Pharmacokinetics

Metabolism , Excretion & Kinetic summary

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- **Sources**
- **Lippincott Illustrated Reviews: Pharmacology 7th Edition**
- **Katzung ; Basic & Clinical Pharmacology 14th Edition**
- **Bennett & Brown ; Clinical pharmacology 11th edition**
- **Essentials of Medical Pharmacology; Lafi 09**

Pharmacokinetics

ABSORPTION

DISTRIBUTION

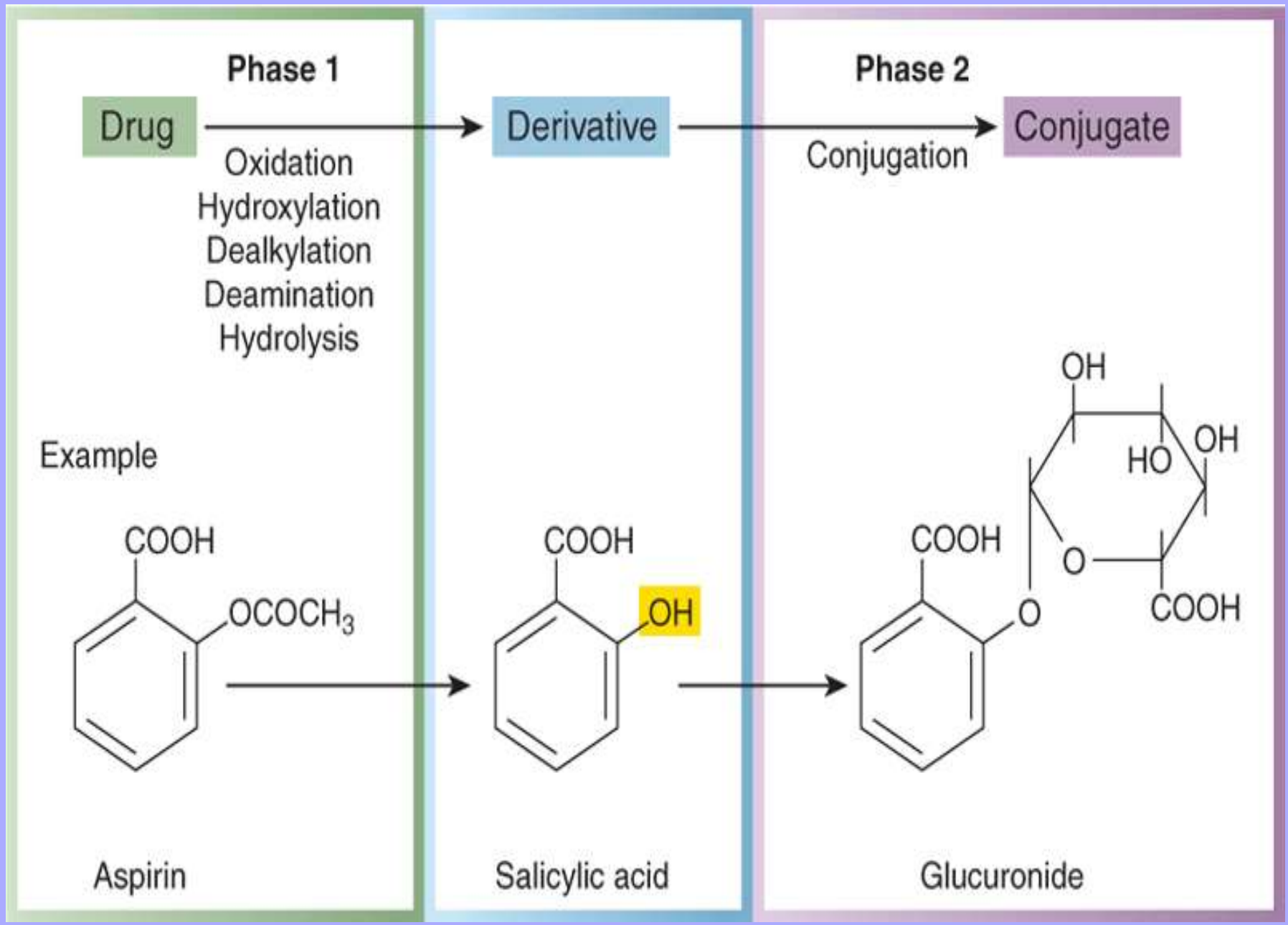
METABOLISM

Excretion

METABOLISM

BIOTRANSFORMATION

- **is the metabolic conversion of drug molecules to more water-soluble** (Less toxic) **metabolites that are more readily excreted .**


Phase 1
Drug
Derivative
Oxidation
Hydroxylation
Dealkylation
Deamination
Hydrolysis
Phase 2
Conjugate
Conjugation
Example
COOH
OCOCH3
COOH
OH
OH
HO
OH
O
COOH
O
COOH
Aspirin
Salicylic acid
Glucuronide

Phase I Metabolism & CYP 450

- Uses enzymes (oxidases) to unmask or introduce polar groups (e.g.,-OHs, -O's) on the drug.

- Phase I mainly uses: "cytochrome p450 family"
  - Heme-containing enzymes

METABOLISM

- **In many cases , metabolism of a drug result s in its conversion to compound s that have little or no pharmacologic activity .**

- In other cases, biotransformation of an active compound may lead to the formation of metabolites that also have pharmacologic actions .

- A **few** compounds (prodrugs) have no activity until they undergo metabolic activation .

Active Drugs	Active Metabolite
Allopurinol	Alloxanthine
Amitriptyline	Nortriptyline
Aspirin	Salicylic acid
Acetaminophen (safe)	N-acetyl-p-benzoquinoneimine (NABQI) Hepatotoxic
Codeine	Morphine
Chloroquine	Hydroxychloroquine
Diazepam	Nordiazepam

Inactive Substance	**Active Metabolite**
Azathioprine	Mercaptopurine
Enalapril	Enalaprilat
Sulphasalazine	5-aminosalicylic acid (mesalazine) plus sulphapyridine (by bacteria in the colon)
Talampicillin	Ampicillin
Acyclovir	Acyclovir triphosphate (by viral thymidine kinase)

Inactive Substance	Active Metabolite
Metronidazole	Reduced- metronidazole (by anaerobic bacteria)
Chloramphenicol succinate	Chloramphenicol
Chloral hydrate	Trichloroethanol
Anistreplase	Deacylated anistreplase
Hexamine	Formaldehyde (by hydrolysis in acidic urine)

Cytochrome P450 isozymes

• **These are major enzyme systems involved in phase I reactions. Localized in the** smooth endoplastic reticulum (microsomal fraction) of cells **(especially liver**, but including **GI tract, lungs, and kidney**).

