FARMAKOKINETIKA OBAT

PERJALANAN OBAT DALAM TUBUH

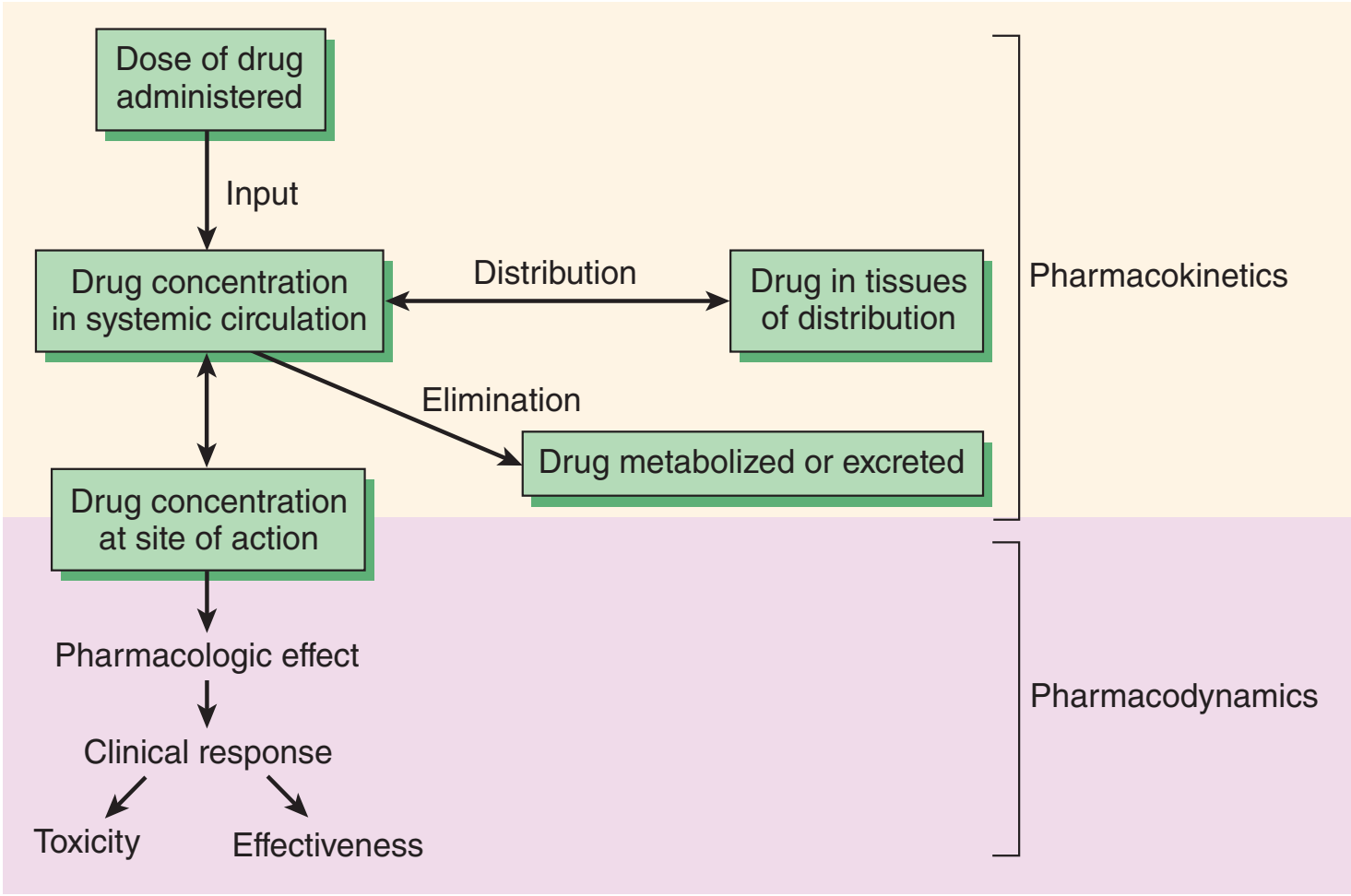


FIGURE 3–1 The relationship between dose and effect can be separated into pharmacokinetic (dose-concentration) and pharmacodynamic (concentration-effect) components. Concentration provides the link between pharmacokinetics and pharmacodynamics and is the focus of the target concentration approach to rational dosing. The three primary processes of pharmacokinetics are input, distribution, and elimination.

