Basic Pharmacology
Pharmacokinetics

- *Pharmacokinetics (PK, ADME):*
  What the body does to drugs ?

A: absortption
D: distribution
M: metabolism
E: excretion

Ionization of Drugs

acidic drug

$$HA \rightleftharpoons A^- + H^+$$

$$K_a = \frac{[A^-]\,[H^+]}{[HA]} \qquad (1)$$

basic drug

$$BH^+ \rightleftharpoons B + H^+$$

$$K_a = \frac{[B]\,[H^+]}{[BH^+]} \qquad (2)$$

$$-\log K_a = -\log[H^+] - \log \frac{[A^-]}{[HA]} \qquad (3)$$

$$-\log K_a = -\log[H^+] - \log \frac{[B]}{[BH^+]} \qquad (4)$$

acidic drug

$$pH = pK_a + \log \frac{[A^-]}{[HA]} \quad (5)$$

basic drug

$$pH = pK_a + \log \frac{[B]}{[BH^+]} \quad (6)$$

$$pH - pK_a = \log \frac{[A^-]}{[HA]}$$

$$HA \rightleftharpoons A^- + H^+$$

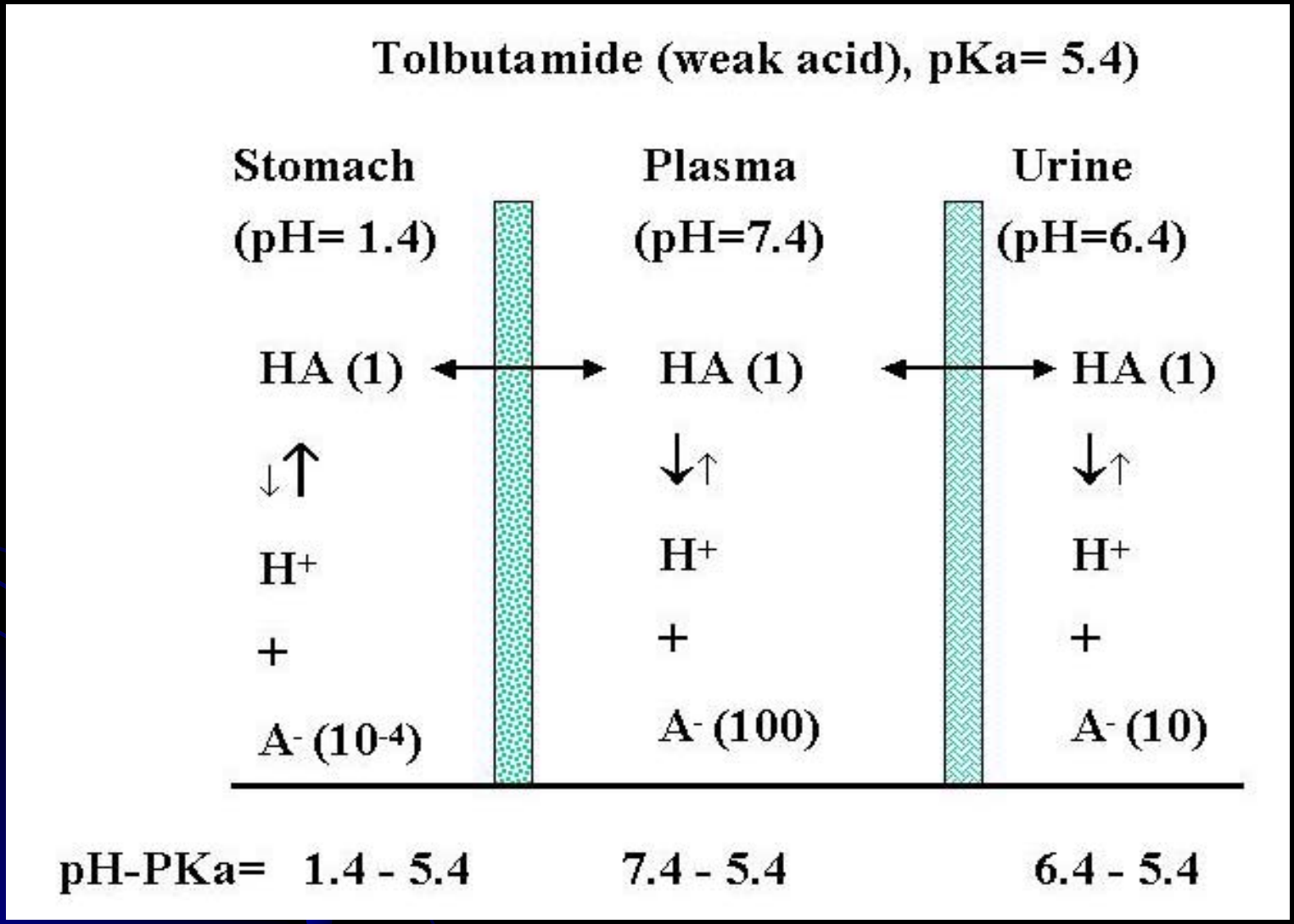
$$pH - pK_a = \log \frac{[B]}{[BH^+]}$$

$$BH^+ \rightleftharpoons B + H^+$$

pH of body fluids

Fluids	pH
Gastric juice	1.0-3.0
Small intestine: duodenum	5.0-6.0
Small intestine: ileum	8
Large intestine	8
Plasma	7.4
Cerebrospinal fluid	7.3
Urine	4.0-8.0

Effects of pH and pKa on the ionization and distribution of drug



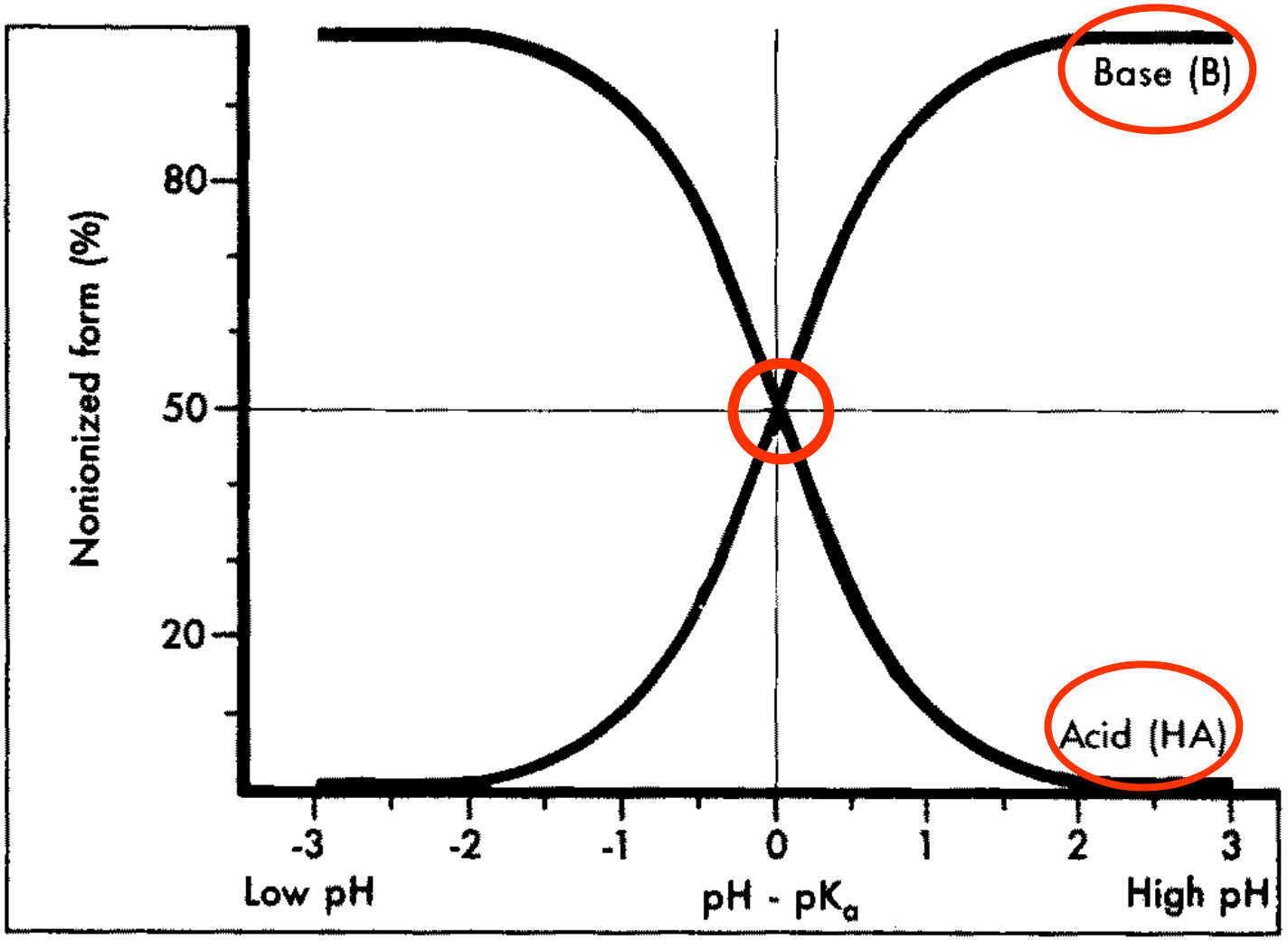


FIGURE 4-2 Degree of acidic or basic drug in nonionized (uncharged) form (*HA*, acid; *B*, base) at different pH values, with pH expressed relative to the drug pK_a.