Cyp450 enzymes

CYP450	Substrate Example	Inducers	Inhibitors	Genetic Polymorphisms
1A2	Theophylline Acetaminophen	Aromatic hydrocarbons (smoke) Cruciferous vegetables	Quinolones Macrolides	No
2C9	Phenytoin Warfarin	General inducers*	—	Yes
2D6	Many cardiovascular and CNS drugs	None known	Haloperidol Quinidine	Yes
3A4	60% of drugs in PDR	General inducers*	General inhibitors† Grapefruit juice	No

* General inducers: anticonvulsants (barbiturates, phenytoin, carbamazepine), antibiotics (rifampin), chronic alcohol, glucocorticoids.

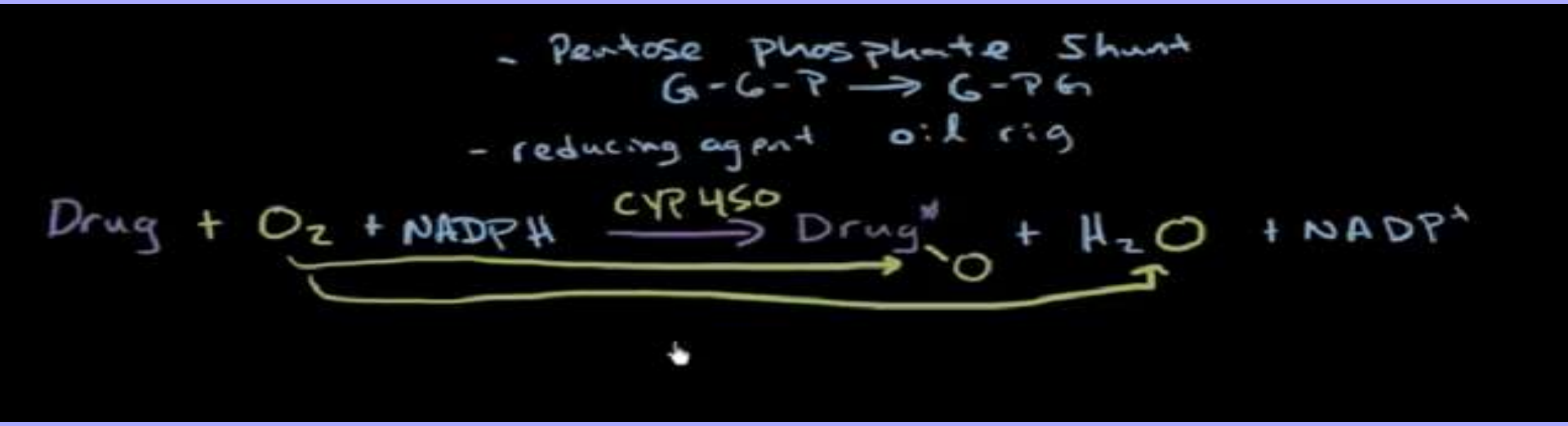
† General inhibitors: antiulcer medications (cimetidine, omeprazole), antibiotics (chloramphenicol, macrolides, ritonavir, ketoconazole), acute alcohol.

Biotransformation

Phase I

• modification of the drug molecule via **oxidation, reduction, or hydrolysis.**

• P450s have an absolute requirement for molecular oxygen and NADPH.
•Oxidations include hydroxylations and dealkylations .



- Clinical application

What factors affect drug biotransformation?

Genetic differences—Each individual has a varying capacity to metabolize a drug through a given pathway. (For example, some individuals are slow acetylators and therefore cannot rapidly inactivate drugs such as isoniazid, procainamide, and hydralazine.)

Induction of the cytochrome P-450 system—may increase biotransformation

Inhibition of the cytochrome P-450 system—If two drugs or compounds are competing for the active site of the same enzyme, then one of the drugs will have a decreased rate of transformation.