FARMAKOKINETIKA OBAT

ADME (Absorbsi, Distribusi, Metabolisme, Ekskresi)

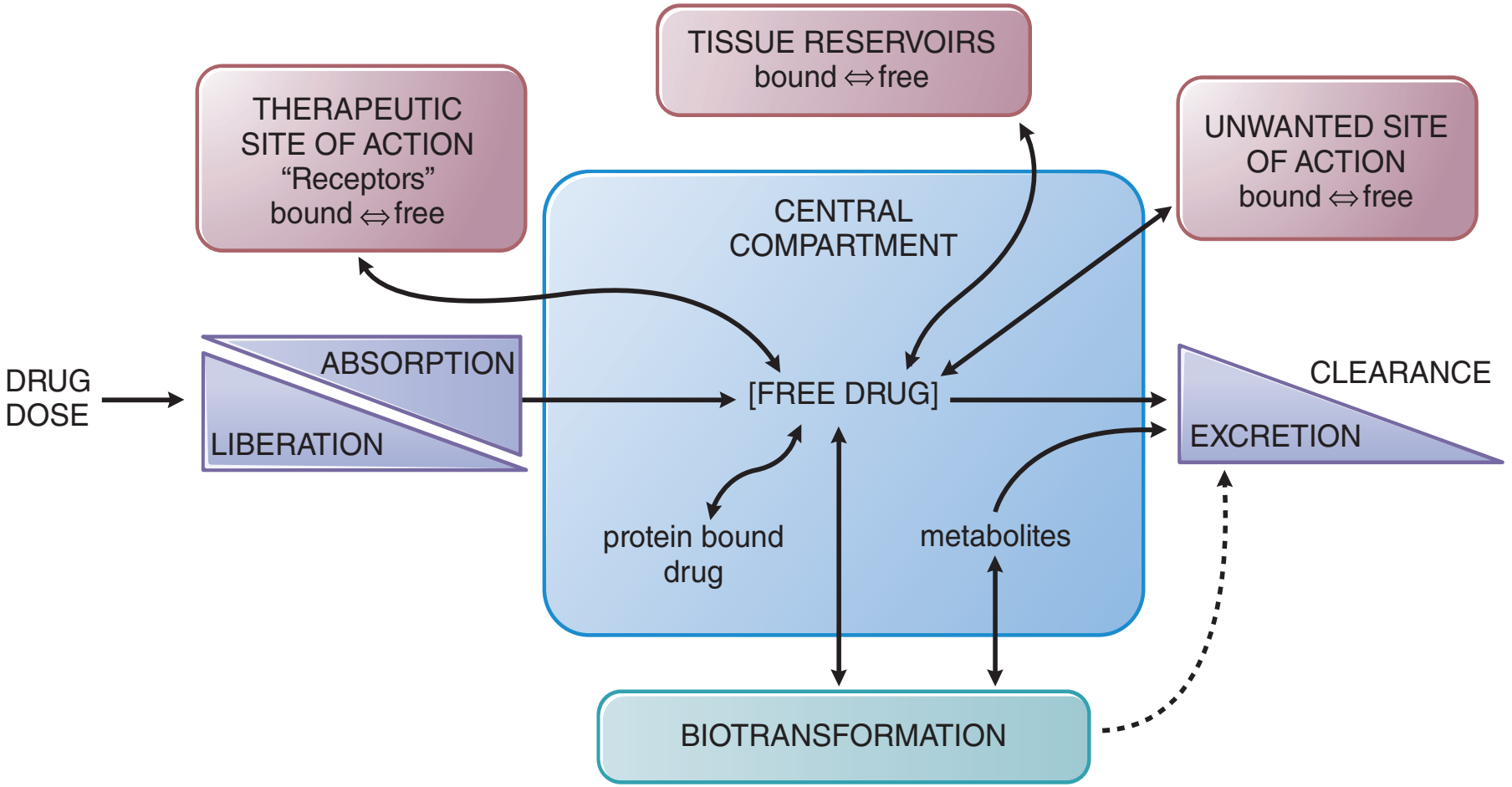


Figure 2–1 *The interrelationship of the absorption, distribution, binding, metabolism, and excretion of a drug and its concentration at its sites of action.* Possible distribution and binding of metabolites in relation to their potential actions at receptors are not depicted.

