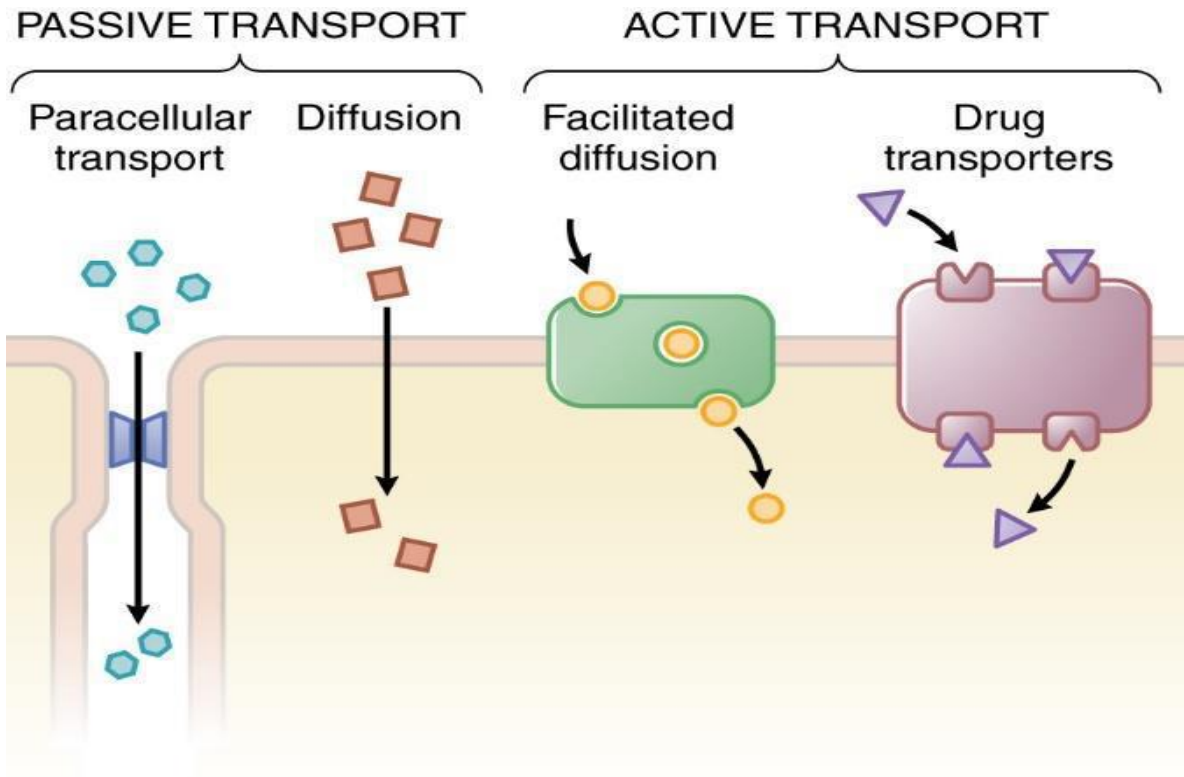
Fick's law of diffusion

Flux (molecules per unit time) =

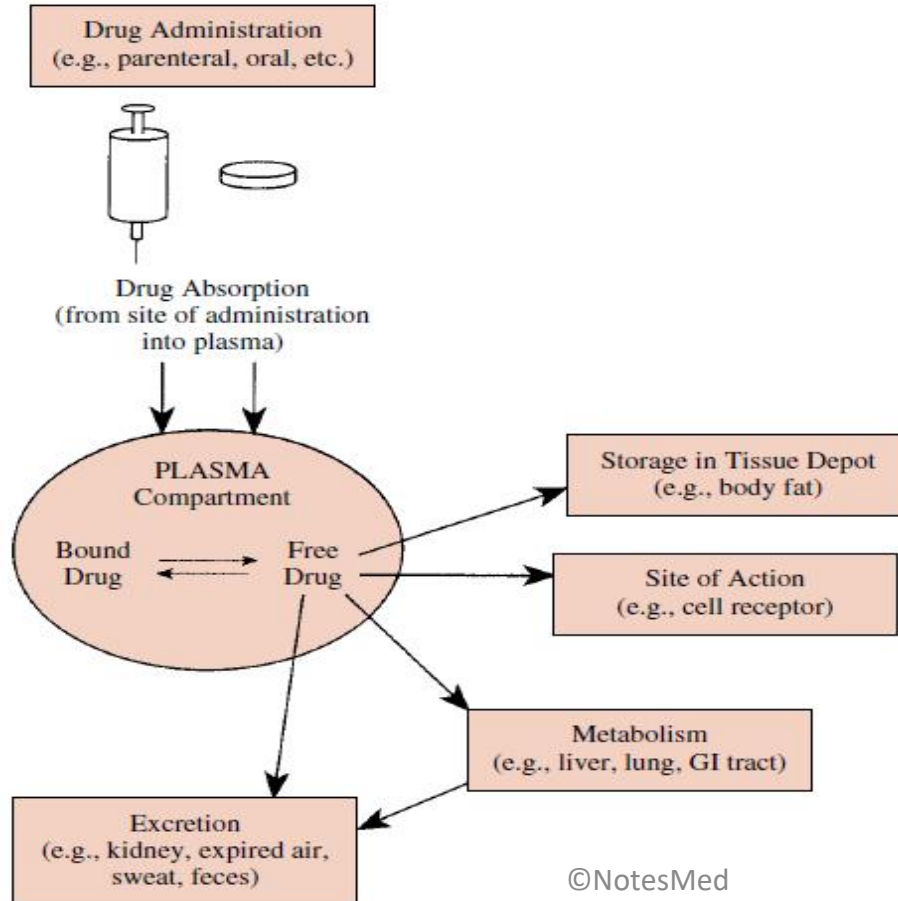
$$(C_1 - C_2) \times \frac{\text{Area} \times \text{Permeability coefficient}}{\text{Thickness}}$$

- Where,
 - C1 is the higher concentration, C2 is the lower concentration,
 - Area is the cross-sectional area of the diffusion path,
 - Permeability coefficient is a measure of the mobility of the drug molecules in the medium of the diffusion path
 - Thickness is the thickness (length) of the diffusion path

Diffusion coefficient is the amount of drug that diffuses across a membrane of given unit area per unit time when the conc. gradient is unity AND it is Constant for each drug or molecule



Factors that affect drug concentration at its site of action



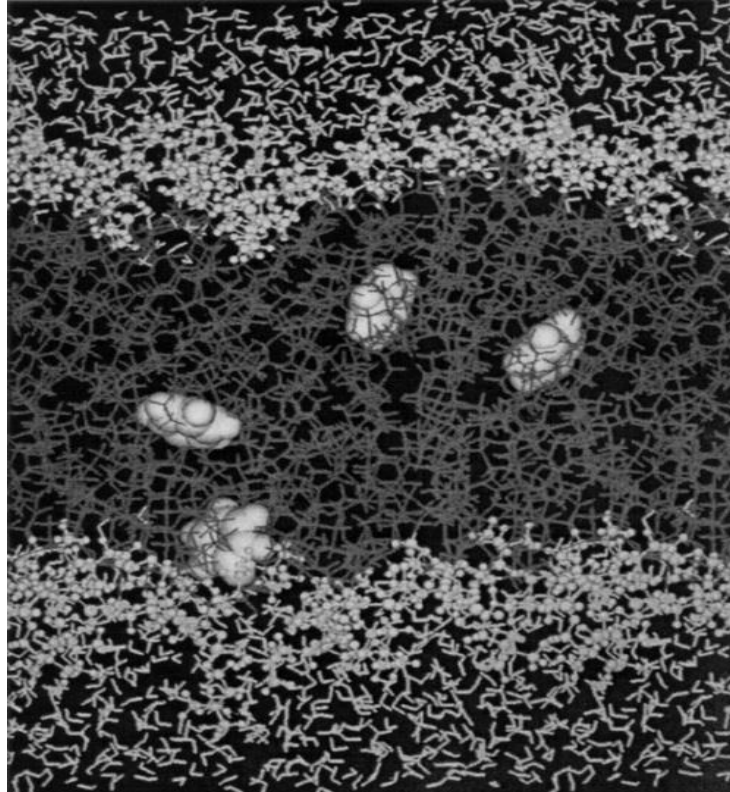
Specialized transport

- **Active transport:**
 - Molecules move from a region of lower to higher concentration against the concentration gradient
 - Requires energy, e.g. transport of sympathomimetic amines into neural tissue
- **Pinocytosis**
 - Process of transport across the cell in particulate form by formation of vesicles
 - Applicable to proteins and other big molecules
 - Contributes little to transport of most drugs n).

Facilitated Diffusion

- **Solute linked carrier (SLC) transporters**
- No energy required
- Translocate the substrates in direction of electrochemical gradient
- Entry of glucose in muscle and fat (GLUT4)
- Drugs that permeate:
 - Antimetabolite-anticancer drugs
 - Antiviral drugs
 - Vitamins like riboflavin, thiamine and B12

Diffusion of benzene with hydrated lipid layer



Active Transport

- Energy dependent
- Energy generated by membrane ATPase
- Transport against electrochemical gradient (Low→High)
- Selective accumulation of substrate on one side of the medium
- Use transport meant for endogenous substance
- Nonselective transporter-P-glycoprotein (P-gp)
- Inhibited by metabolic poisons-sodium cyanide, sodium fluoride or 2,4-dinitrophenol
- Examples of drugs: 5-fluorouracil, nitrogen mustard, digitalis, sympathomimetic amines, choline
- Two types
 - Primary active
 - Secondary active

Primary Active Transport

- Directly coupled with ATP hydrolysis
- Transporters (Evacuators)
 - Superfamily of ATP Binding Cassette (ABC) whose intracellular loop have ATPase activity
- Mediate efflux of the solute from the cytoplasm, either to ECF or intracellular organelle
- P-gp→most well known primary active transporter, pumps out many drugs/metabolites
- Other important transporter
 - Multidrug resistance associated protein 2 (MRP2)
 - Breast cancer resistance protein (BCRP)
- E.g.: antibiotics, anticancer drugs, HIV protease inhibitors, digoxin and anticonvulsants

Secondary Active Transport

- One ion (mostly Na⁺) or the solute supplies driving force for the transport of other ion/solute
- Two types
 - Symport/Co-transport
 - Both solutes move in same direction
 - E.g. Na⁺/K⁺/2Cl⁻-symporter(inhibited by loop diuretics)
 - Antiport/Exchange transport
 - Solutes move in opposite directions
 - E.g. Na⁺ and H⁺ exchanger
- Secondary active transporters
 - Solute linked carrier (SLC) transporters
 - Organic anion transporting polypeptide (OATP)
 - Organic cation transporter (OCT)
 - Nor-epinephrine transporter
 - Serotonin transporter
 - Vesicular monoamine transporter (VMAT-2)
 - Sodium-glucose transporter (SGLT1 & SGLT2)

Transport Mechanisms in Bacteria

<u>Transport mechanism</u>	<u>Example</u>
Passive diffusion across lipid bilayer	Fluoroquinolones Tetracyclines (hydrophobic)
Facilitated diffusion (nonselective)	β -Lactams Tetracyclines (hydrophilic)
Mediated transport (selective)	Imipenem Catechols
Active transport	Aminoglycosides Cycloserine