AUC (area under the curve)

$$\text{Clearance} = \frac{\text{dose}}{\text{AUC}} = \frac{\text{mg}}{\text{mg/L x h}} \qquad \text{IV dose}$$

$$\text{Clearance} = \frac{\text{F x dose}}{\text{AUC}} \qquad \text{oral dose}$$

F: bioavailability (=1 for IV)

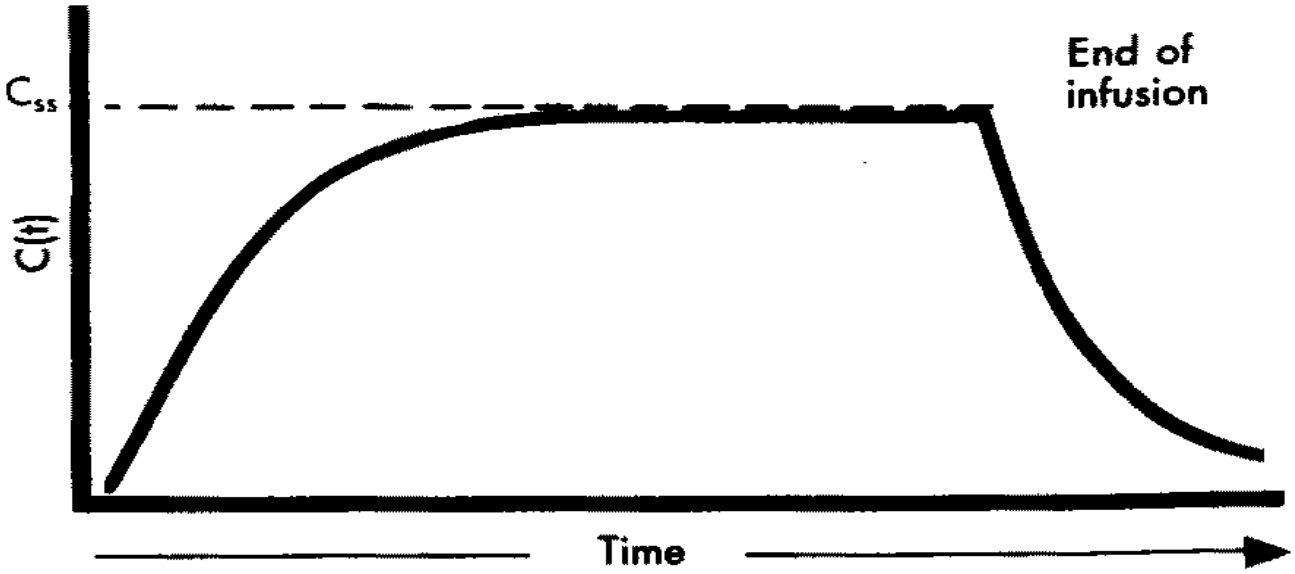


FIGURE 5-10 Typical profile showing variation of drug plasma concentration with time for continuous IV injection at a constant rate and without a loading dose. C_{ss} is the concentration at plateau, or steady state, where rate of drug input equals rate of drug disappearance. At termination of infusion, decay in the concentration will be the same as for any acute IV injection with C_o being equal to C_{ss}.

Table 3–2. Physical volumes (in L/kg body weight) of some body compartments into which drugs may be distributed.

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.

[1]An average figure. Total body water in a young lean man might be 0.7 L/kg; in an obese woman, 0.5 L/kg.

Compartments and volumes of body fluid:

- ***Major compartments:***

  Plasma 3 L

  Extracellular 14 L

  Total body water 45 L

- *Volume of distribution* (Vd)