Disease, especially of the liver

Age and gender

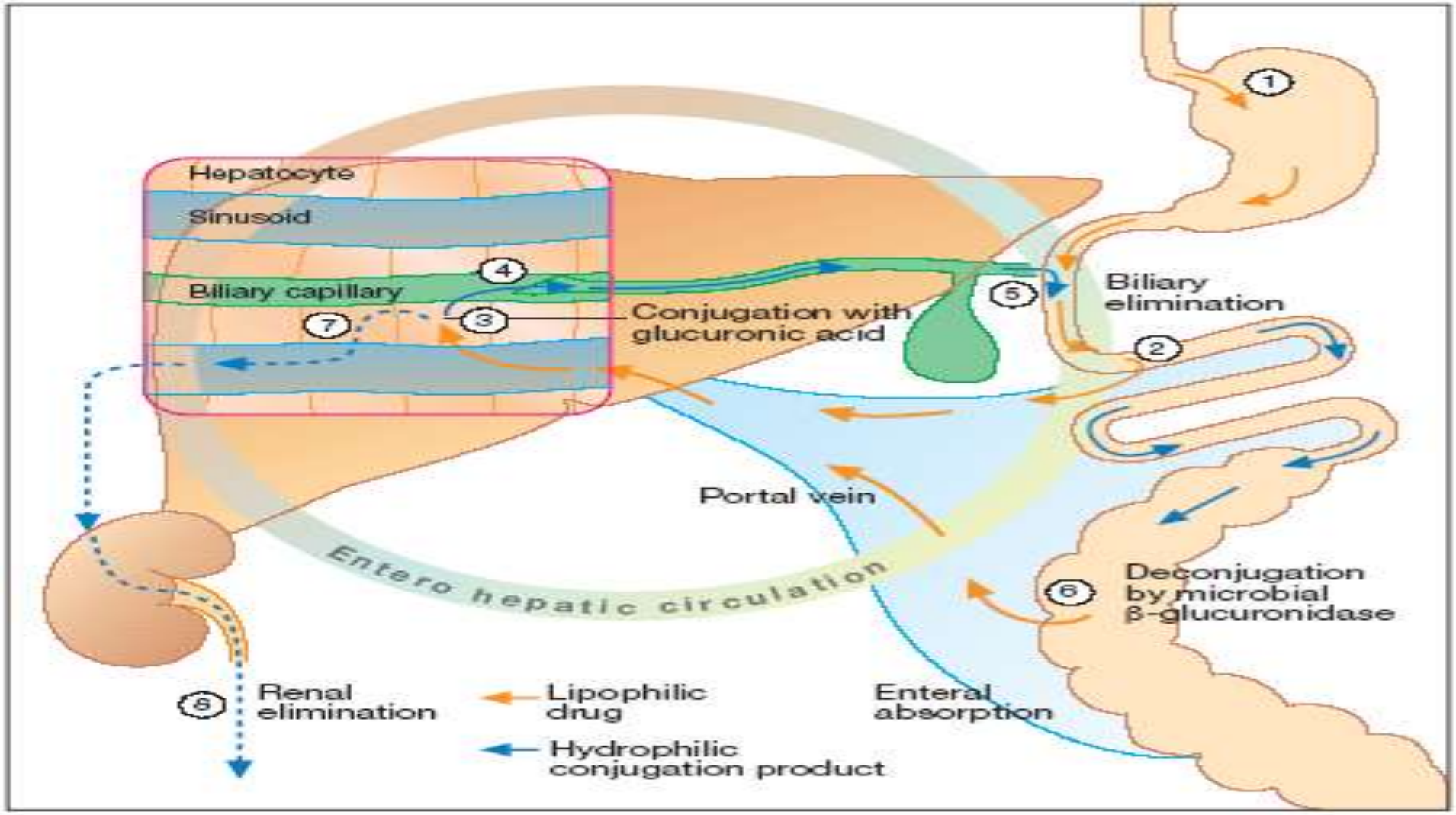

Thank you

ELIMINATION
Hepatic
Renal

ELIMINATION

processes involved in the elimination of drugs from the body (plasma or tissues) and their kinetic characteristics

Elimination Hepatic , Renal & Others



Renal and Hepatic elimination

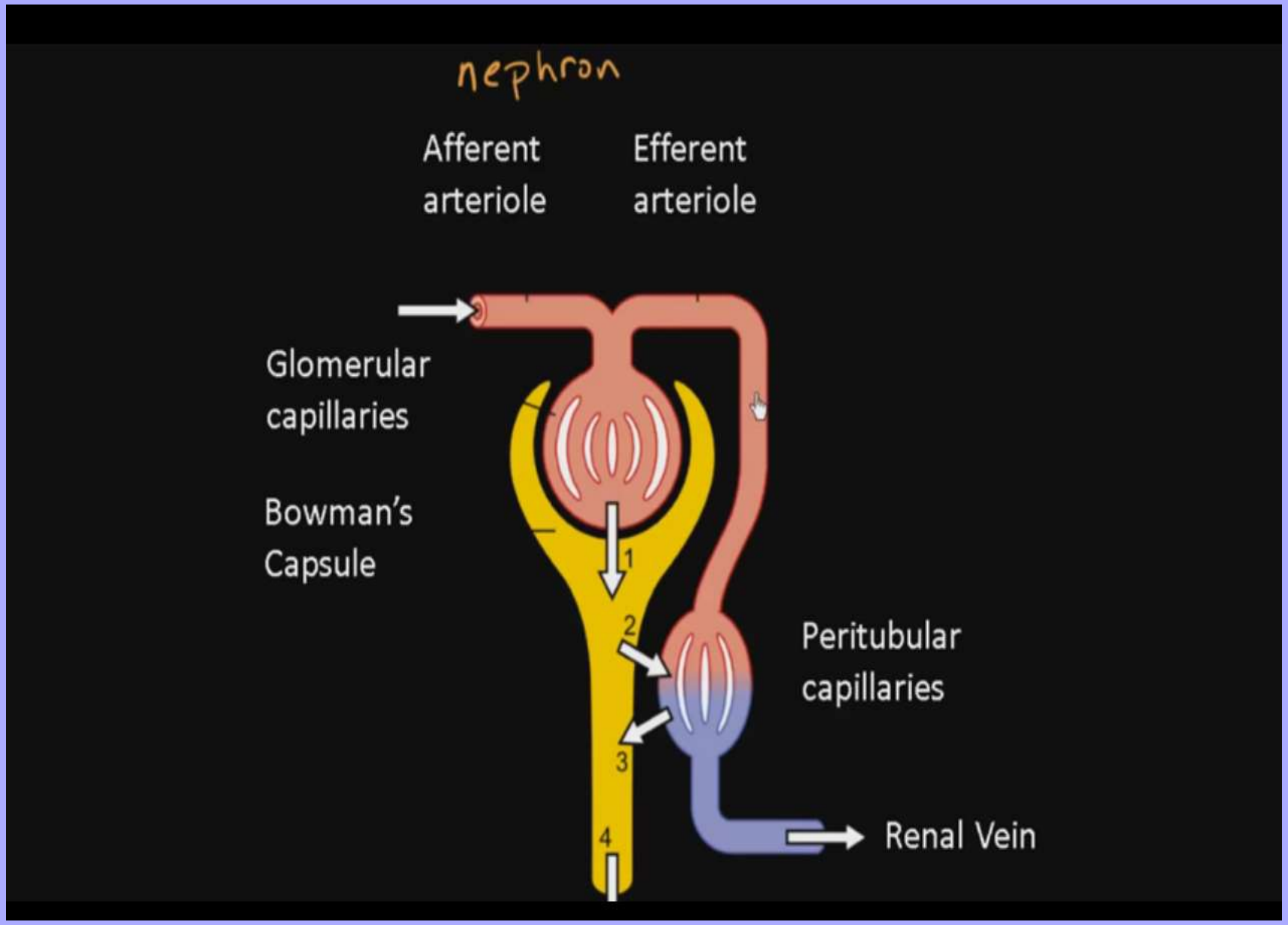
- Urination = elimination by kidney
- Defecation = hepatic elimination via bile
- Most drugs require both.
- Clinical application i.e renal failure

The major modes of drug elimination are

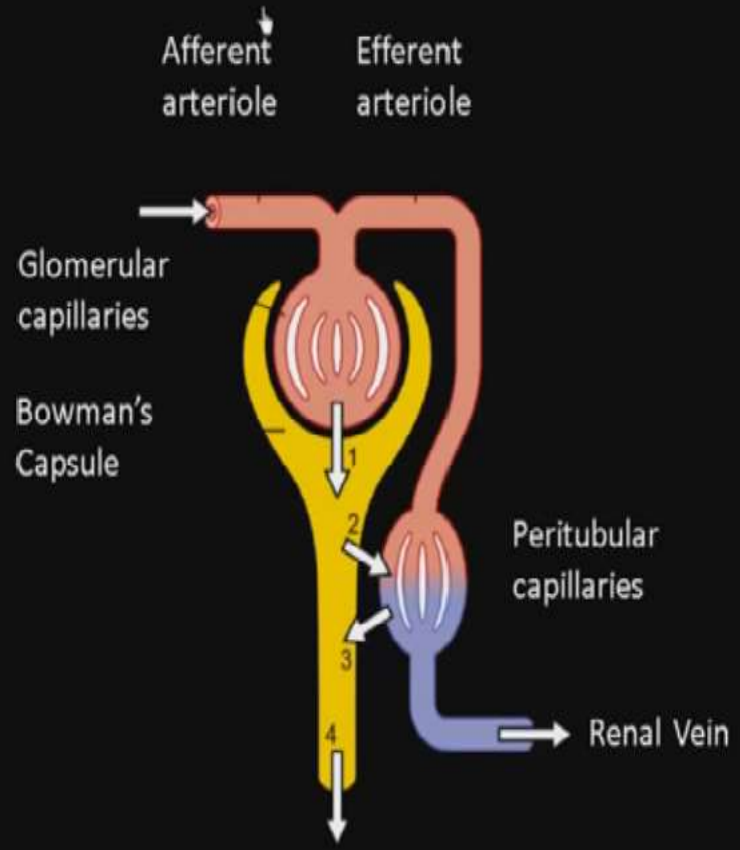
1. • **Hepatic Biotransformation** to inactive metabolites and **Biliary excretion** (if more tan 300 kd)
2. • Excretion via **the kidney** less than 300 kd
3. • Excretion via **other modes,** including
   - •Lung
   - • Sweat
   - •Plasma
   - •tissues