Drug absorption

- Movement of a drug from the site of administration into the systemic circulation (blood stream).
- Quantity as well as rate of absorbed drug is clinically important
- Both fraction of administered dose & rate of absorption are important

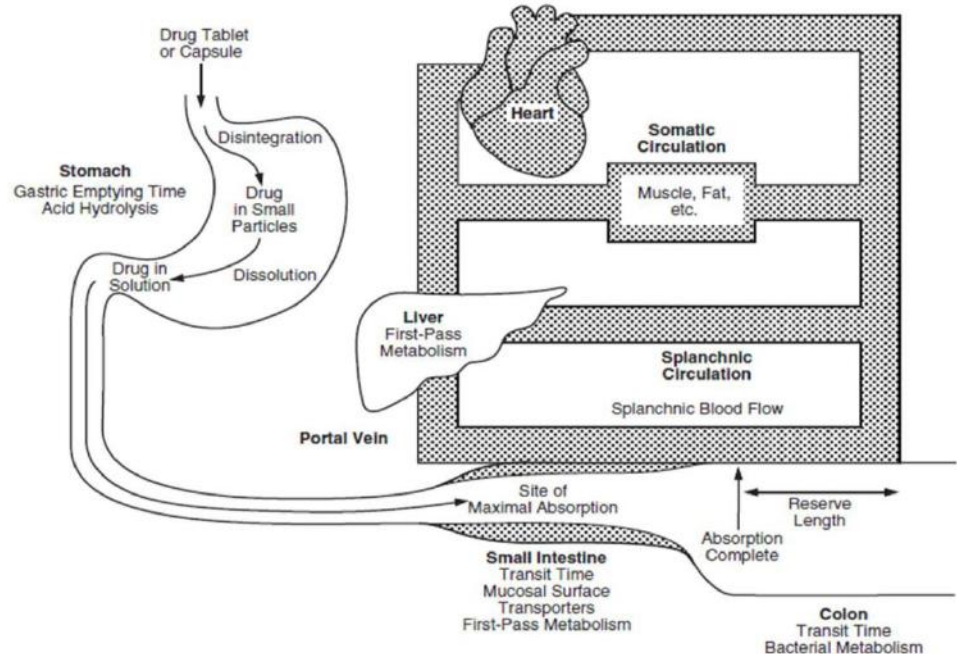
Drug absorption

- Absorption of drugs from GIT is mainly by passive diffusion through lipid sheath.
- Absorption of drugs from GIT is compromised as a result of drug loss due to:

1. Efflux by the P-gp localized in enterocytes
2. First pass metabolism
3. Vomiting
4. Disease affecting absorption

- **Extent of absorption:**

- i.v > i.m > s.c > sublingual > rectal > oral



Factors affecting absorption

1. **Aqueous solubility**

- Dissolution, disintegration

2. **Ionization**

3. **Concentration**

- Drug given in concentrated solution absorbed faster than from dilute solution

4. **Area of absorbing surface**

- Larger the surface area, faster is the absorption

5. **Vascularity of absorbing surface**

- Increased blood flow hastens drug absorption

6. **Route of administration**

7. **Concurrently ingested drugs**

- Luminal effect: formation of insoluble complexes e.g. tetracycline and iron preparations with calcium salts and antacids; phenytoin with Sucralfate
- Gut wall effects: altering motility (anticholinergics), mucosal damage (neomycin, methotrexate)

Other factors affecting absorption

- Gastric emptying time and double peak phenomenon
- GI blood flow
- Presence of food in the GIT
- Food intake
- Disease states

Methods for delaying absorption

- Using an appropriate dosage form → retard tablets, Spansules, depot inj., s. cimplants, etc.
- Changing physical characteristics of drug, e.g. Insulin zinc suspension, procaine penicillin G, etc.
- Adding vasoconstrictor drug, e.g. Adrenaline and lignocaine
- Applying tourniquet and Inj. Local Anaesthetic below tourniquet

Methods to facilitate absorption

- Adding hyaluronidase to injection fluid
→ increases rate of diffusion through interstitial spaces and speeds up drug absorption
- Increase the local blood flow by applying hot fomentation or doing massage

Oral Administration

- Solubility
- Ionization
- Dissolution
- Presence of food in stomach
- Degradation by acid
- Co-administration of other drug
- Eflux transporter

Subcutaneous and Intramuscular Administration

- Lipid soluble drugs
- Paracellular spaces

- Absorption through Lymphatics
- Application of heat and exercise
- Effect of other drugs

Topical administration

- Lipid solubility
- Surface area
- Site of application

Effect of ionization

- Most of the drugs are weak electrolytes and hence get ionized in the GIT according to their pKavalues and the surrounding pH
- Dissociation constant (pKa) → pH at which the drug is 50% ionized or pH at which the concentrations of the ionized and nonionized forms are equal
- Degree of ionization affects the rate of absorption
 - Non ionized portion is more lipid soluble
 - Electrostatic charge of an ionized molecule attracts water dipoles and results in polar (relatively water-soluble and lipid insoluble complex)
- Extent of ionization of weak electrolytes is governed by the Henderson –Hasselbalch equation

Henderson –Hasselbalch Equation

- Express the relationship between pKa, pH & extent of ionization
- **$pK_a - pH = \text{Log}[\text{protonated form}/\text{Unprotonated form}]$**
- **For weak acids**
 - $pH = pK_a + \text{Log}[\text{conc. of Non-ionized acid}/\text{conc. of ionized}]$
- **For weak bases**
 - $pH = pK_a + \text{Log}[\text{Conc. of ionized base}/\text{conc. of non-ionized base}]$

Implication : Henderson –Hasselbalch Equation

- Weak acids
 - Weak acid-neutral molecule that can reversibly dissociate into an anion (a negatively charged molecule) and a proton (a hydrogen ion)
 - Form salts with cations, e.g. Sod. Phenobarbitone, sod. Sulfadiazine, pot. Penicillin-v, sod. Phenytoin, etc.
 - Ionize more at alkaline pH
 - 1 scale change in pH causes 10 fold change in ionization
- Weak bases
 - Weak base-neutral molecule that can form a cation (a positively charged molecule) by combining with a proton
 - Form salts with anions, e.g. Atropine sulfate, ephedrine HCl, chloroquine phosphate, etc.
 - Conversely ionize more at acidic pH

Implication : Henderson –Hasselbalch

Equation

- Basic drugs more absorbed in intestine (basic environment)
- Acidic drugs more absorbed in stomach (acidic environment)
- **Ion/Drug trapping**
 - Unionized form of acidic drugs which crosses the surface membrane of gastric mucosal cell →reverts to the ionized form within the cell (pH 7.0)→slowly passes to the extracellular fluid
 - A weak electrolyte crossing a membrane to encounter a pH from which it is not able to escape easily
 - Contribute to gastric mucosal cell damage caused by aspirin.
- Basic drugs attain higher concentration intracellularly (pH 7.0 vs 7.4 of plasma)
- Lipid-soluble nonelectrolytes (e.g. ethanol, diethyl-ether) readily cross biological membranes and their transport is pH independent.

pH Partition Hypothesis

- If pH varies on both sides of cell membrane
 - Drug will ionize to different degrees on the two sides (ion trapping)
 - Total conc. will be unequal on either sides
 - The compartment having more ionized drug will contain more conc.
- Weak acid will be better absorbed from the stomach

Clinical implications of Amines

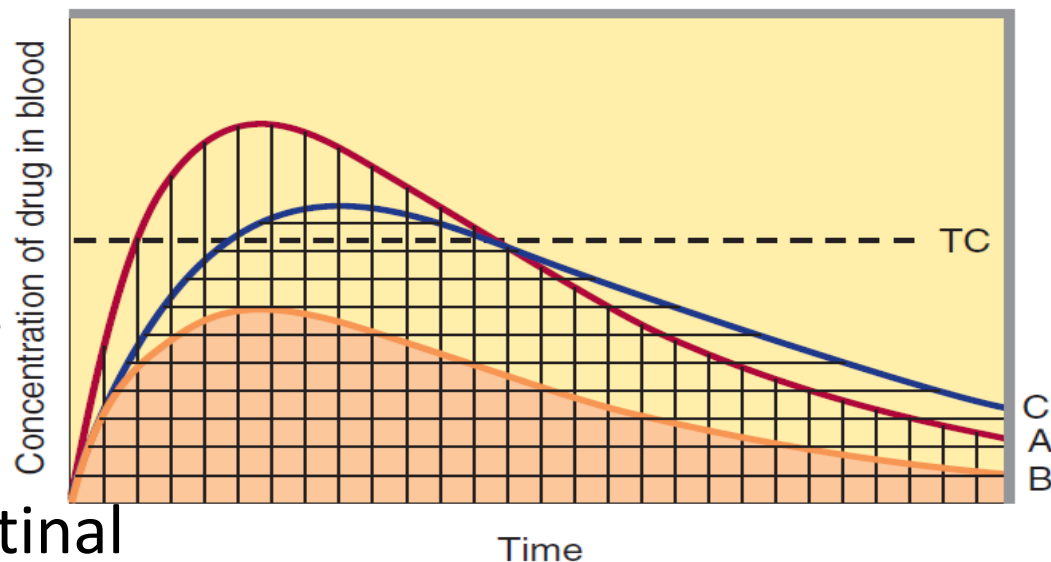
- Primary, secondary and tertiary amines
 - Reversibly bind a proton with unshared electrons
 - Vary their lipid solubility with pH
- Quaternary amines
 - Permanently charged and has no unshared electrons with which to reversibly bind a proton
 - Always poorly lipid-soluble charged form
- Acidic drugs are ionized more in alkaline urine—do not back diffuse in the kidney tubules and are excreted faster.
- Basic drugs are excreted faster if urine is acidified

Body fluids with potential for drug “trapping” through the pH-partitioning phenomenon

Body Fluid	Range of pH	Total Fluid: Blood Concentration Ratios for Sulfadiazine (acid, pK _a 6.5) ¹	Total Fluid: Blood Concentration Ratios for Pyrimethamine (base, pK _a 7.0) ¹
Urine	5.0–8.0	0.12–4.65	72.24–0.79
Breast milk	6.4–7.6 ²	0.2–1.77	3.56–0.89
Jejunum, ileum contents	7.5–8.0 ³	1.23–3.54	0.94–0.79
Stomach contents	1.92–2.59 ²	0.11 ⁴	85,993–18,386
Prostatic secretions	6.45–7.4 ²	0.21	3.25–1.0
Vaginal secretions	3.4–4.2 ³	0.11 ⁴	2848–452