  $Vd = T / C$

  T : amount of drug in the body

  C: concentration of drug in blood

e.g.: Warfarin

5 – 10 L

Chloroquine

15,000 – 40,000 L

Pharmacokinetic parameters

- *Cmax : (μg/ml, μM)*
- *Tmax: (min, hr)*

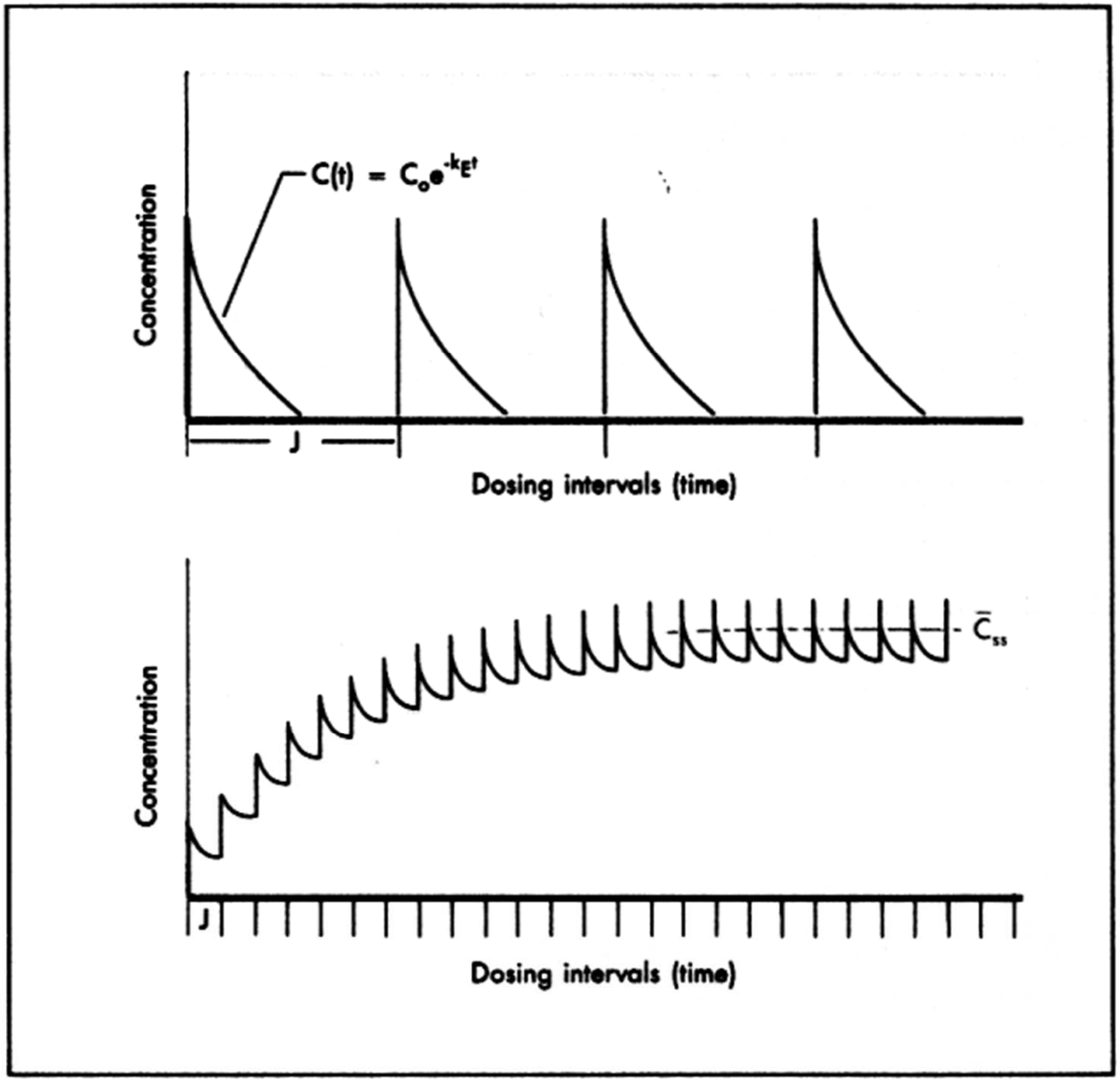
- Half-life ($t_{1/2}$)

  $T_{1/2}$ = 0.693 Vd / Cl

  (Cl, Clearance; Vd, volume of distribution)

  - AUC (area under the curve)

i.v.


C(t) = C$_o$e$^{-k_E t}$
Concentration
τ
Dosing intervals (time)
A
$\bar{C}_{ss}$
Concentration
τ
Dosing intervals (time)
B

Absorption, Distribution and Elimination

1. Absorption

- **First-pass effect (clonazepam, chlorpromazine, penicillin, polypeptides)**
- **Routes of administration (later)**

2. Distribution

- Lipid solubility
- **Redistribution** (thiopental)
- Blood flow
- Protein binding (acidic drug mainly to albumin; basic drug mainly to α1 acid glycoprotein), SSBG, TBG
- Barriers (BBB, placenta barrier)

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Chloroquine and quinacrine

15,000 – 40,000 L

A. Liver clearance: metabolism

- Hepatic blood flow **(Q)**: 90 L/h (70Kg)
- **First pass-effect:**

  Extraction ratio (E) = $C_{in} - C_{out} / C_{in}$

  (CL_{liver}/Q)