Renal Elimination

1. Filtration (GFR)
2. Active secretion
3. Reabsorption (active or passive).


nephron
Afferent arteriole
Efferent arteriole
Glomerular capillaries
Bowman's Capsule
1
2
3
4
Peritubular capillaries
Renal Vein

Renal Excretion = Filtration – Reabsorption + Secretion

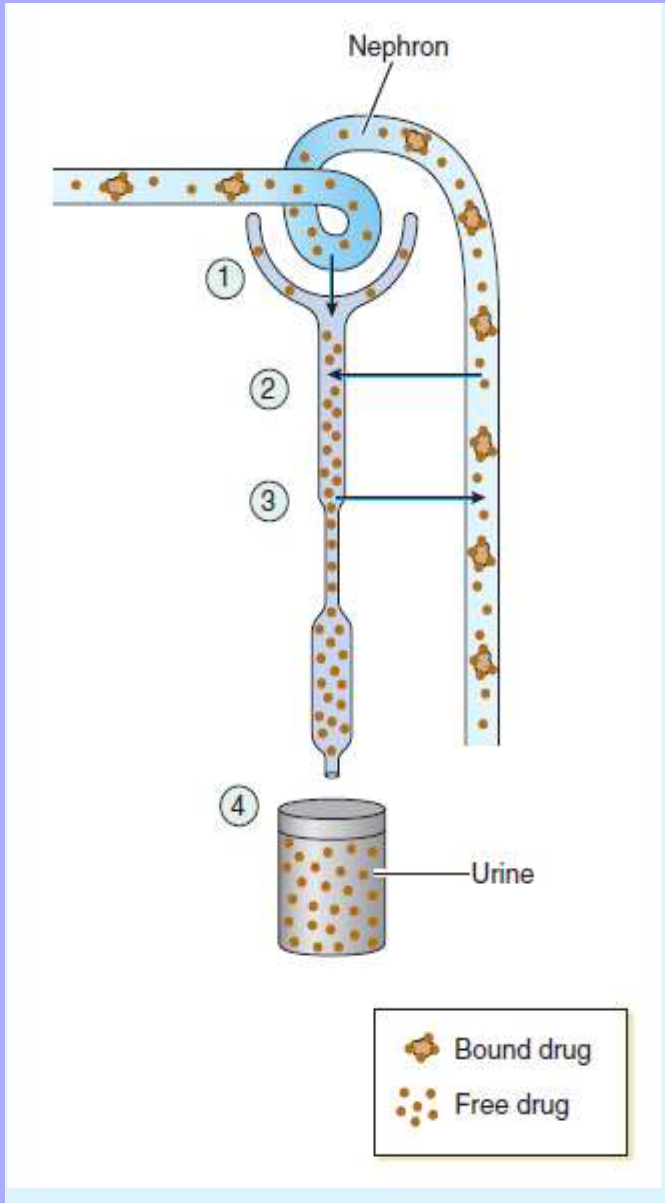


- **Only free, unbound drug is filtered .**

- Both ionized and non ionized forms of a drug are filtered.

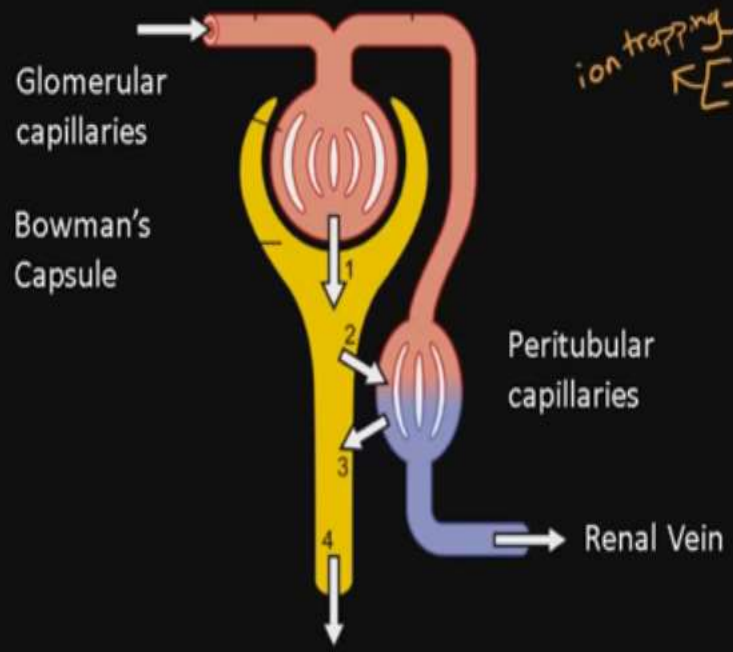
- Only non ionized forms undergo **active secretion** and **active or passive reabsorption .**

- **Ionized forms of drugs are "trapped " in the filtrate .**



Renal Excretion = Filtration – Reabsorption + Secretion

nephron



metabolized or unmetabolized

1. Filtration

"Free" drug ⇒ unbound to albumin

2. Reabsorption

ion trapping prefers lipid soluble drugs

we can Δ the pH & charge

3. Secretion

4. Excretion

• **Changes in tubular pH can affect the elimination of drugs** by altering the ratio of ionised to unionised form.

Normally the urine is slightly acidic and favours the excretion of **weakly basic drugs (e.g. amphetamine, pethidine),** while oral sodium bicarbonate will prolong their effects.

•Acidification of urine —> increases **ionization** of weak bases —> **increases renal elimination**
•(e.g. amphetamine, pethidine), so avoid alkalinazation to avoid overdose.