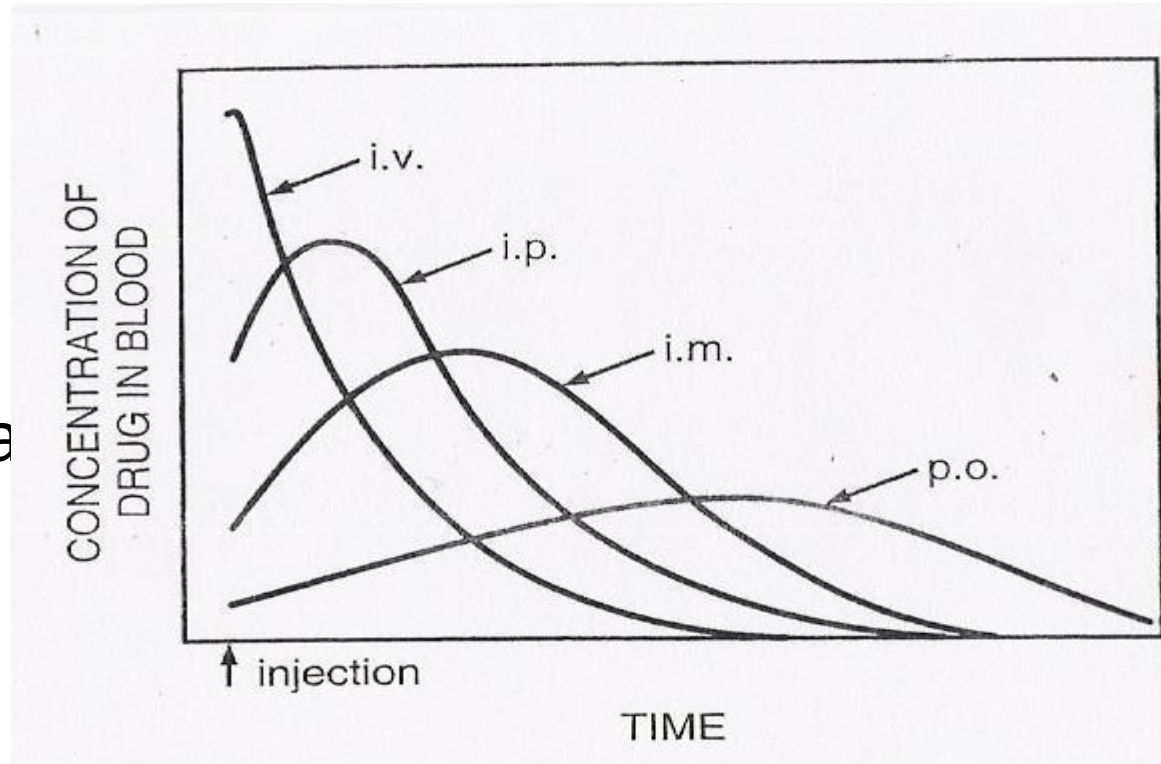
Bioavailability

- $BA = AUC/Dose$
- i.v. drug has 100% BA
- BA lower after oral ingestion because
 - Incompletely absorbed.
- Absorbed drug may undergo first pass metabolism in the intestinal wall/liver or be excreted in bile



Route of Administration Determines Bioavailability (AUC)

1. Peak plasma concentration (C_{max})
2. Time to attain the peak plasma concentration (t_{max})
3. Area under curve (AUC) of plasma concentration



Routes of administration & bioavailability

Route	Bioavailability (%)	Characteristics
Intravenous (IV)	100 (by definition)	Most rapid onset
Intramuscular (IM)	75 to ≤ 100	Large volumes often feasible; may be painful
Subcutaneous (SC)	75 to ≤ 100	Smaller volumes than IM; may be painful
Oral (PO)	5 to < 100	Most convenient; first-pass effect may be significant
Rectal (PR)	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

Bioequivalence

- If two or more similar dosage forms of the same drug reach the blood circulation at the same relative rate and to the same relative extent → **Bioequivalent preparations**
- Rate and extent of bioavailability of the active drug from standard is not significantly different under suitable test conditions
- Differences less than 25% in BA
- Problem
 - Therapeutic failure (due to decreased BA)
 - Drug intoxication (due to increased BA)
- Two or more dosage forms of the same drug-same labeled quantities of the drug as specified in pharmacopoeia → **Chemically equivalent drugs**
- Two brand products of one drug-identical pharmacological response → **Clinically equivalent drugs**
- One structurally different drug-same therapeutic response as another drug → **Therapeutically equivalent drugs**

Apparent volume of distribution (V)

- Lipid-insoluble drugs do not enter
- Drugs extensively bound to plasma proteins largely restricted to the vascular compartment
- Pathological states
 - E.g. congestive heart failure, uremia, cirrhosis of liver, etc.
 - Alter the volume of many drugs by altering
 - Distribution of body water
 - Permeability of membranes
 - Binding proteins
 - By accumulation of metabolites that displace the drug from binding sites

Volume of distribution

$$\text{Volume of distribution (Vd)} : \frac{\text{Dose administered i.v}}{\text{Plasma concentration}}$$

- Drugs with low Vd are contained mostly in the plasma, because
 - Highly water soluble (plasma water content is higher than tissues)
 - Highly protein bound (which prevents them from freely diffusing into tissues)
- Drugs with high Vd are mostly in tissues, and plasma levels may not reflect body burden.

Volume of distribution

Drugs with high Vd	Drugs with low Vd
Digoxin Carbamazepine Lidocaine Procainamide Quinidine	Amikacin Gentamycin Vancomycin Tobramycin Theophylline Phenytoin Ethanol Valproic acid

Redistribution

- Highly lipid-soluble drugs get initially distributed to organs with high blood flow, i.e. Brain, heart, kidney, etc.
- Later, less vascular but more bulky tissues (muscle, fat) take up the drug
- Plasma concentration falls
- Drug is withdrawn from the highly perfused sites
- Greater the lipid solubility of the drug, faster is its redistribution. E.g. Thiopentone

Distribution of drugs in Body compartments

Compartment and Volume	Examples of Drugs
Water	
Total body water (0.6 L/kg ¹)	Small water-soluble molecules: eg, ethanol
Extracellular water (0.2 L/kg)	Larger water-soluble molecules: eg, gentamicin
Blood (0.08 L/kg); plasma (0.04 L/kg)	Strongly plasma protein-bound molecules and very large molecules: eg, heparin
Fat (0.2-0.35 L/kg)	Highly lipid-soluble molecules: eg, DDT
Bone (0.07 L/kg)	Certain ions: eg, lead, fluoride

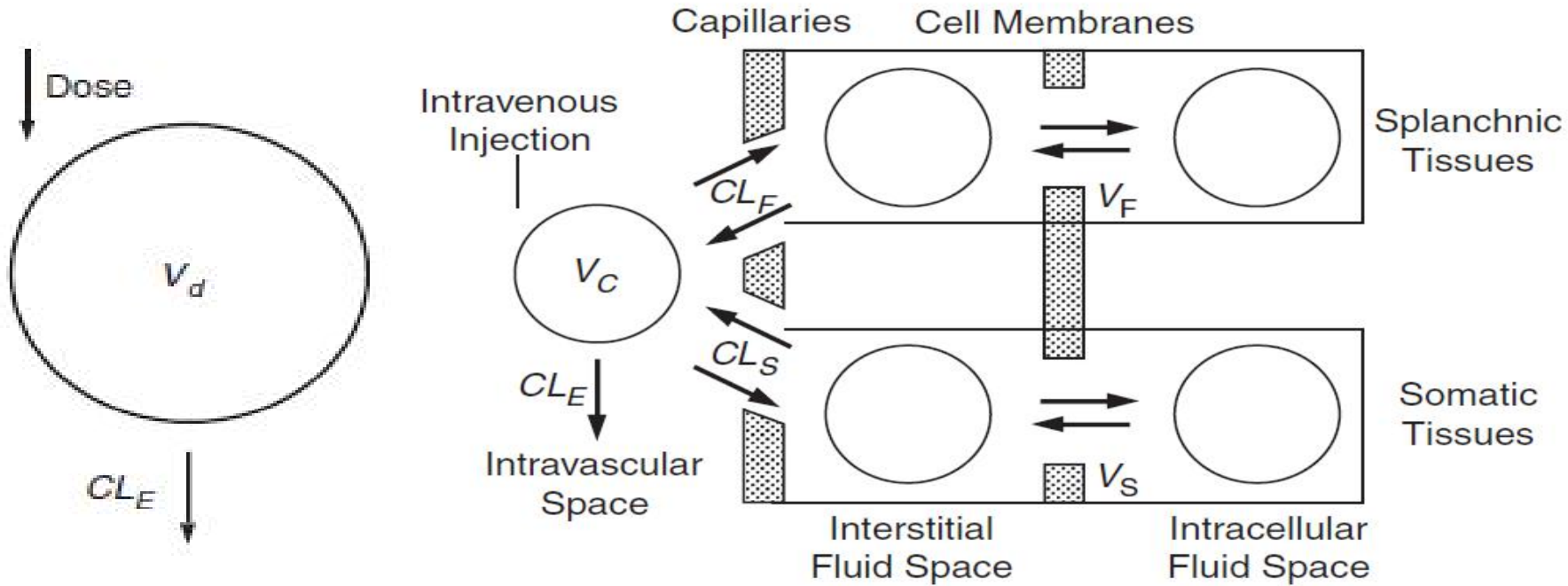
Predictions of Volume of distribution

- Volume of distribution is commonly calculated for a particular patient using body weight (70-kg body weight)
- Patients with edema, ascites, or pleural effusions offer a larger volume of distribution to the aminoglycoside antibiotics (eg, gentamicin) than is predicted by body weight.
- If a patient is obese, drugs that do not readily penetrate fat (eg, gentamicin and digoxin) should have their volumes calculated from fat-free mass (FFM).
- Total body weight (WT) is in kilograms and height (HTM) is in meters:

$$\text{For women: FFM (kg)} = \frac{37.99 \times \text{HTM}^2 \times \text{WT}}{35.98 \times \text{HTM}^2 + \text{WT}}$$

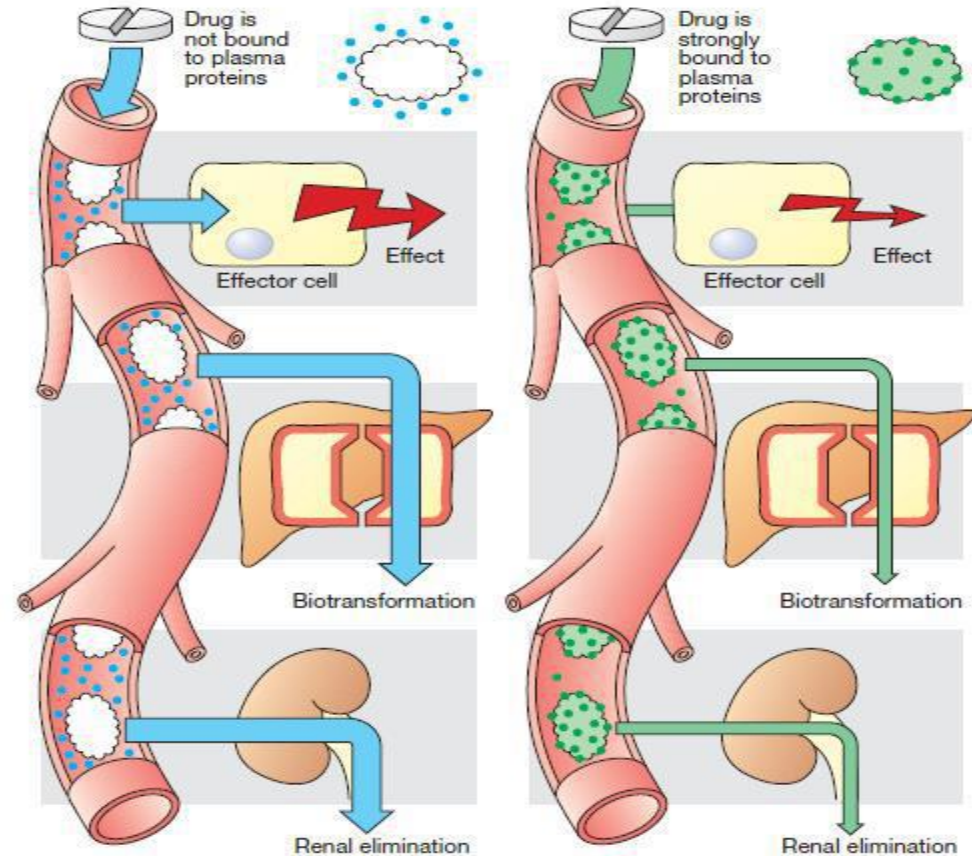
$$\text{For men: FFM (kg)} = \frac{42.92 \times \text{HTM}^2 \times \text{WT}}{30.93 \times \text{HTM}^2 + \text{WT}}$$