- GI

B. Systemic clearance:

1. **Renal**
2. **Lung**
3. **Breast milk**
4. **Sweat, saliva, tear, exsquamation**

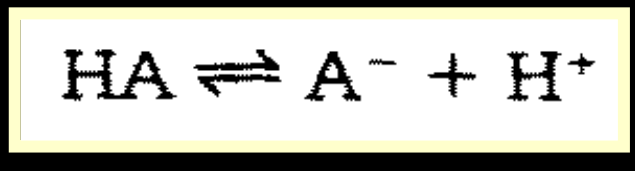
Renal clearance

- Glomerular filtration : GFR= 2 ml/kg/min, 125 ml/min, molecules smaller than 1.5 **nm** readily pass through
- Tubular secretion : active transport; remove bound and free drug
- Tubular reabsorption : mainly passive diffusion

Clr: clearance (volume of plasma cleared of drug per unit time; ml/min in unit)

$$Clr = \frac{\text{Rate of drug removal by the kidney (mg/min)}}{\text{Concentration of drug in the renal artery (mg/ml)}}$$

Effects pf urine pH : can be adjusted by $NaHCO_3$, or NH_4Cl



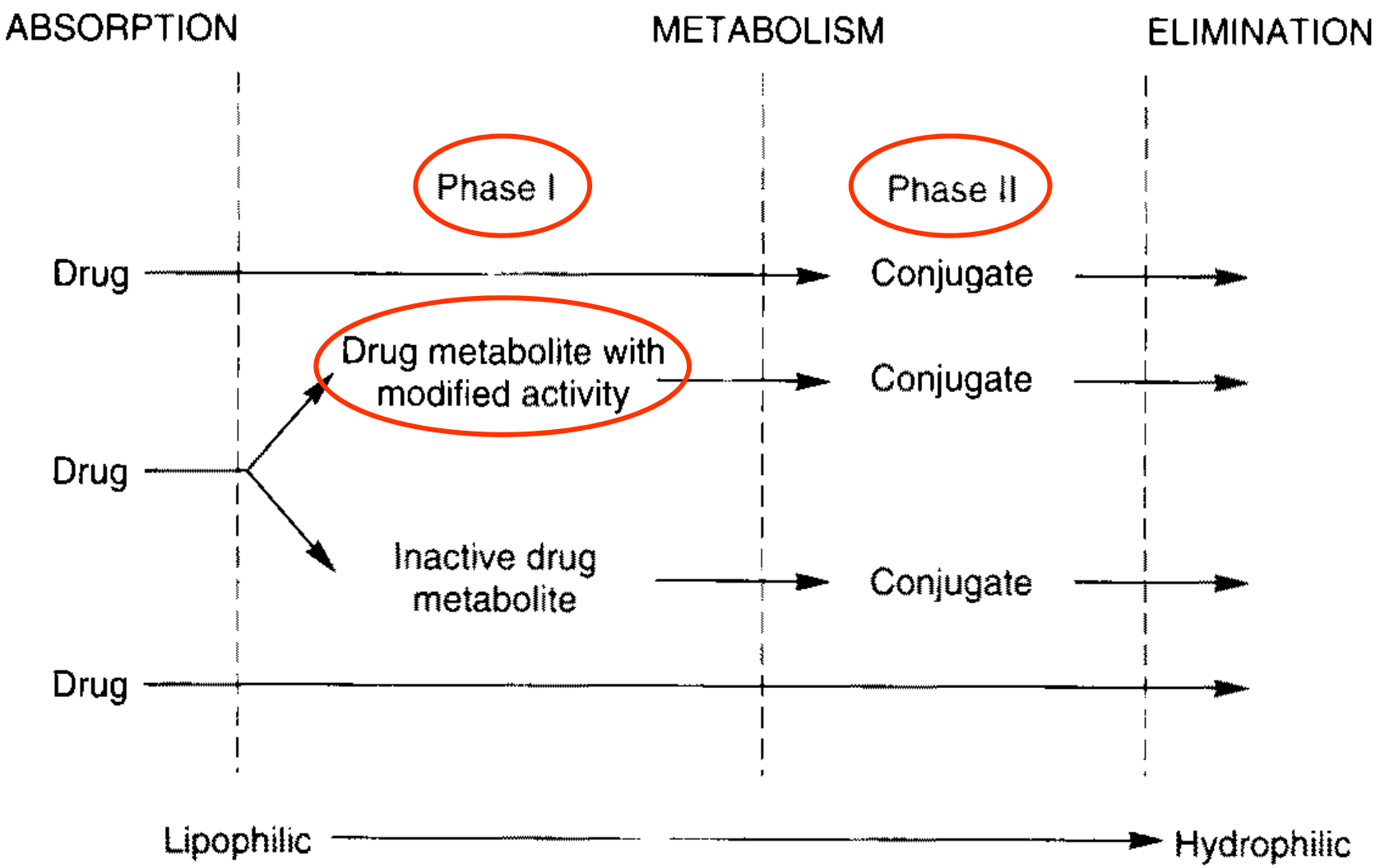
Bases	Acids
CLEARED RAPIDLY BY MAKING URINE MORE ACIDIC	**CLEARED RAPIDLY BY MAKING URINE MORE ALKALINE**
Amphetamine	Acetazolamide
Chloroquine	Nitrofurantoin
Imipramine	Phenobarbital
Levophanol	Probenecid
Mecamylamine	Salicylates
Quinine	Sulfathiazole