ABSORPSI & DISTRIBUSI

MEKANISME OBAT MASUK KE DALAM SEL (PADA PROSES ABSORPSI DAN DISTRIBUSI OBAT DI DALAM TUBUH/SEL

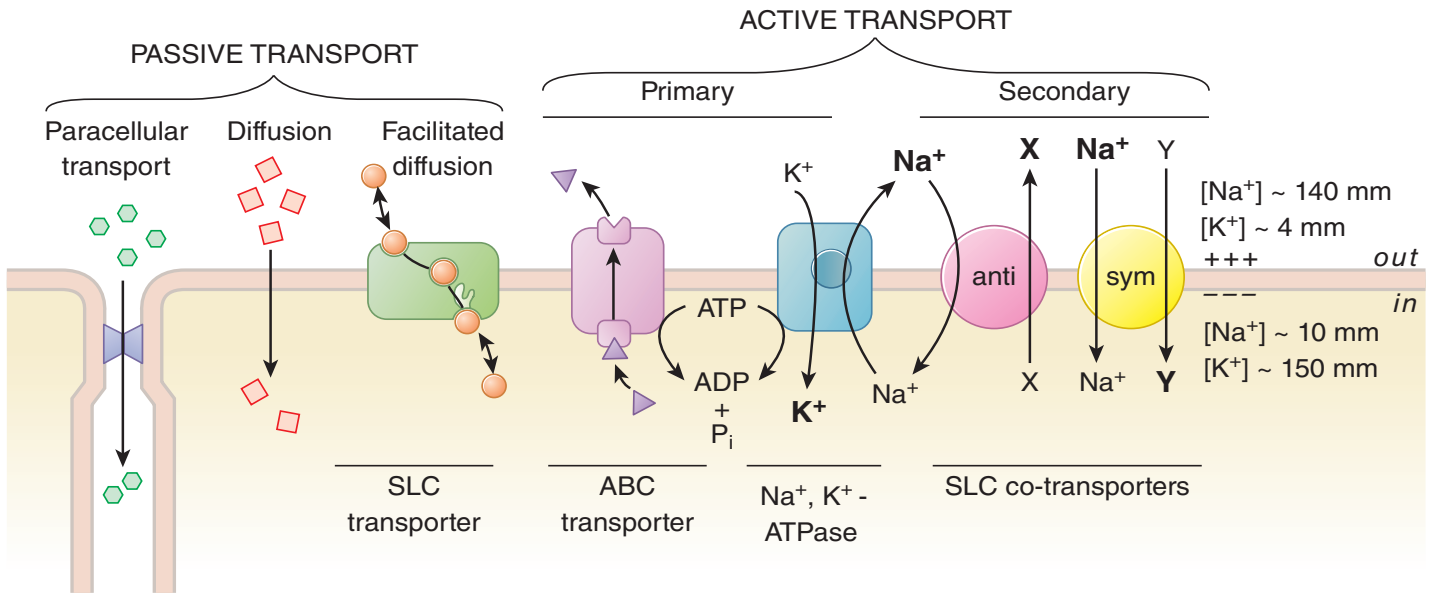


Figure 2–2 *Drugs move across membrane and cellular barriers in a variety of ways.* See details in Figures 5–1 through 5–5.