Concepts Underlying Clinical Pharmacokinetics



Plasma protein binding

- Acidic drugs generally bind to plasma albumin and basic drugs to α_1 acid glycoprotein
- Binding to albumin is quantitatively more important
- **Highly plasma protein bound drugs**
 - Largely restricted to the vascular compartment
 - Bound fraction not available for action
 - Long acting
 - Cannot be removed by hemodialysis
 - Importance in TDM
 - Replace by another drug
 - Effect of hypoalbuminaemia



Plasma Proteins Binding

- Albumin: binds many acidic drugs and a few basic drugs
- Beta-globulin and an α_1 acid glycoprotein have also been found to bind certain basic drugs
- **Example**
 - Warfarin (anticoagulant) protein bound ~98%
 - 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

A bound drug has no effect

Amount bound depends on:

- Free drug concentration
- The protein concentration
- Affinity for binding sites
- % bound:
$$\frac{[\text{bound drug}]}{[\text{bound drug}] + [\text{free drug}]} \times 100$$

Blood brain barrier

- Molecular and morphological barrier
- Lack of large intercellular pores
- Lipoidal barrier
- Efflux transporters
 - P-gp
 - Anion transporter
- Enzymatic BBB
 - MAO
 - Cholinesterase
- BBB is deficient
 - Anterior hypothalamus
 - Median eminence
 - Area postrema near the fourth ventricle-CTZ and vomiting center

Blood brain barrier

- Only lipid soluble non-ionized forms of drugs permeate easily
 - Ether, chloroform, Barbiturates (thiopental), Morphine, Levodopa, Amphetamine, Ephedrine, Propranolol, etc.
- Polar compounds do not cross BBB
 - Dopamine, Serotonin, Streptomycin, Quaternary compounds (d-Tubocurarine, hexamethonium, neostigmine, acetylcholine), etc.
- Inflammatory conditions alter the permeability
 - Drugs like penicillin, chloramphenicol, ampicillin, etc. crosses BBB (otherwise have poor penetration)
- **CSF-brain barrier: extremely permeable to drug molecules from CSF→brain**
 - E.g. Intrathecal routes (cross barrier and reach brain)→penicillins, methotrexate, LA, etc.

Passage Across Placenta

- Incomplete barrier
- Free passage to lipophilic drugs (lipoidal barrier)
- Limited passage to non lipophilic drugs
- P-gp, BCRP, MRP3 limit foetalexposure to maternally administered drugs
- Influx transporters +
- Site for drug biotransformation as well

Drugs concentrated in tissues

- *Skeletal muscle, heart —digoxin, emetine (bound to muscle proteins)*
- *Liver—chloroquine, tetracyclines, emetine, digoxin*
- *Kidney—digoxin, chloroquine, emetine*
- *Thyroid—iodine*
- *Brain—chlorpromazine, acetazolamide, isoniazid*
- *Retina—chloroquine (bound to nucleoproteins)*
- *Iris—ephedrine, atropine (bound to melanin)*
- *Bone and teeth —tetracyclines, heavy metals (bound to mucopolysaccharides of connective tissue), bisphosphonates (bound to hydroxyapatite)*
- *Adipose tissue —thiopentone, ether, minocycline, phenoxybenzamine dissolve in neutral fat due to high lipid-solubility; remain stored due to poor blood supply of fat*

First pass metabolism/First pass effect/Pre-systemic metabolism

- Drug metabolism occurring before drug enters systemic circulation
- **Sites: Liver, Intestinal mucosa, Bronchial muscle**
- Net effects
 - Decreased BA of the drug
 - Diminished therapeutic response
- **Hepatic first-pass effect can be avoided by**
 - iv drug administration
 - use of sublingual tablets and transdermal preparations
 - use of rectal suppositories
- Sublingual absorption → direct access to systemic veins (not portal veins)
- Suppositories in the lower rectum enter vessels that drain into the inferior vena cava, thus bypassing the liver (but also tend to move upward)

First pass effect

- **Attributes of drugs with high first pass metabolism:**
 - a) Oral dose is considerably higher than sublingual or parenteral dose.
 - b) Marked individual variation in the oral dose due to differences in the extent of first pass metabolism
 - c) Oral bioavailability is apparently increased in patients with severe liver disease
 - d) Oral bioavailability of a drug is increased if another drug competing with it in first pass metabolism is given concurrently, e.g. chlorpromazine and propranolol

<i>Low</i>	<i>Intermediate</i>	<i>High</i>	
		<i>not given orally</i>	<i>high oral dose</i>
Phenobarbitone	Aspirin	Isoprenaline	Propranolol
Phenylbutazone	Quinidine	Lidocaine	Alprenolol
Tolbutamide	Desipramine	Hydrocortisone	Verapamil
Theophylline	Nortriptyline	Testosterone	Salbutamol
Pindolol	Chlorpromazine		Glyceryl trinitrate
Isosorbide	Pentazocine		Morphine
mononitrate	Metoprolol		Pethidine

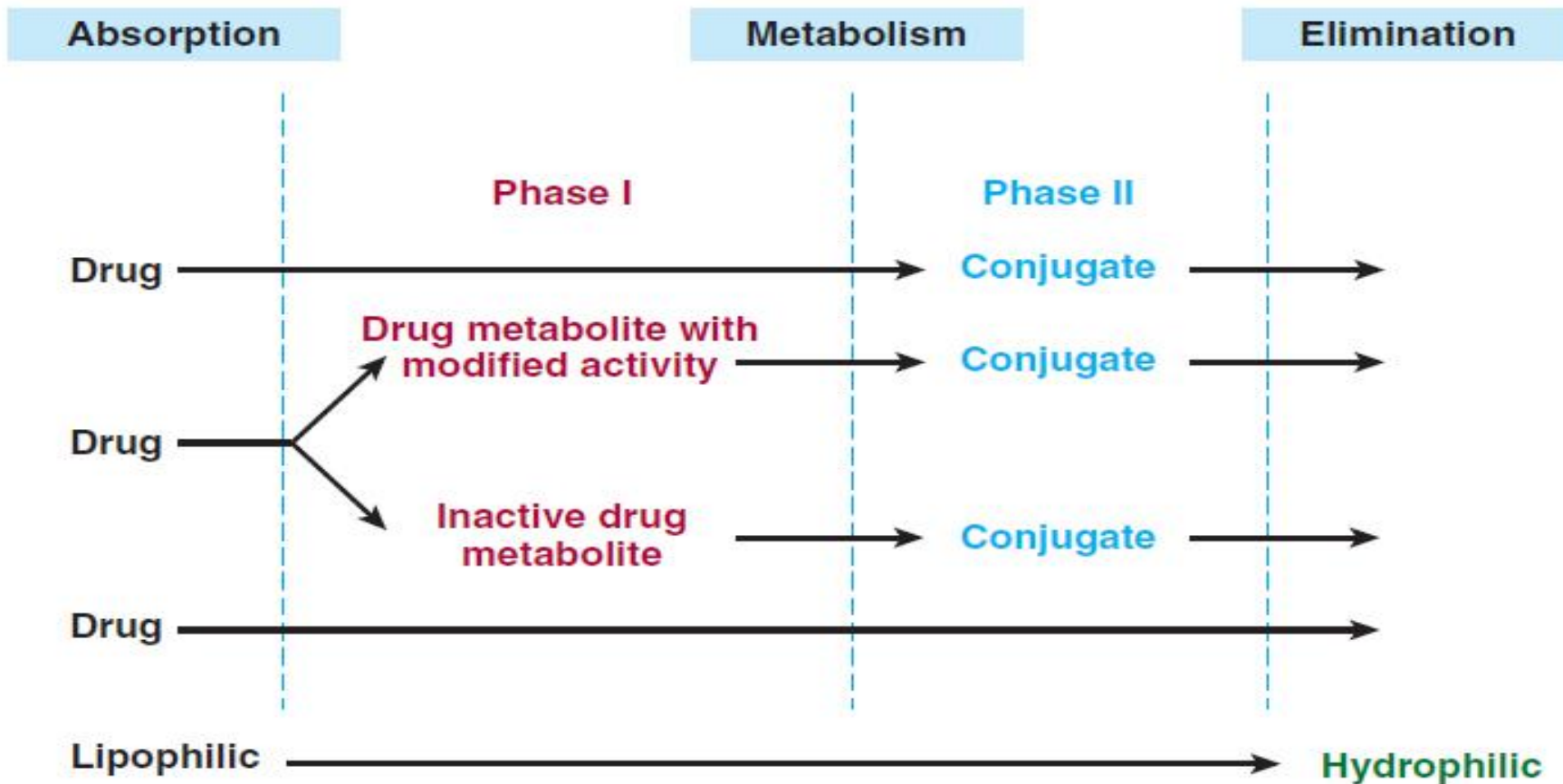
Metabolism

- Chemical alteration of the drug in the body.
- Primary site for drug metabolism → liver
- Other sites of metabolism → kidney, intestine, lungs, plasma, skin & brain.
- Biotransformation of drugs may lead to the following:
 - Inactivation-e.g. Phenobarbitone → Hydroxyphenobarbitone
 - Active metabolite from an active drug -e.g. Diazepam → Oxazepam; Amitriptyline → Nortriptyline; Codeine → Morphine
 - Activation of inactive drug
- Prodrugs-drugs which are inactive as such and need conversion in the body to one or more active metabolites
- Levodopa → Dopamine; Enalapril → Enalaprilat;
- α -Methyldopa → α -methylnorepinephrine; Dipivefrine → Epinephrine