1. Modes of drug metabolism in liver

Phase 1 ***: oxidation, reduction, hydrolysis*** **→ increased polarity, easy excretion in the urine**

- **Aspirin (acetylsalicylate) → salicylic acid**

Phase 2 ***: conjugation*** **→ usually increases water solubility after conjugation with glucuronic acid, sulfate, glutathione; but decreases water solubility after acetylation**


ABSORPTION
METABOLISM
ELIMINATION
Phase I
Phase II
Drug
Conjugate
Drug metabolite with modified activity
Conjugate
Drug
Inactive drug metabolite
Conjugate
Drug
Lipophilic
Hydrophilic

1. Modes of drug metabolism in liver

- **Drug-metabolizing enzymes: lipophilic membranes of the endoplasmic reticulum of liver and other tissues。**
- **Microsomes: above lamellar membranes are isolated by homogenation and fractionation of the cells, and the re-form into vesicles which contain rough and smooth surface endoplasmic reticulum。**
- **Liver microsomal enzymes**

Microsomal enzymes

- microsomal enzymes, NADPH, O_2
  1. NADPH-dependent cytochrome P450 reductase (flavoprotein)
  2. Cytochrome P450 (hemoprotein):
     1. 1A**2** (12%)
     2. 2A6 (4%)
     3. 2C9 (20%)
     4. 2D6 (4%)
     5. 2E1 (6%)
     6. 3A4 (28%) **(60% of the prescribed drugs)**

Table 4–2. Human liver P450s (CYPs), and some of the drugs metabolized (substrates), inducers, and drugs used for screening (noninvasive markers).

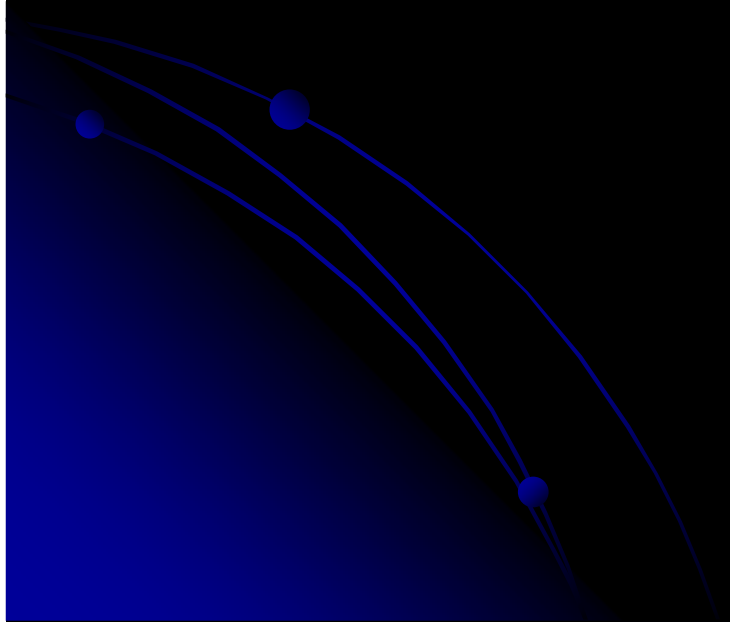
CYP	Substrates	Inducers	Noninvasive Markers
1A2	Acetaminophen, antipyrine, caffeine, clomipramine, phenacetin, tamoxifen, theophylline, warfarin	Smoking charcoal-broiled foods, cruciferous vegetables, omeprazole	Caffeine
2A6	Coumarin		Coumarin
2C9	Hexobarbital, ibuprofen, phenytoin, tolbutamide, trimethadione, sulfaphenazole, *S*-warfarin, ticrynafen	Barbiturates, rifampin	Tolbutamide, warfarin
2C19	Diazepam, *S*-mephenytoin, naproxen, nirvanol, omeprazole, propranolol	Barbiturates, rifampin	*S*-mephenytoin
2D6	Bufuralol, bupranolol, clomipramine, clozapine, codeine, debrisoquin, dextromethorphan, encainide, flecainide, fluoxetine, guanoxan, haloperidol, hydrocodone, 4-methoxy-amphetamine, metoprolol, mexiletine, oxycodone, paroxetine, phenformin, propafenone, propoxyphene, risperidone, selegilene (deprenyl), sparteine, thioridazine, timolol, tricyclic antidepressants	None known	Debrisoquin, dextromethorphan
2E1	Acetaminophen, chlorzoxazone, enflurane, halothane, ethanol (a minor pathway)	Ethanol, isoniazid	Chlorzoxazone
3A4	Acetaminophen, alfentanil, amiodarone, astemizole, cocaine, cortisol, cyclosporine, dapsone, diazepam, dihydroergot-amine, dihydropyridines, diltiazem, ethinyl estradiol, gestodene, indinavir, lidocaine, lovastatin, macrolides, methadone, miconazole, midazolam, mifepristone (RU 486), paclitaxel, progesterone, quinidine, rapamycin, ritonavir, saquinavir, spironolactone, sulfamethoxazole, sufentanil, tacrolimus, tamoxifen, terfenadine, testosterone, tetrahydro-cannabinol, triazolam, troleandomycin, verapamil	Barbiturates, carbamazepine, glucocorticoids, macrolide antibiotics, phenytoin, rifampin	Erythromycin, 6β-hydroxycortisol