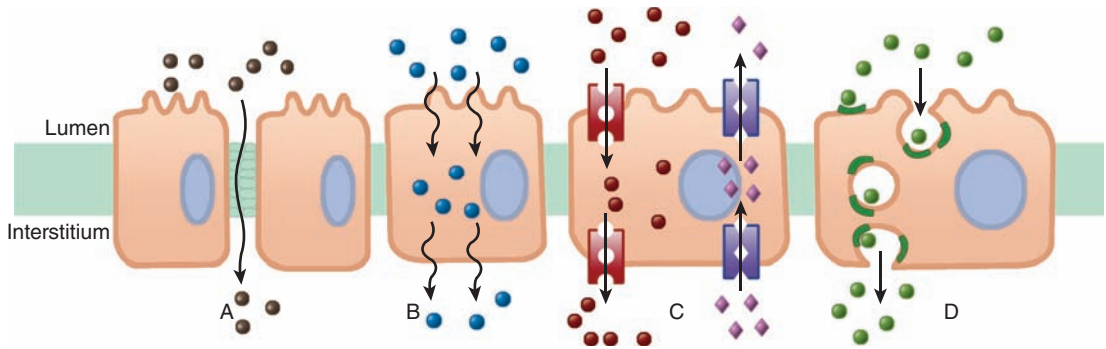


FIGURE 1–4 Mechanisms of drug permeation. Drugs may diffuse passively through aqueous channels in the intercellular junctions (eg, tight junctions, **A**), or through lipid cell membranes (**B**). Drugs with the appropriate characteristics may be transported by carriers into or out of cells (**C**). Very impermeant drugs may also bind to cell surface receptors (dark binding sites), be engulfed by the cell membrane (endocytosis), and then released inside the cell or expelled via the membrane-limited vesicles out of the cell into the extracellular space (exocytosis, **D**).

ABSORPSI

FAKTOR YG MEMPENGARUHI ABSORPSI OBAT SECARA DIFUSI

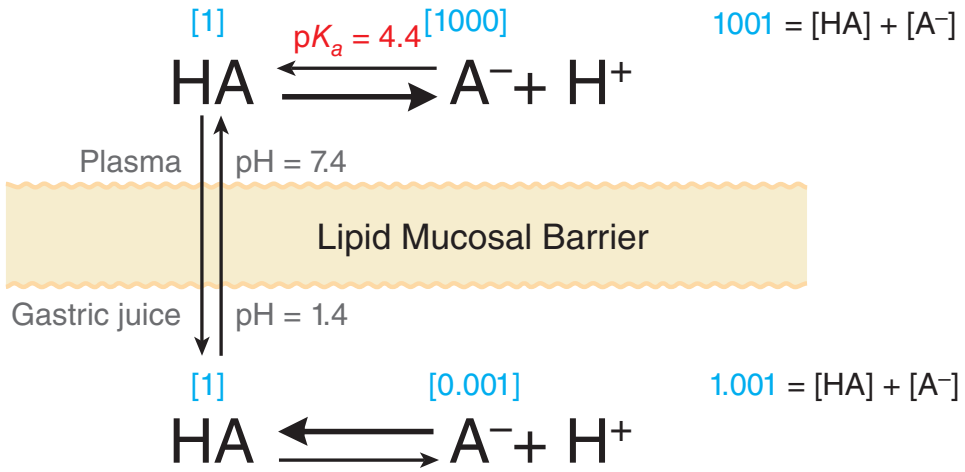


Figure 2–3 *Influence of pH on the distribution of a weak acid* (pK_a = 4.4) *between plasma and gastric juice separated by a lipid barrier.* **A weak acid dissociates to different extents** in plasma (pH 7.4) and gastric acid (pH 1.4): The higher pH facilitates dissociation; the lower pH reduces dissociation. The uncharged form, HA, equilibrates across the membrane. Blue numbers in brackets show relative equilibrium concentrations of HA and A^-, as calculated from Equation 2–1.

B. Fick's Law of Diffusion

The passive flux of molecules down a concentration gradient is given by Fick's law:

$$\text{Flux (molecules per unit time)} = (C_1 - C_2) \times \frac{\text{Area} \times \text{Permeability coefficient}}{\text{Thickness}}$$

Obat yg bersifat asam akan mudah diabsorpsi pada kondisi asam dilambung. Namun luas area difusi lambung lebih kecil dibandingkan usus, sehingga absorpsi obat lebih baik di usus. Pengosongan lambung mempercepat proses absorpsi obat.

METABOLISME

absorbed intact from the small intestine and transported first via the portal system to the liver, where they undergo extensive metabolism. This process is called the **first-pass effect**