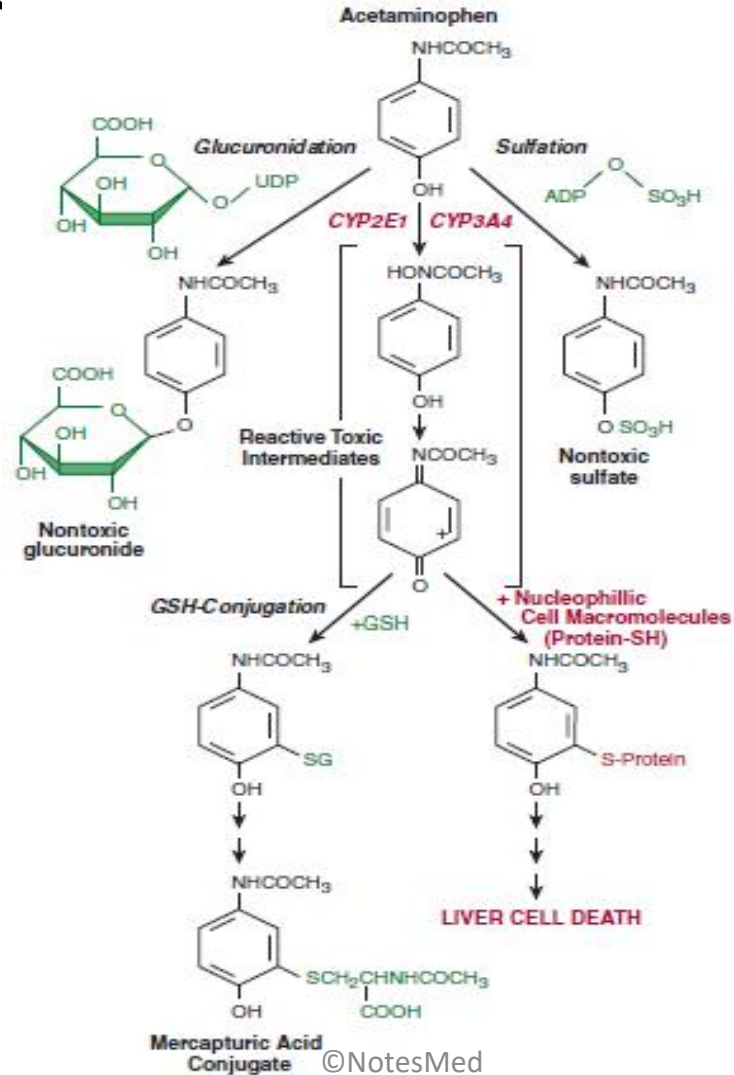
Biotransformation reactions

- **Nonsynthetic/Phase I/Functionalization reactions/Degradative reactions:** a functional group is generated or exposed—metabolite may be active or inactive
 - Oxidation
 - Reduction
 - Hydrolysis
 - Cyclization
 - Decyclization
- **Synthetic/Conjugation/ Phase II reactions:** an endogenous radical is conjugated to the drug—metabolite is mostly inactive
 - Glucuronide conjugation (only microsomal conjugation)
 - Methylation
 - Acetylation
 - Sulfate conjugation
 - Glutathione conjugation
 - Glycine conjugation

Phase I and phase II reactions



Acetaminophen metabolism



Microsomal Enzyme Induction

- **Different inducers for certain cytochrome P-450 isoenzyme families:**
 - Anticonvulsants (phenobarbitone, phenytoin, carbamazepine), rifampin, glucocorticoids induce CYP3A isoenzymes.
 - Phenobarbitone also induces CYP2B1 and rifampin also induces CYP2D6
 - Isoniazid and chronic alcohol consumption induce CYP2E1
 - Charcoalbroiledmeat, omeprazole and industrial pollutants induce CYP1A isoenzyme
 - Other important enzyme inducers are: phenylbutazone, griseofulvin, etc.

Microsomal Enzyme Induction

- *Hofmann elimination*
 - This refers to inactivation of the drug in the body fluids by spontaneous molecular rearrangement without the agency of any enzyme, e.g. atracurium
- Induction involves microsomal enzymes in liver as well as other organs and increases the rate of metabolism by 2–4 fold.
- Induction takes 4–14 days to reach its peak and is maintained till the inducing agent is being given. Thereafter the enzymes return to their original value over 1–3 weeks.

Microsomal enzymes

Monooxygenases, Cytochrome P450, UGTs, Epoxide Hydrolases

Nonmicrosomalenzymes

Esterases, Amidases, some FlavoproteinOxidases and most
Conjugases

Enzyme inducers

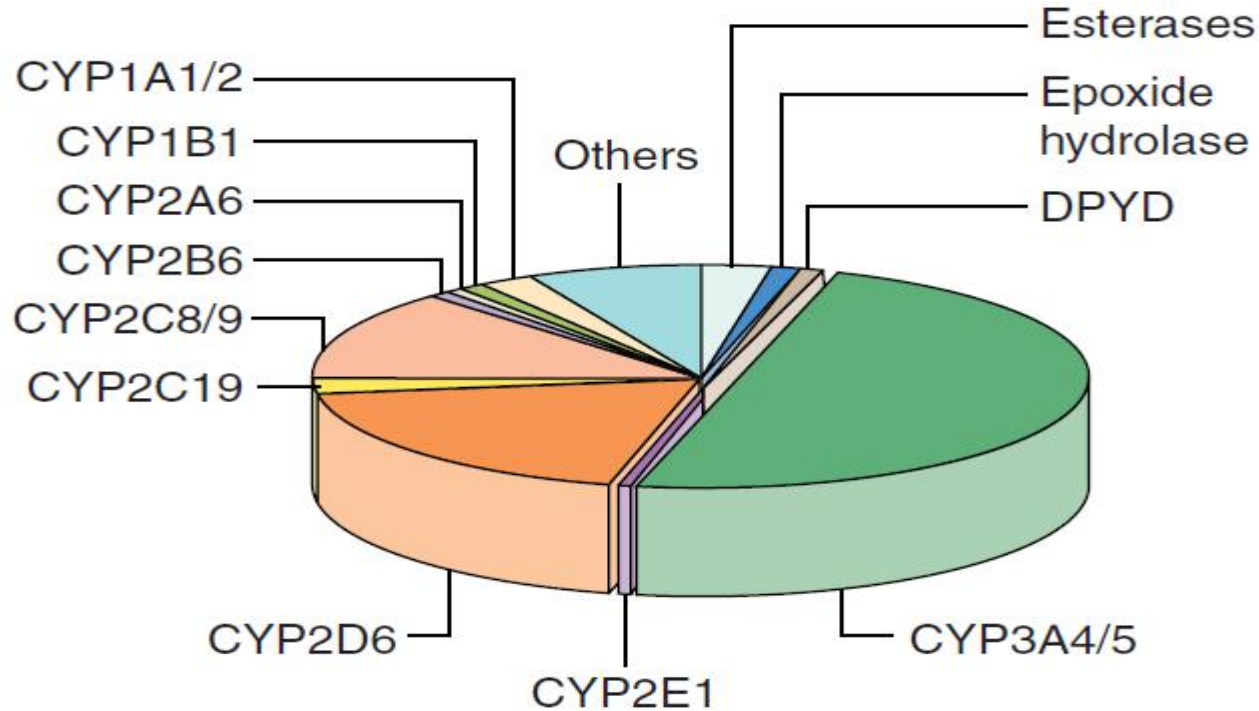
- Increase the metabolism of other drugs
 - Griseofulvin, Phenytoin, Rifampin, Smoking, Carbamazepine, Phenobarbitone [GPRS Cell Phone]

Enzyme inhibitors

Decrease the metabolism of the drugs metabolized by microsomal enzymes; predispose to the toxicity by such agents.

Valproate, Ketoconazole, Cimetidine, Ciprofloxacin, Erythromycin, Isoniazid [Vitamin K Cannot Cause Enzyme Inhibition]

Relative contributions of various cytochrome P450 isoforms



Selected Cytochrome P450 Substrates, Inhibitors and Inducers

	Substrates	Inhibitors	Inducers
CYP3A4	Alprazolam	Amprenavir	Amprenavir
	Atorvastatin	Cimetidine	Carbamazepine
	Carbamazepine	Clarithromycin	Barbiturates
	Clarithromycin	Erythromycin	Dexamethasone
	Dapsone	Fluconazole	Phenytoin
	Erythromycin	Ketoconazole	Rifampin
	Estrogens	Ritonavir	Ritonavir
CYP1A2	Caffeine	Cimetidine	Broccoli
	Haloperidol	Ciprofloxacin	Carbamazepine
	Propranolol	Clarithromycin	Rifampin
	Theophylline	Erythromycin	Modafinil
	Olanzapine	Norfloxacin	Smoking
CYP2C19	Indomethacin	Cimetidine	Prednisone
	Omeprazole	Omeprazole	Carbamazepine

Consequences of microsomal enzyme induction

1. Decreased intensity and/or duration of action of drugs that are inactivated by metabolism, e.g. failure of contraception with oral contraceptives.
2. Increased intensity of action of drugs that are activated by metabolism. Acute paracetamol toxicity is due to one of its metabolites—toxicity occurs at lower doses in patients receiving enzyme inducers.
3. **Tolerance**—if the drug induces its own metabolism (autoinduction), e.g. carbamazepine, rifampin.
4. Some endogenous substrates (steroids, bilirubin) are also metabolized faster.

Consequences of microsomal enzyme induction

5. Precipitation of acute intermittent porphyria: enzyme induction increases porphyrin synthesis by derepressing δ -aminolevulinic acid synthetase.
6. Intermittent use of an inducer may interfere with adjustment of dose of another drug prescribed on regular basis, e.g. oral anticoagulants, oral hypoglycaemics, antiepileptics, antihypertensives.
7. Interference with chronic toxicity testing in animals.

Clinical Relevance of Drug Metabolism

- **Individual Differences**-dose and frequency of administration required to achieve effective therapeutic blood and tissue levels vary in different patients
- **Genetic Factors**
 - Phase I enzyme polymorphisms
 - CYP2A6 –Warfarin-increased risk of bleeding; CYP2C19-Omeprazole-reduced therapeutic efficacy; CYP2D6-Codeine-Increased metabolic activation to morphine

Clinical Relevance of Drug Metabolism

- **Phase II Enzyme Polymorphisms**
 - Polymorphism of the TPMT (thiopurine S-methyltransferase) gene-high risk of thiopurine drug-induced fatal hematopoietic toxicity
 - Defect in slow acetylators (of isoniazid and similar amines) appears to be caused by the synthesis of less of the NAT2 enzyme-associated with a higher incidence of isoniazid-induced peripheral neuritis, drug-induced autoimmune disorders, and bicyclic aromatic amine-induced bladder cancer.
- **Role of Pharmacogenetic Testing in Clinically Safe & Effective Drug Therapy**

Clinical Relevance of Drug Metabolism

- **Age & Sex**
 - Increased susceptibility to the pharmacologic or toxic activity of drugs has been reported in very young and very old patients compared with young adults
 - Sex-dependent differences in drug metabolism also exist in humans for ethanol, propranolol, some benzodiazepines, estrogens, and salicylates
- **Drug-Drug Interactions during Metabolism**
 - Enzyme inducers and enzyme inhibitors
- **Interactions between Drugs & Endogenous Compounds**
 - Some drugs require conjugation with endogenous substrates such as GSH, glucuronic acid, or sulfate for their inactivation