• Alkalinazation of urine —> increases **ionization** of weak acids —> **increases renal elimination .**
i.e helpful in Aspirin , barbiturate overdose

- In reverse manner

- Alkalinazation of urine —> increases **ionization** of weak acids —> **increases renal elimination .**
i.e helpful in Aspirin , barbiturate overdose

Elimination Kinetics

half-life (t1/2)

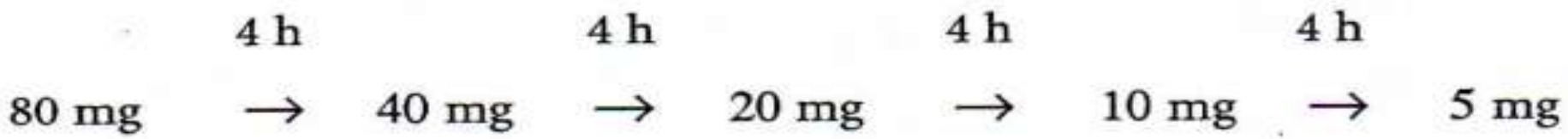
- **Time to eliminate 50% of a given amount (or to decrease plasma level to 50% of a former level)**

is called the elimination half-life (t1/2).

First-Order elimination rate

• **<u>A constant fraction</u> of the drug is eliminated per unit time**

• For example, if 80 mg of a drug is administered and its elimination half-life — 4 h, the time course of its elimination is:



First-Order elimination rate

- Rate of elimination is **directly proportional to plasma level** (or the amount present) the higher the amount , the more rapid the elimination .

- **Most drug s follow first-order elimination rates**

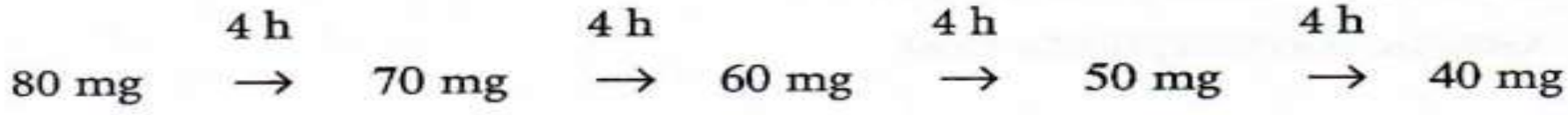
- **t1/ 2 is a constant**

Zero-Order elimination rate

- **A constant amount**

of drug is eliminated per unit time;

for example, if 80 mg is administered and 10 mg is eliminated every 4 h, the time course of drug elimination is:



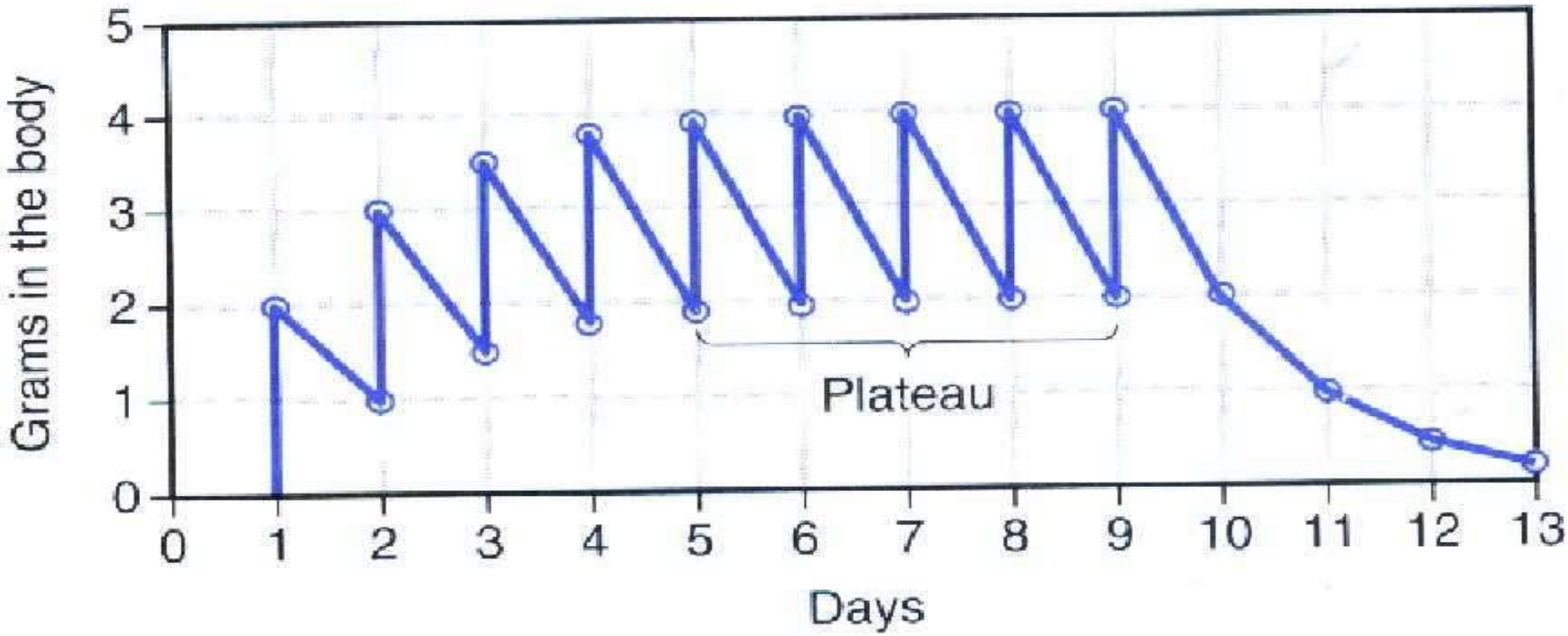
Zero-Order elimination rate

•Rate of elimination is **independent of plasma concentration** (or amount in the body).

• Drugs with zero-order elimination have no fixed half-life **(t 1/2 is a variable).**

•**<u>Drugs with zero-order elimination include</u>**

• Ethanol (except low blood levels),
• Phenytoin (high therapeutic doses)
• Salicylates (toxic doses).



Plateau Principle

The time to reach steady state is dependent only on the elimination half-life of a drug and is independent of **dose size and frequency** of administration.