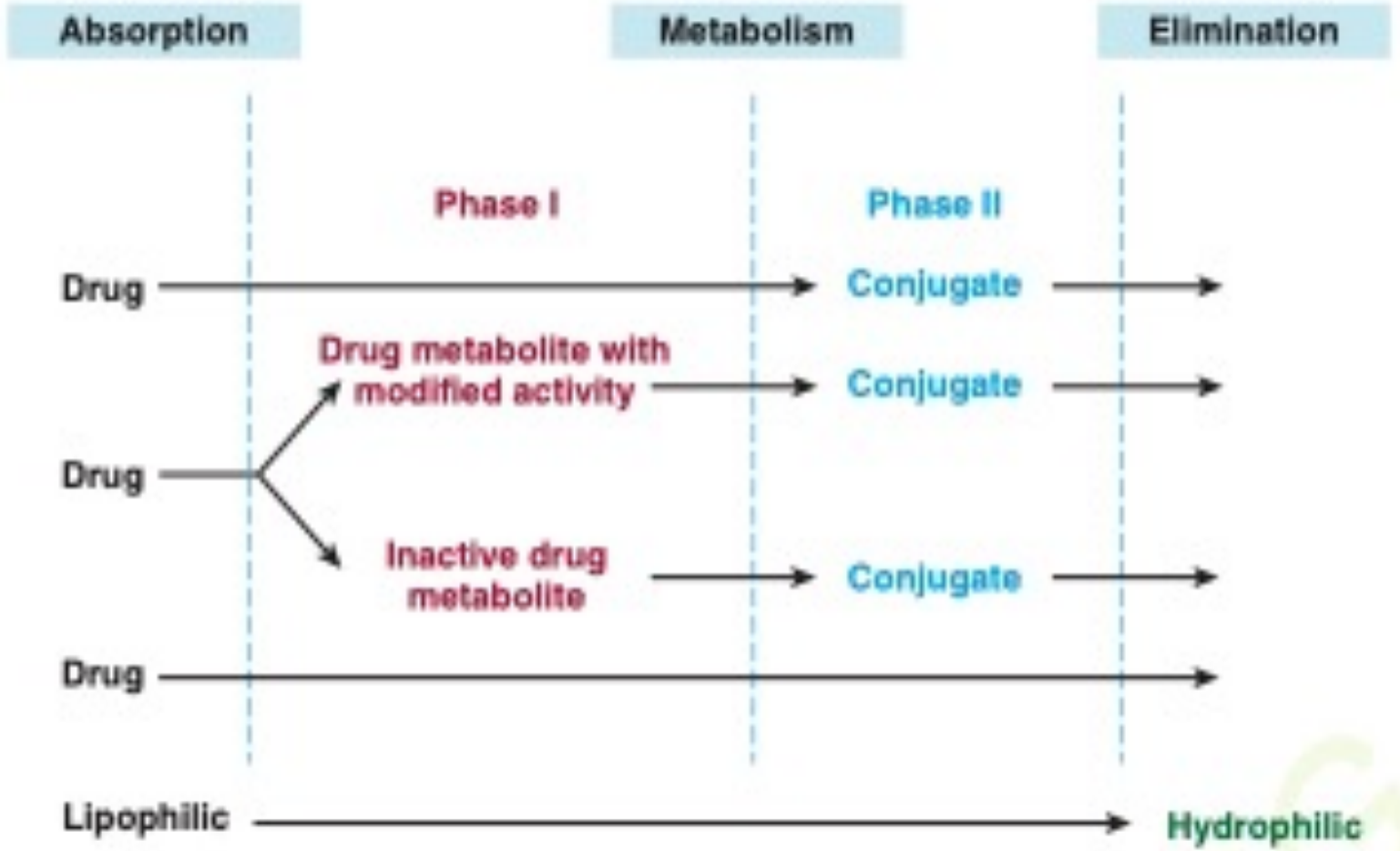


FIGURE 4–1 Phase I and phase II reactions, and direct elimination, in drug biodisposition. Phase II reactions may also precede phase I reactions.