Table 4–3. Phase II reactions.

Type of Conjugation	Endogenous Reactant	Transferase (Location)	Types of Substrates	Examples
Glucuronidation	UDP glucuronic acid	UDP glucuronosyl-transferase (microsomes)	Phenols, alcohols, carboxylic acids, hydroxylamines, sulfonamides	Nitrophenol, morphine, acetaminophen, diazepam, *N*-hydroxydapsone, sulfathiazole, meprobamate, digitoxin, digoxin
Acetylation	Acetyl-CoA	*N*-Acetyltransferase (cytosol)	Amines	Sulfonamides, isoniazid, clonazepam, dapsone, mescaline
Glutathione conjugation	Glutathione	GSH-*S*-transferase (cytosol microsomes)	Epoxides, arene oxides, nitro groups, hydroxylamines	Ethacrynic acid, bromobenzene
Glycine conjugation	Glycine	Acyl-CoA glycinetransferase (mitochondria)	Acyl-CoA derivatives of carboxylic acids	Salicylic acid, benzoic acid, nicotinic acid, cinnamic acid, cholic acid, deoxycholic acid
Sulfate conjugation	Phosphoadenosyl phosphosulfate	Sulfotransferase (cytosol)	Phenols, alcohols, aromatic amines	Estrone, aniline, phenol, 3-hydroxycoumarin, acetaminophen, methyldopa
Methylation	*S*-Adenosylmethionine	Transmethylases (cytosol)	Catecholamines, phenols, amines	Dopamine, epinephrine, pyridine, histamine, thiouracil
Water conjugation	Water	Epoxide hydrolase (microsomes)	Arene oxides, *cis*-disubstituted and monosubstituted oxiranes	Benzopyrene 7,8-epoxide, styrene 1,2-oxide, carbamazepine epoxide
		(cytosol)	Alkene oxides, fatty acid epoxides	Leukotriene A_4

Active metabolites and Prodrugs

- ***Prodrug:*** **Gabapentin, fosinopril**
- ***Toxic metabolites:*****Acetaminophen, Isoniazid**



Genetic polymorphisms of drug metabolism

Table 4–4. Some examples of genetic polymorphisms in drug metabolism.

Defect	Drug and Therapeutic Use	Clinical Consequences[1]
Oxidation	Bufuralol (β-adrenoceptor blocker)	Exacerbation of β-blockade, nausea
Oxidation	Debrisoquin (antihypertensive)	Orthostatic hypotension
Oxidation	Ethanol	Facial flushing, cardiovascular symptoms
N-Acetylation	Hydralazine (antihypertensive)	Lupus erythematosus-like syndrome
N-Acetylation	Isoniazid (antitubercular)	Peripheral neuropathy
Oxidation	Mephenytoin (antiepileptic)	Overdose toxicity
Oxidation	Sparteine	Oxytocic symptoms
Ester hydrolysis	Succinylcholine (neuromuscular blocker)	Prolonged apnea
Oxidation	Tolbutamide (hypoglycemic)	Cardiotoxicity

[1]Observed or predictable.