Effect of Loading Dose

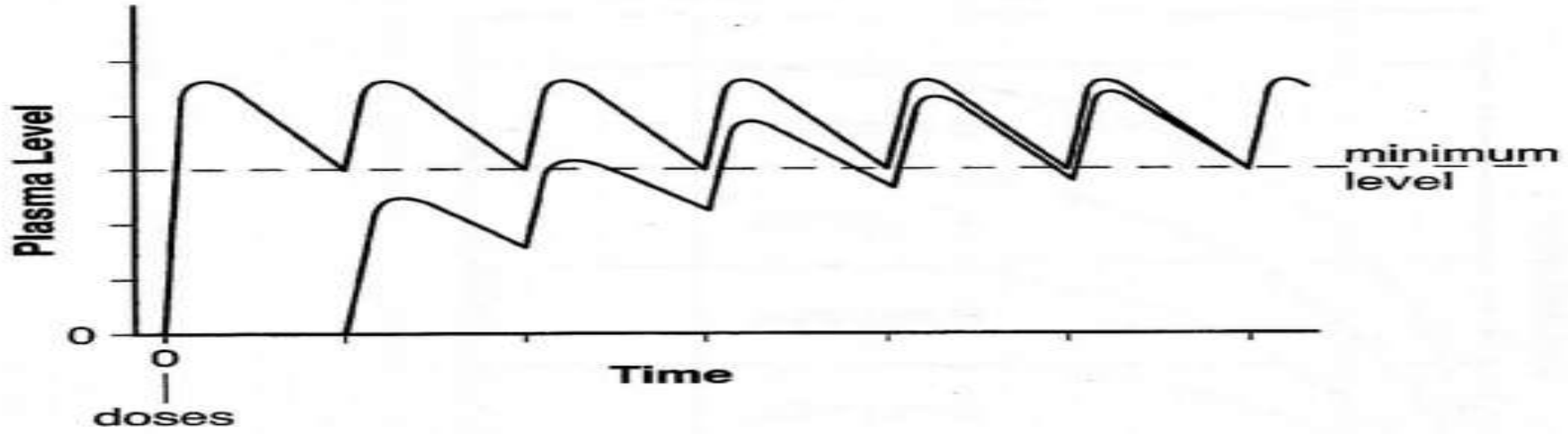


Figure I-1-13. Effect of a Loading Dose on the Time Required to Achieve the Minimal Effective Plasma Concentration

- It take s 4—5 half-lives to achieve steady state .

• I n some situations , it may be necessary to give a higher dose (loading dose) to more rapidly achieve effective blood levels (C).

•Such loading doses are often one time only and are estimated to put into the body the amount of drug that should be there at a stead y state .

Kinetic summery

The **pharmacokinetic characteristics** of a drug are dependent upon the processes of **absorption, distribution, metabolism, and excretion**

An important element concerning drug biodistribution is permeation, which is the ability to cross membranes, cellular and otherwise.

A drug's ability to permeate is dependent on its

- **solubility,**
- **the concentration gradient**
- **available surface area**
- **degree of vascularity**

Ionization affects permeation

because unionized molecules are minimally water soluble but do cross biomembranes, a feat beyond the capacity of ionized molecules.

Absorption

concerns the processes of entry into the systemic circulation. Except for the intravascular route, some absorptive process is always involved. These have the same determinants as those of permeation. Because absorption may not be 100% efficient, less than the entire dose administered may get into the circulation.

the first-pass effect

Any **orally** administered **hydrophilic drug** will be absorbed first into the **portal vein and sent directly to the liver**, where it **may be partially deactivated**..

The distribution of a drug into the various compartments of the body is dependent upon its permeation properties and its tendency to bind to plasma proteins.

The placental and blood-brain barriers are of particular importance in considering distribution.

The Vd

is a kinetic parameter that correlates the dose given to the plasma level obtained:

the greater the Vd value, the less the plasma concentration.

- **As well as having the ability to cross the blood-brain barrier, lipophilic drugs have a tendency to be deposited in fat tissue.**
- **As blood concentrations fall, some of this stored drug is released. This is called redistribution.**

Because with each administration more lipophilic drug is absorbed into the fat, the duration of action of such a drug increases with the number of doses until the lipid stores are saturated.

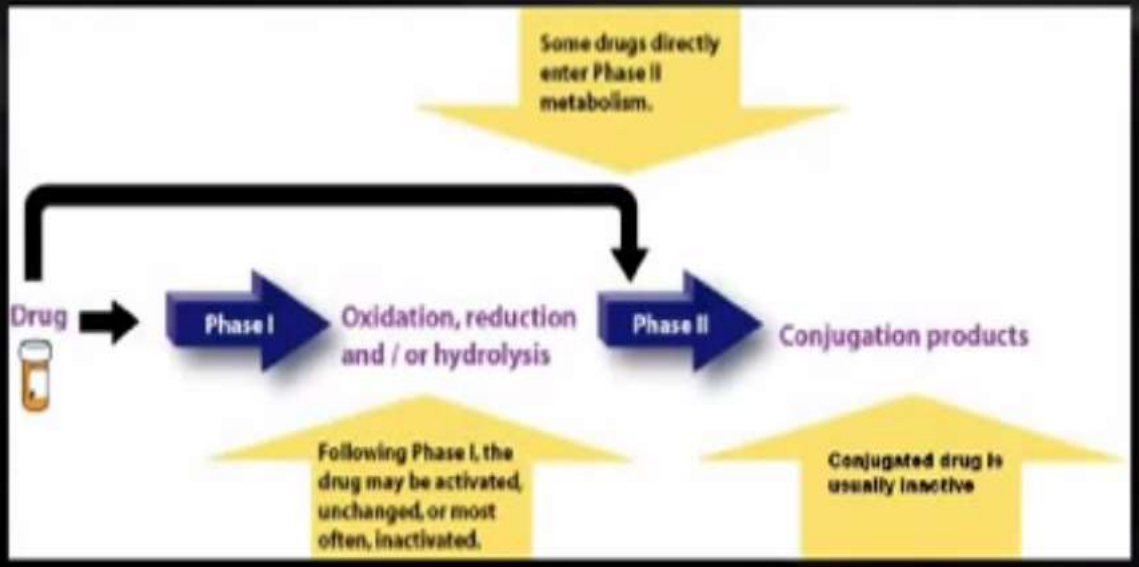
Biotransformation

is the metabolic conversion of drugs, generally to less active compounds but sometimes to isoactive or more active forms.