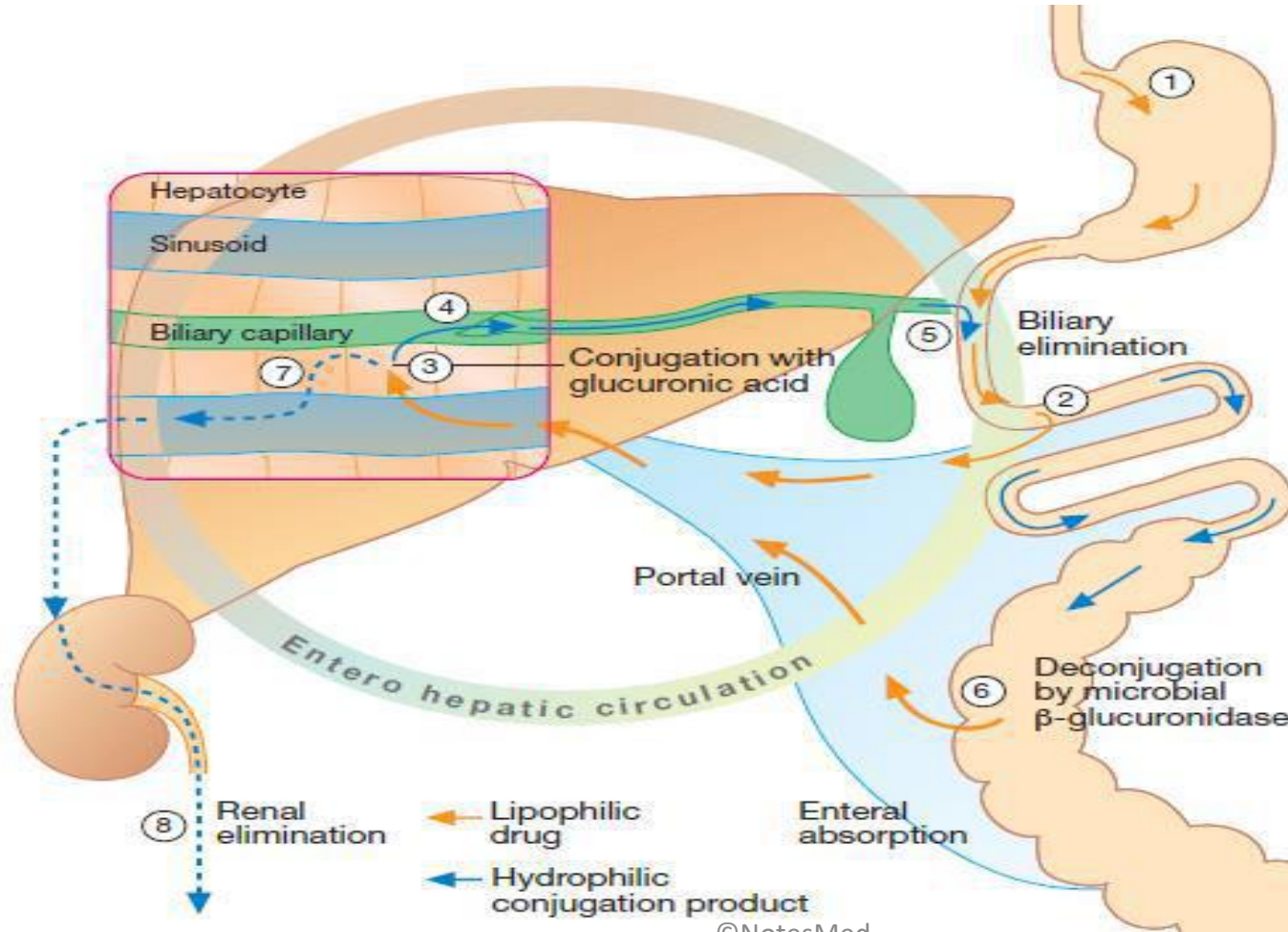
Diseases Affecting Drug Metabolism

- Alcoholic hepatitis, active or inactive alcoholic cirrhosis, hemochromatosis, chronic active hepatitis, biliary cirrhosis, and acute viral or drug-induced hepatitis
 - impair hepatic drug-metabolizing enzymes, particularly microsomal oxidases, and thereby markedly affect drug elimination.
- Cardiac disease
 - by limiting blood flow to the liver, may impair disposition of those drugs whose metabolism is flow-limited

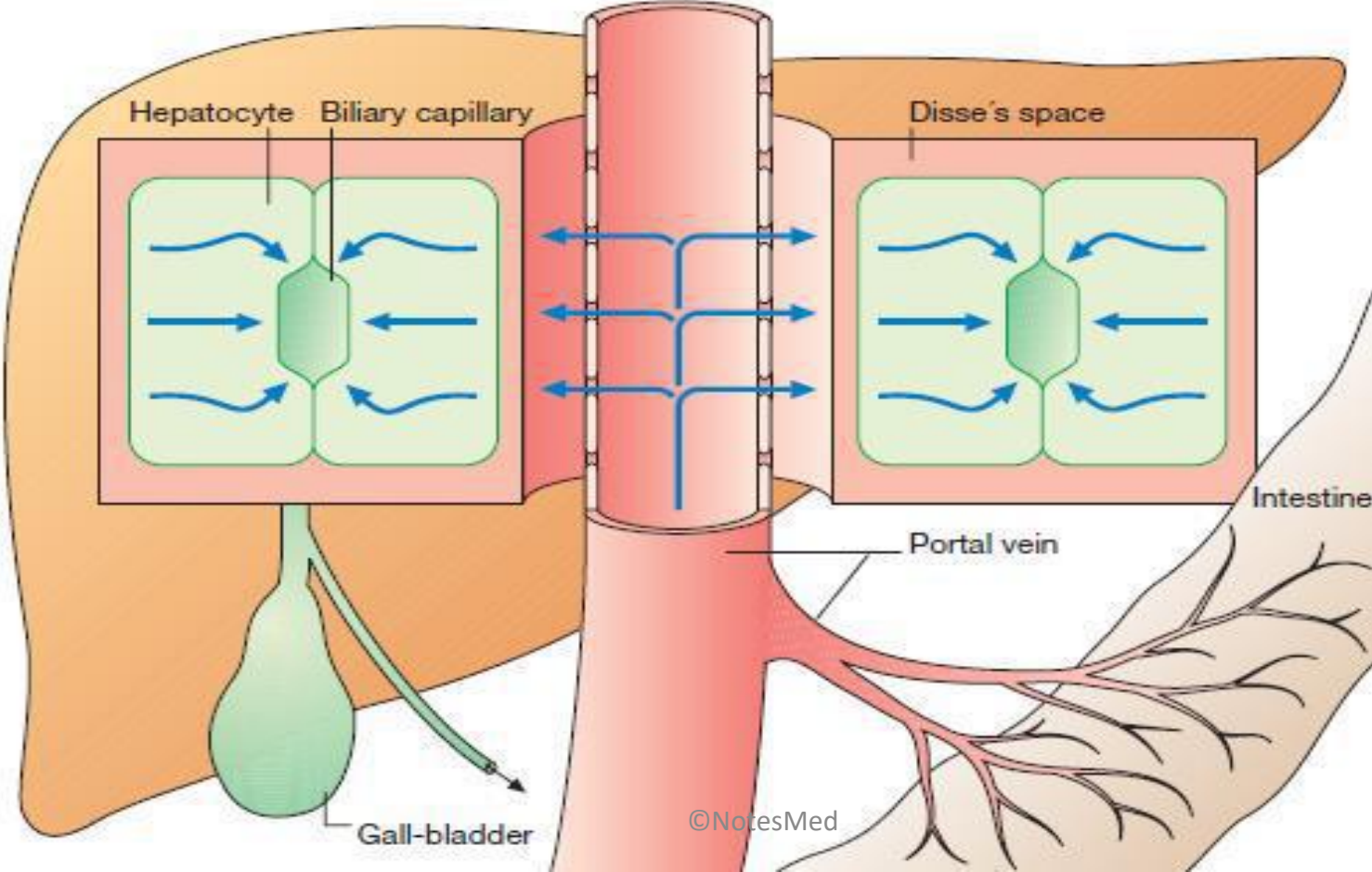
Diseases Affecting Drug Metabolism

- Pulmonary disease
 - by impaired hydrolysis of procainamide and procaine in patients with chronic respiratory insufficiency and the increased half-life of antipyrine (a P450 functional probe) in patients with lung cancer
- Hypothyroidism
 - increases the half-life of antipyrine, digoxin, methimazole, and some β blockers, whereas hyperthyroidism has the opposite effect

Enterohepatic cycling of drugs



Enterohepatic cycling of drugs



Excretion

- Passage out of systemically absorbed drug
- **Route of excretion**
 - Urine
 - Faeces
 - Exhaled air
 - Saliva and sweat
 - Milk

Renal Excretion

- Responsible for excreting all water soluble substance
- Net renal excretion = (Glomerular filtration + tubular secretion) – tubular reabsorption
- Glomerular capillaries have large pores
- Glomerular filtration of drug depends upon
 - PPB
 - GFR

Tubular Reabsorption

- Passive diffusion
- Depends upon :
 - Lipid solubility
 - Ionization of drug
 - Effect of urinary PH
- **Reabsorption by nonionic diffusion**
 - Affects weak acids and weak bases
 - Only important if excretion of free drug is major elimination path
 - Examples: Weak acids: Phenobarbital Weak bases: Quinidine
- **Active reabsorption**
 - Affects ions, not proved for other drugs
 - Examples: Halides: Fluoride, bromide Alkaline metals: Lithium

Tubular Secretion

- Active transfer of organic acids and bases
- Nonspecific transporters
 - OATP (organic acid transport) : penicillin, probenecid, uric acid, salicylates, indomethacin, methotrexate etc.
 - OCT (organic base transport) : thiazides, amiloride, triamterene, furosemide, quinine, procainamide, choline, cimetidine etc.
- Proximal tubules
- **Effect**
 - Salicylates block uricosuricaction of probenecid and Sulfinpyrazone and also decrease tubular secretion of Mtx
 - Probenecid decrease concoef nitrofurantoinin urine, increase the duration of action of penicillin
 - Sulfinpyrazone inhibits excretion of tolbutamide
 - Quinidine decreases renal and biliary clearance of digoxin by inhibiting efflux carrier

Kinetics of Elimination

- **Clearance (CL) : the theoretical volume of plasma from which the drug is completely removed in unit time**
- $CL = \text{Rate of elimination} / C$ (Plasma Concentration)

- **First order kinetics**
 - Rate of elimination is directly proportional to the drug concentration
 - CL remains constant
 - Half life remains constant
 - Most of the drugs follow

- **Zero order kinetics**
 - Rate of elimination is remains constant irrespective to the drug concentration
 - Saturation kinetics
 - CL decrease with concentration
 - Constant amount of the drug is eliminated in unit time
 - E.g. Warfarin, Alcohol, Theophylline, Tolbutamide, Phenytoin

Plasma Half Life ($t_{1/2}$)

- *Time taken for its plasma conc. to be reduced to half of its original value.*
 - Alpha phase: initial rapid due to distribution
 - Beta phase: due to elimination
- Two half lives calculated from the two slopes of curve
- Elimination half life is simply called the half life of drug
 - $t_{1/2} = 0.693/k$
 - $K = CL/V$
 - $t_{1/2} = 0.693 \times V/CL$
- Complete drug elimination : 4-5 half lives
- First order kinetics : $t_{1/2}$ remains constant
- Zero order kinetics : $t_{1/2}$ increase with dose

Repeated drug administration

- Steady state plasma conc.(C_{pss})
- **C_{pss} = Dose rate / CL**
- Dose rate = target C_{pss} X CL
- Steady state reached in 4-5 half lives
- Dose rate – C_{pss} is linear only in cases of drugs eliminated by first order kinetics
- For drugs where kinetics change from first order to zero order then C_{pss} will be out of proportion to the change in dose rate
- **Rate of drug elimination = (V_{max})(C)/K_m+C**

Maintenance Dose

- Dose which is required to be repeated at specified interval after attainment of target C_{ps} to maintain C_{pss}
- **Maintenance Dose Rate = target $C_{pss} \times CL$**
- After oral adm:
- Dose rate = target $C_{pss} \times CL / F(\text{bioavailability})$