3. Drug interaction

- **Pharmacodynamic**
- **Pharmacokinetic**
  - **Induction of metabolic enzymes (ethanol, barbiturate, smoke)**
  - **Inhibition of metabolic enzymes (cimetidine, erythromycin, ketoconazole)**

Table 4–5. Partial list of drugs that enhance drug metabolism in humans.

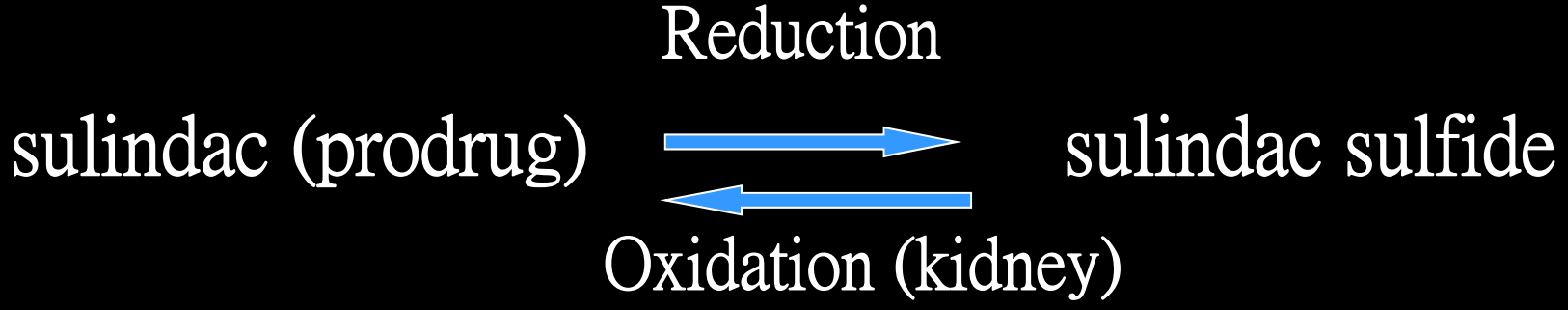
Inducer	Drug Whose Metabolism Is Enhanced
Benzo[*a*]pyrene	Theophylline
Chlorcyclizine	Steroid hormones
Ethchlorvynol	Warfarin
Glutethimide	Antipyrine, glutethimide, warfarin
Griseofulvin	Warfarin
Phenobarbital and other barbiturates[1]	Barbiturates, chloramphenicol, chlorpromazine, cortisol, coumarin anticoagulants, desmethylimipramine, digitoxin, doxorubicin, estradiol, phenylbutazone, phenytoin, quinine, testosterone
Phenylbutazone	Aminopyrine, cortisol, digitoxin
Phenytoin	Cortisol, dexamethasone, digitoxin, theophylline
Rifampin	Coumarin anticoagulants, digitoxin, glucocorticoids, methadone, metoprolol, oral contraceptives, prednisone, propranolol, quinidine

[1]Secobarbital is an exception. See Table 4–6 and text.

Table 4–6. Partial list of drugs that inhibit drug metabolism in humans.

Inhibitor	Drug Whose Metabolism Is Inhibited
Allopurinol, chloramphenicol, isoniazid	Antipyrine, dicumarol, probenecid, tolbutamide
Cimetidine	Chlordiazepoxide, diazepam, warfarin, others
Dicumarol	Phenytoin
Diethylpentenamide	Diethylpentenamide
Disulfiram	Antipyrine, ethanol, phenytoin, warfarin
Ethanol	Chlordiazepoxide (?), diazepam (?), methanol
Grapefruit juice[1]	Alprazolam, atorvastatin, cisapride, cyclosporine, midazolam, triazolam
Ketoconazole	Cyclosporine, astemizole, terfenadine
Nortriptyline	Antipyrine
Oral contraceptives	Antipyrine
Phenylbutazone	Phenytoin, tolbutamide
Secobarbital	Secobarbital
Troleandomycin	Theophylline, methylprednisolone

4. Tissue other than liver



sulindac sulfide -- active cyclooxygenase inhibitor
(for rheumatoid disease)

Factors modifying drug action

5. Body weight (Clark equation)

6. Route of administration

- **Oral (p.o., gastric, enteral)**
- **Injection (I.V., S.C., I.M., intrathecal)**
- **Rectal**
- **Sublingual**
- **Skin (topical), transdermal**
- **Inhalation**
- **Vaginal, suppository**

Table 3–3. Routes of administration, bioavailability, and general characteristics.

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

Factors modifying drug action (Pharmacokinetics)

7. Rate of excretion

- **Initial dose**
- **Maintenance dose**

e.g. digitalis, antibiotics

8. PK effects in drug interaction

a. **Plasma binding**
b. **Liver microsomal enzyme induction or inhibition**
c. **Drug absorption or excretion**