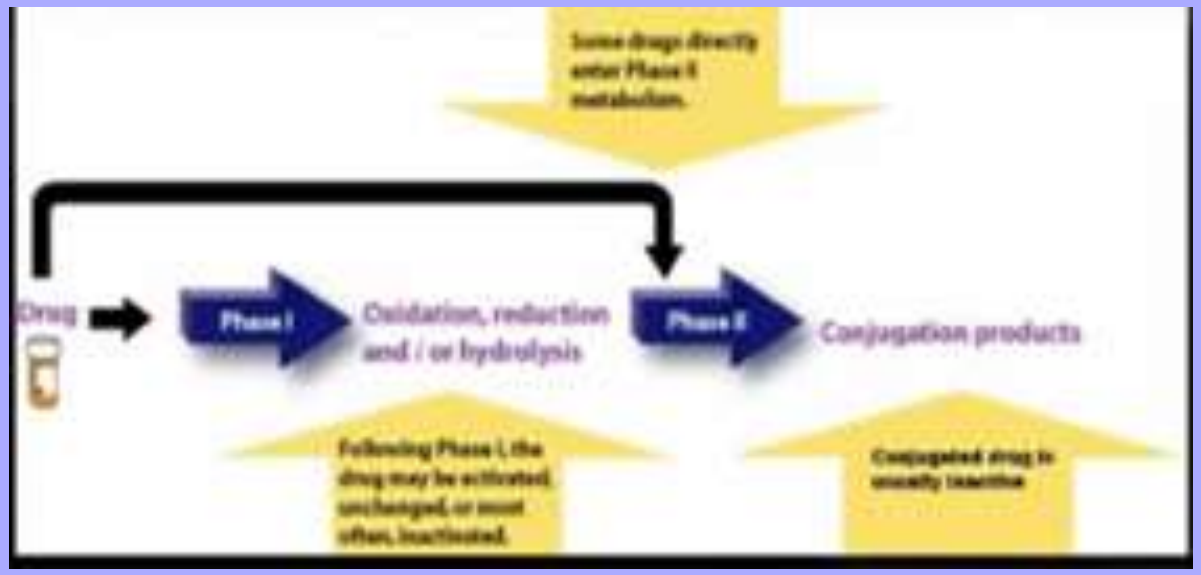
Phase I biotransformation occurs via oxidation, reduction, or hydrolysis.

Phase II metabolism occurs via conjugation.

Biotransformation



Drugs may go through phase I only, phase II only, both phase I and II, or not be metabolized at all.



The cytochrome P-450 isozymes

are a family of microsomal enzymes that collectively have the capacity to transform thousands of different molecules.

CYP Enzyme Family

Extremely elaborate family of different enzymes.

Major human enzymes include CYP2D6, CYP3A4, and CYP2C9.

CYP3A4 is involved in the metabolism of steroids, vitamins, and over 50% of prescribed drugs.

CYP2D6 is involved in the metabolism of 25% of prescribed drugs and shows significant genetic variation between individuals.

CYP3A4

"Workhorse" of the CYPs – very broad in terms of drugs and other compounds it can metabolize

- Steroids (estradiol, testosterone)
- Vitamin D
- Immunosuppressants (cyclosporine, tacrolimus)
- HIV protease inhibitors
- Calcium channel blockers
- Statins

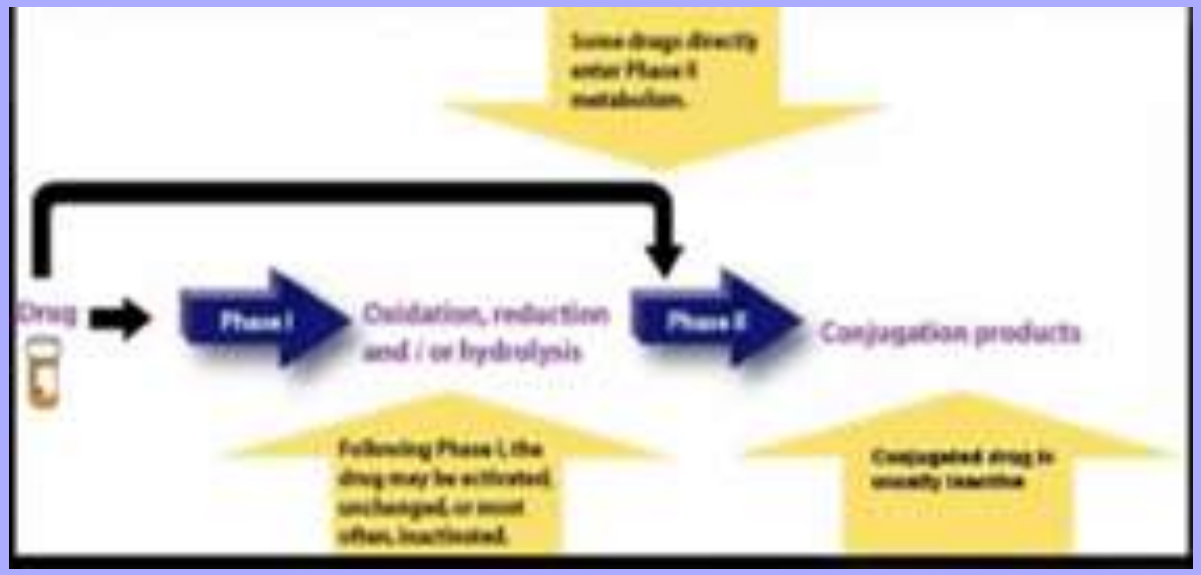
CYP2D6

Metabolizes 25% of prescribed drugs

- Tricyclic antidepressants: amitriptyline, imipramine
- Typical antipsychotics: haloperidol, chlorpromazine
- Beta-blockers: metoprolol, propranolol
- Opiates: converts codeine to morphine

Shows genetic variation

- Approx. 5% of population "poor" metabolizers (little or no CYP2D6 activity)
  - Can get toxic on typical doses of TCAs, β-blockers, etc.
  - Or for codeine, get no pain relief because not converted to morphine



- **Phase II reactions involve conjugation, sometimes after a phase I hydroxylation.**
- **The conjugation may be glucuronidation, acetylation, sulfation, or addition of glutathione.**

Modes of drug elimination

biotransformation and biliary excretion , renal excretion, and excretion by other routes (e.g. sweat, lungs, etc.).

Most drugs follow first-order elimination rates (renal clearance is only first order).