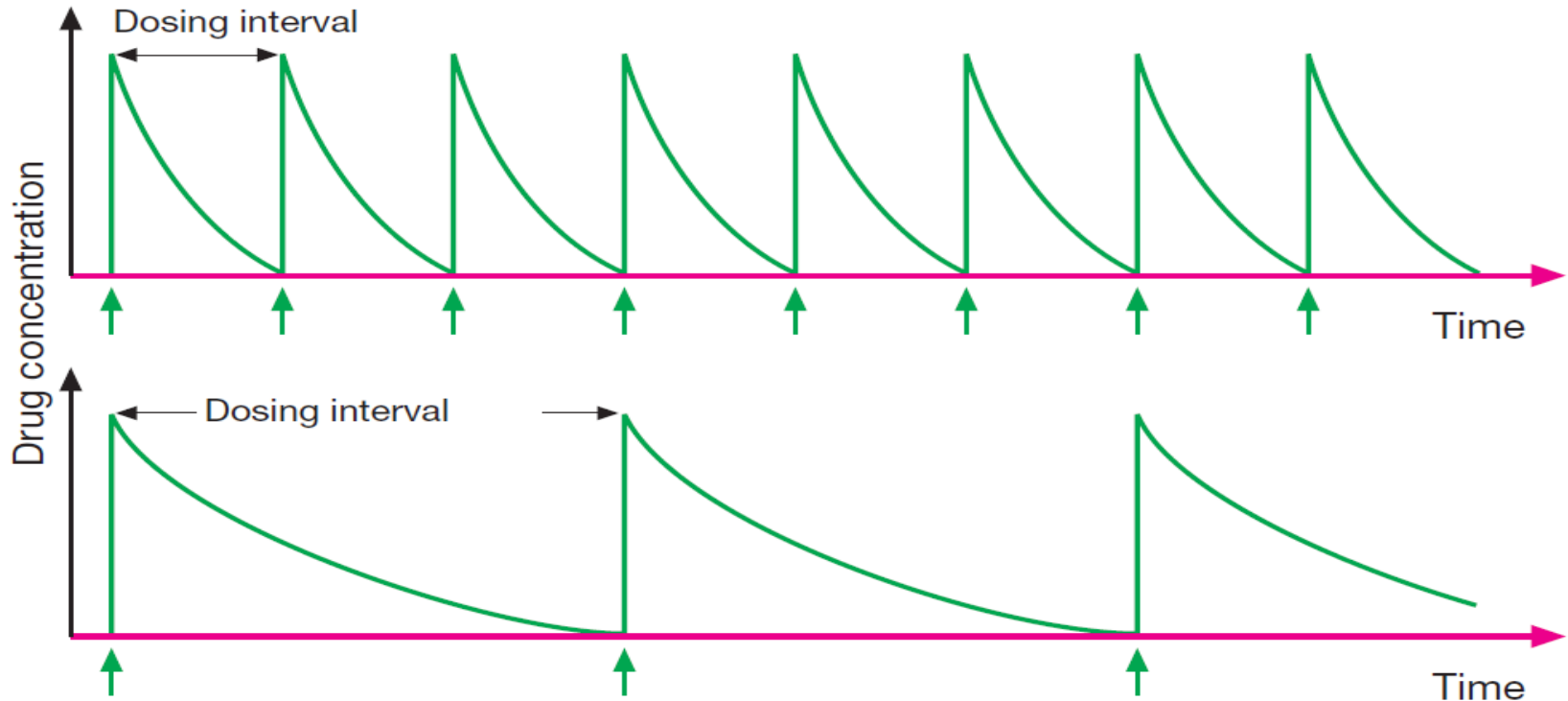
Loading Dose

- Single or few quickly repeated dose administration beginning to attain target concentration
- **Loading Dose = Target CpX V/F**
- Drugs : Digoxin, Chloroquine, Doxycycline etc

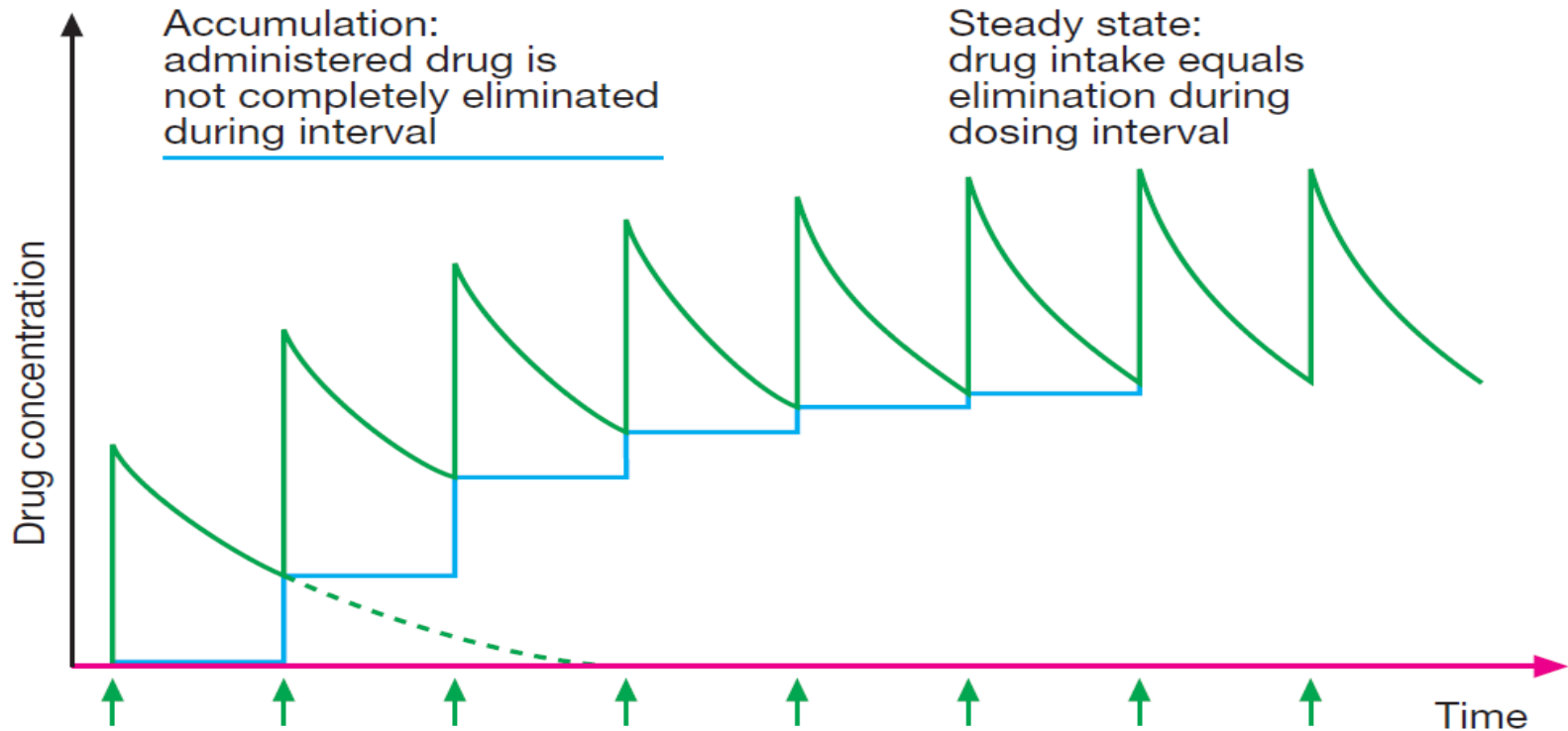
Dosing Schedules

1. Drugs having very short half life → constant iv infusion
e.g. Norepinephrine-1 to 2 min, Dopamine-5 min, Dobutamine-2 min, Oxytocin-3 to 5 min, etc.
 2. Drugs having short half life (30 min-2 hrs) → increase the dose and administered at every 6-8 hrly (inconvenient to administer them at every half life)
 3. Drugs having half life 4 to 12 hrs → administered at a every half life interval
 4. Drugs having medium half life (12-24 hrs) given at 12 hrly interval
 5. Drugs with $t_{1/2}=24$ hrs → half of the therapeutic dose given at every half of the half life
 6. Drugs having longer half life → high V_d , Slow rate of clearance and cumulative in nature → loading dose (priming dose) to reduce time needed to reach steady state plasma concentration followed by maintenance dose to maintain already attained steady state plasma concentration
- e.g. Digoxin-40 hrs(640L), Desipramine-20-60 hrs(30-60L), Digitoxin-168 hrs(38L), Diazepam-40 hrs(50-70L), Chloroquine-40 hrs(130L)

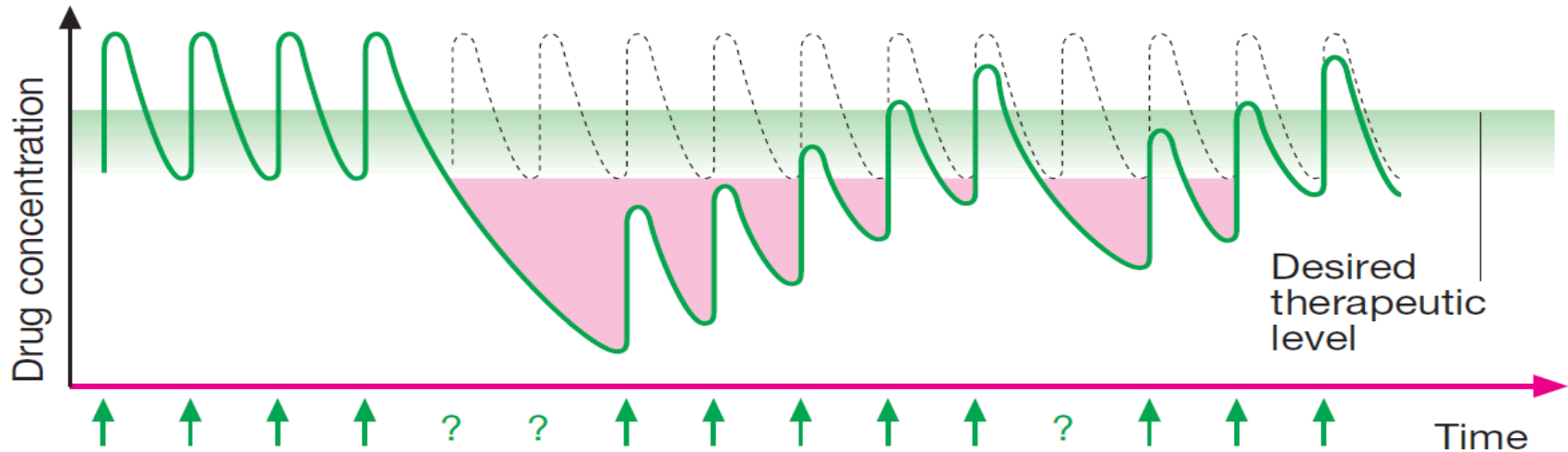
Time course of drug concentration in blood during regular intake