- **Renal clearance (CLR)**

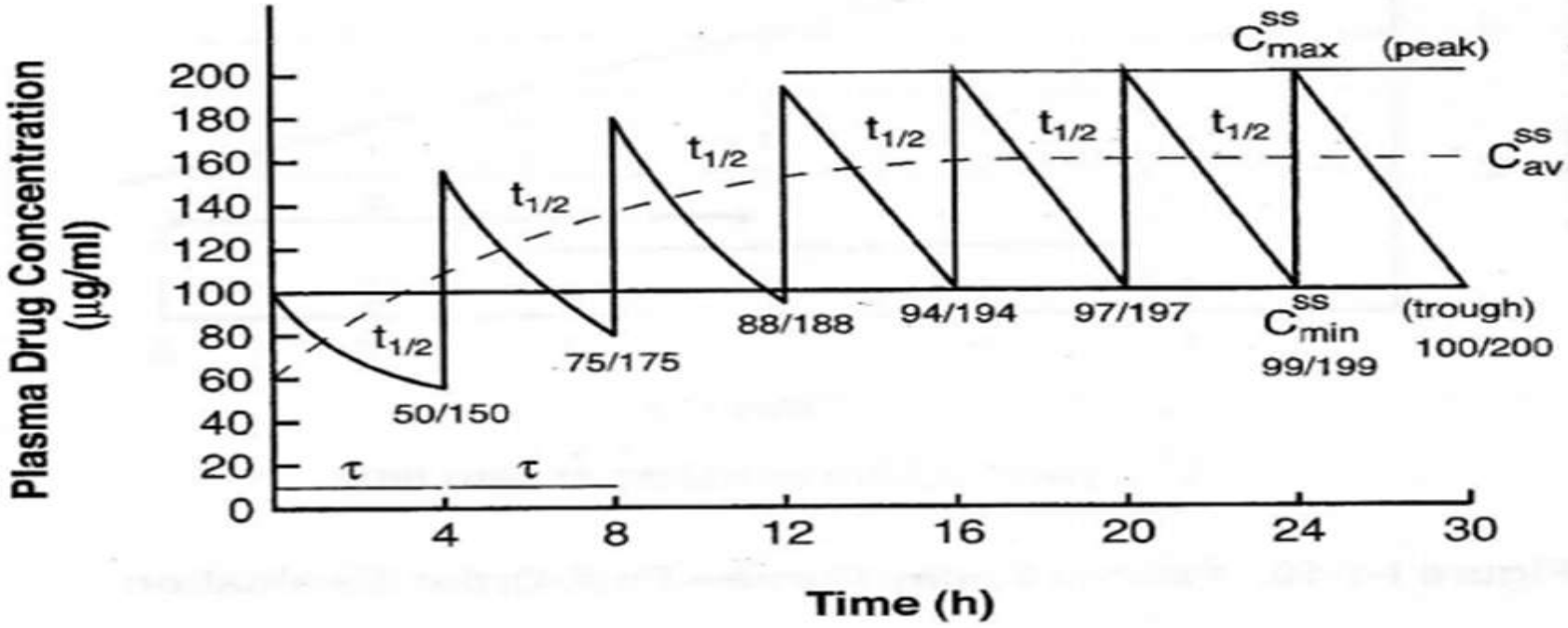
represents **the volume of blood cleared by the kidney per unit time** and is a constant for drugs with first-order elimination kinetics.

Total body clearance =
Renal + Non renal clearance.

Renal Elimination
GFR
Creatinine clearance

Cl = GFR when there is no reabsorption or secretion and no plasma protein binding

- Protein-bound drug is not cleared;
Cl = free fraction x GFR



A steady state is achieved when the rate coming in equals the rate going out.

The time to reach a steady state is dependent only on the elimination half-life.

It is independent of

- **dose and**
- **frequency of administration or**
- **rate of infusion**

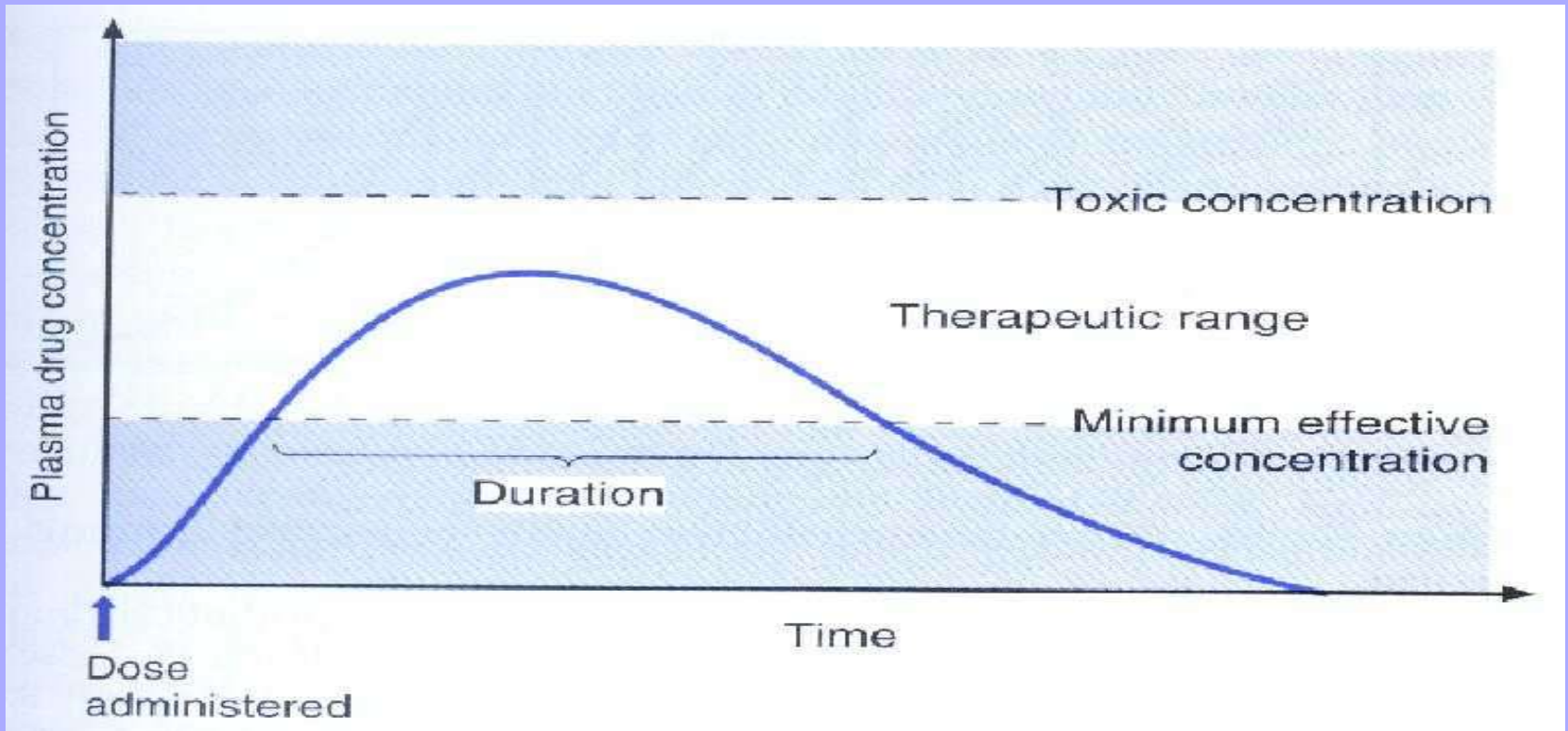


Figure 5–13. Single-dose time course.

- **The clinician usually wants to maintain steady-state concentrations of a drug and a minimum of toxicity.**
- **Clearance is the measure of the ability of the body to eliminate the drug.**

- Pharmacokinetics determine **how rapidly and for how long the drug will appear at the target organ.**
- Pharmacokinetics:

dose-concentration


Thank you