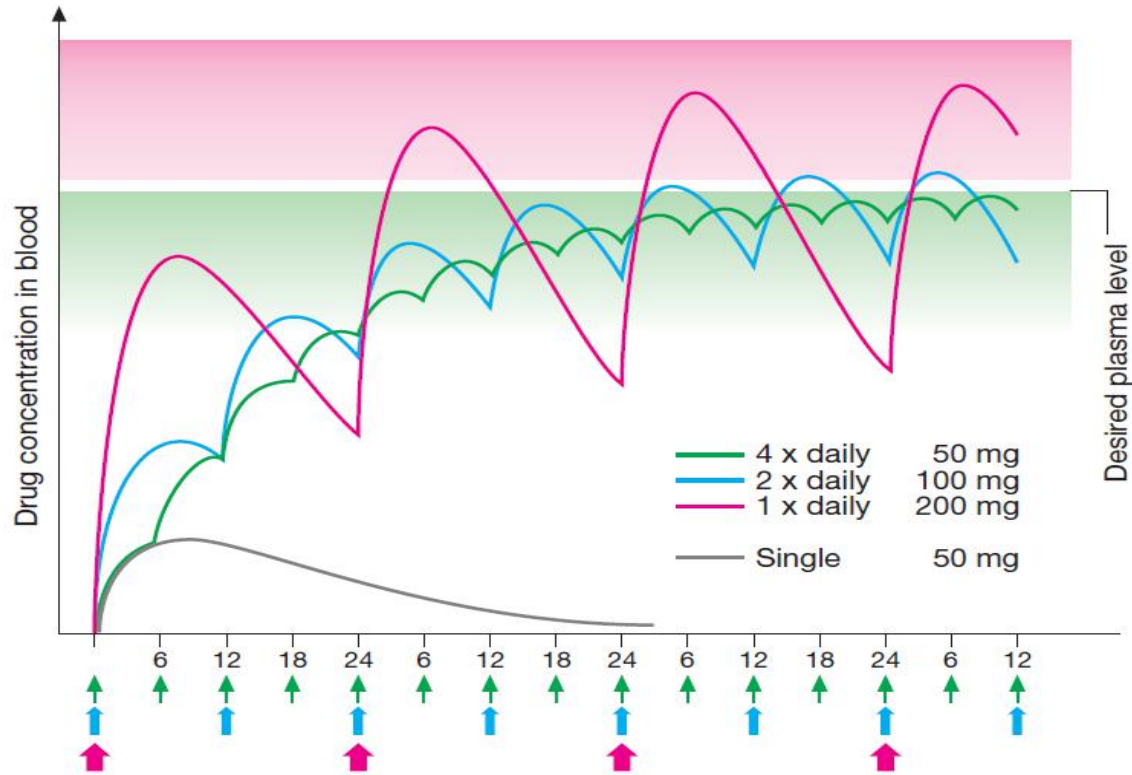
Time course of drug concentration in blood during regular intake



Time course of drug concentration with irregular intake



Accumulation: dose, dose interval, and fluctuation of plasma level



Prolongation of drug action

- **Advantages:**
 - Decrease in frequency
 - Improved patient compliance
 - Plasma Fluctuations decreased
 - Drug effect can be maintained without disturbing sleep
 - However all drugs do not need to be made long acting
 - Brief therapeutic effect
 - Long duration of action

Prolongation of drug action

- **Methods used for prolonging drug action:**
 - By prolonging absorption from the site of administration
 - Oral: SR tabs, Spansules, CR tabs
 - Parenteral : oily solution, inclusion of vasoconstrictor, insoluble form
 - TDD system : adhesive patches
 - By increasing PPB : preparation of drug congener
 - By retarding rate of metabolism : addition of another group, inhibition of enzyme
 - By retarding renal excretion

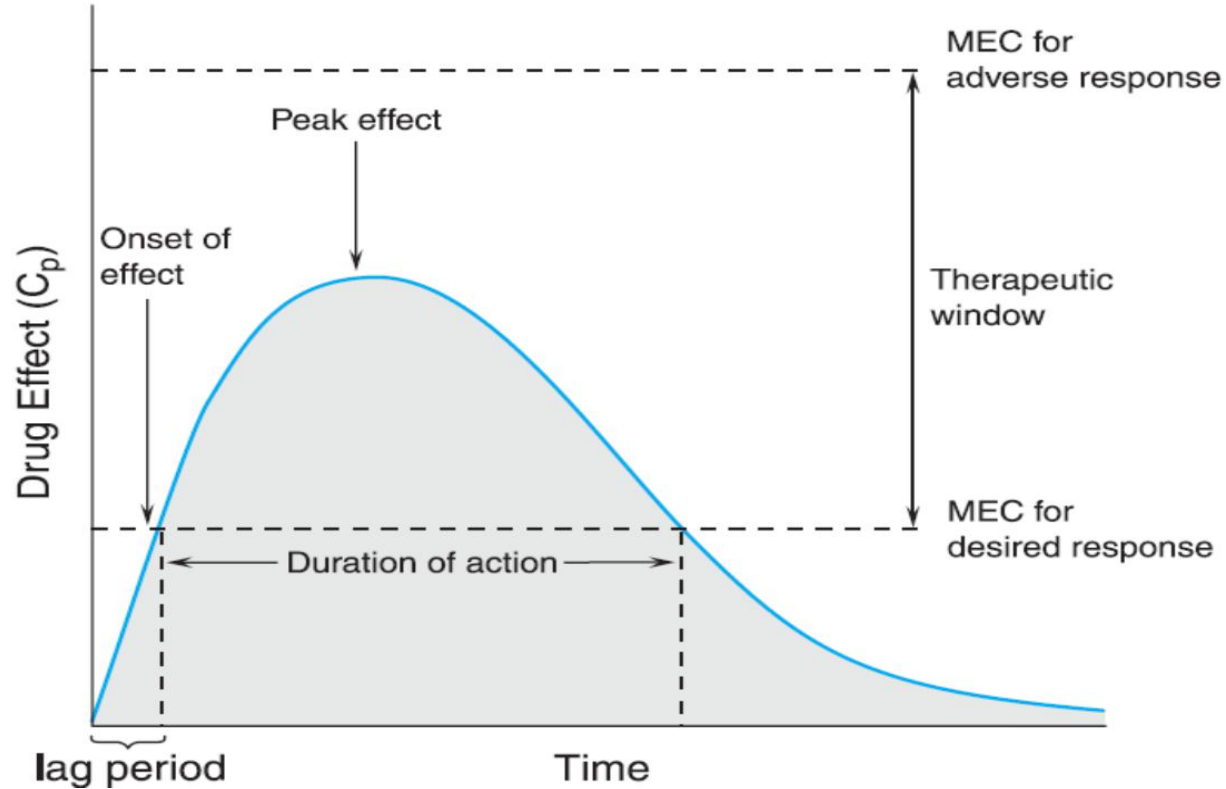
Plateau Principle

- When constant dose of a drug is repeated before the expiry of 4 half lives
 - Achieve higher peak conc.
 - As some remnant of previous dose will be present in the body
 - Steady state reached in 4-5 half lives unless dose interval is much longer than $t_{1/2}$
- If dose rate is changed , a new average C_{pss} will be attained after 4-5 half lives

Therapeutic range

- That concentration would set the lower limit of utility of the drug, called Minimum Effective Concentration (MEC).
- At some concentrations may be toxic, called Maximum Therapeutic Concentration or Minimum Toxic Concentration(MTC).
- Patient studies have generated upper MTC and lower MEC plasma concentration ranges that are deemed safe and effective in treating disease
→“therapeuticrange” for the drug.

Therapeutic window



Major sources of pharmacokinetic variability

- Lack of Patient Compliance
- Age –neonates, children, elderly
- Physiology –gender, pregnancy
- Disease –hepatic, renal, cardiovascular, respiratory
- Drug-to-drug interactions
- Environmental influences

Therapeutic Drug Monitoring (TDM)

- Measurement of drug concentration at the sites of action is practically not possible
- Concentration in biological fluids would be reflective of the concentration at these sites after the attainment of equilibrium (steady state in blood/ plasma) by the drug in the body
- Measurement of drug concentration in biological fluid as a tool to optimize the drug therapy
- Appropriate adjustment of doses can be done

History of TDM

- 1960 –development of principles of TDM
- 1970 –automation of laboratory methods
- 1980 –widespread expansion of TDM
- 1990 –calculated the restraint about the use of TDM
- Introduced in India in the mid and late 1980s and the last 30 years have seen it grow
- Today there are over 20 therapeutic drugs which are routinely monitored

Therapeutic Drug Monitoring (TDM)

- **Useful in following situation**
 - Drugs with low safety margins
 - Individual variation is large
 - Potentially toxic drugs
 - Poisoning
 - Failure of response
 - Patient compliance

Purpose of TDM

- To confirm 'effective' concentrations
- To investigate therapeutic failure
- To check compliance
- To avoid or anticipate toxic concentrations
- Before increasing to unusually large doses
- Limited role in toxicology -drug screen

No Role of TDM in:

- Drugs whose value is easily measurable - antihypertensive, hypoglycemic, diuretics, oral anticoagulants, general anesthetics.
- Drugs activated in the body –levodopa.
- ‘Hit and run drugs’ (whose effects lasts much longer than the drug itself) –reserpine, guanethidine, MAO inhibitors, omeprazole.
- Drugs with irreversible actions –organophosphate anticholinesterases, phenoxybenzamine.

Sample information required for accurate interpretation

- Time of sample in relation to last dose
- Duration of treatment with the current dose
- Dosing schedule
- Age, gender
- Other drug therapy
- Relevant disease states
- Reason for request (e.g. lack of effect, routine monitoring, suspected toxicity)

When should Samples be Collected for Estimating Drug Levels?

Time for taking sample for TDM depends upon the purpose

1. For confirming the compliance to treatment → random sample
2. Poisoning → sample taken at the earliest and repeated
 - To confirm diagnosis and then repeated to monitor the progress
3. For dose adjustments → sample just before the next dose
4. For drugs with short half lives (<24 hours) → blood sample taken once the drug concentration has attained steady state

When should Samples be Collected for Estimating Drug Levels?

5. **For drugs with longer half lives (≥ 24 hours) ?sample taken before the attainment of steady state**
 - To ensure that individuals with impaired metabolism or renal excretion are not at risk of developing toxicity after the administration of initial dosage regimen
 - Sample taken any time after the distribution phase is appropriate e.g. digoxin levels are assayed at 6-24 hours after the last oral dose
6. **For drugs like aminoglycosides ?sample taken from both peak and trough**
 - Peak concentration of aminoglycosides determines the antimicrobial effect
 - Trough concentration determines their toxic potential.
 - For peak concentration of aminoglycosides, sampling is done 1-2 hours post dose to avoid distribution phase

Which Biological Fluids should be Used for TDM?

- Serum and plasma concentration
- Whole blood concentration (Cyclosporine)
 - measured because its distribution between RBCs and plasma is affected by temperature
- Saliva (lithium)

Potential problems in use of TDM

- Missing information
- Analytical methods
- Altered plasma protein binding
- Presence of active metabolites
- Stereoisomerism
- Quality control
- Blood collection procedures
- Blood/plasma/serum/unbound drug concentrations

TDM Methods

- Colorimeter
- Gas-liquid chromatography (GLC)
 - separation method using high temperature to cause sample vaporization.
 - vaporization separates various molecules in the sample at their different fractions.
- Flame photometry
- **High-pressure liquid chromatography (HPLC)**
- Immunoassay

Compliance

- Therapeutic success depends on the patient actually taking the drug according to the prescribed dosage regimen—"Drugs don't work if you don't take them."
- Noncompliance with the prescribed dosing schedule →major reason for therapeutic failure
- Only about 50% of patients follow the prescribed dosage regimen in a reasonably satisfactory fashion
- Approximately one-third comply only partly, and about one in six patients is essentially noncompliant
- Missed doses more common than too many doses