METABOLISME

FASE 2 DAPAT MENDAHULUI FASE 1

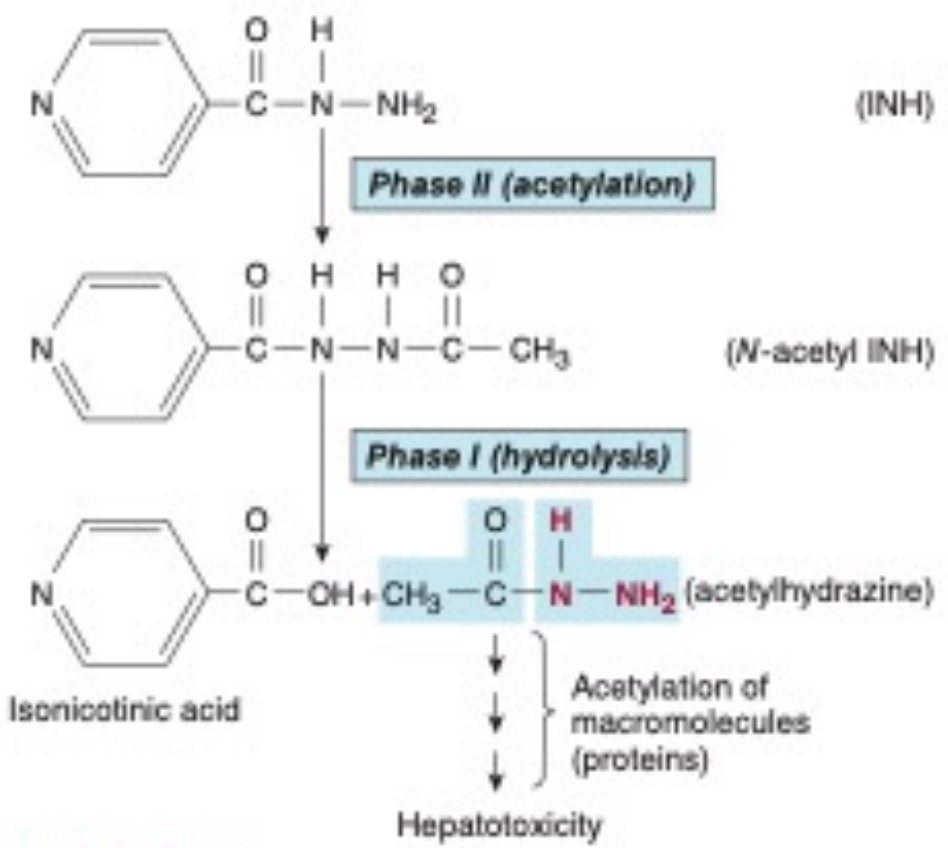


FIGURE 4–2 Phase II activation of isoniazid (INH) to a hepatotoxic metabolite.

FASE 1

Jenis reaksi

TABLE 4–1 Phase I reactions.

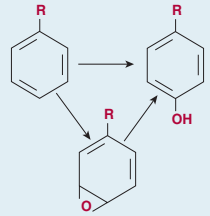
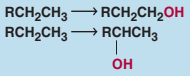
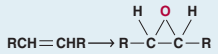
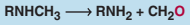
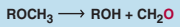
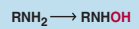
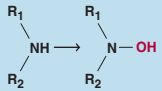
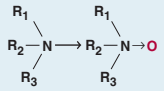
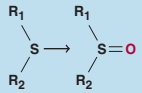
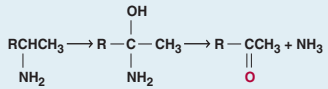
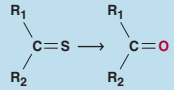
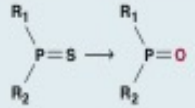
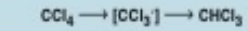
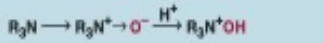
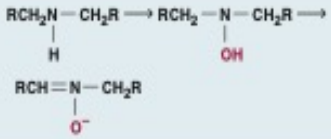
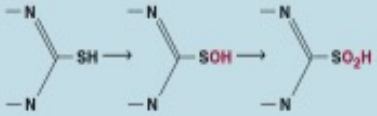
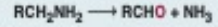
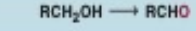
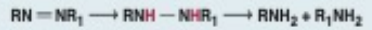
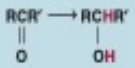
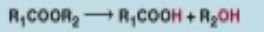
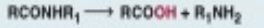
Reaction Class	Structural Change	Drug Substrates
Oxidations		
Cytochrome P450-dependent oxidations:	Bergantung pada enzim Cytochrome p450	
Aromatic hydroxylations		Acetanilide, propranolol, phenobarbital, phenytoin, phenylbutazone, amphetamine, warfarin, 17α-ethinyl estradiol, naphthalene, benzpyrene
Aliphatic hydroxylations		Amobarbital, pentobarbital, secobarbital, chlorpropamide, ibuprofen, meprobamate, glutethimide, phenylbutazone, digitoxin
Epoxidation		Aldrin
Oxidative dealkylation		
N-Dealkylation		Morphine, ethylmorphine, benzphetamine, aminopyrine, caffeine, theophylline
O-Dealkylation		Codeine, *p*-nitroanisole
S-Dealkylation		6-Methylthiopurine, methitural
***N*-Oxidation**		
Primary amines		Aniline, chlorphentermine
Secondary amines		2-Acetylaminofluorene, acetaminophen
Tertiary amines		Nicotine, methaqualone
***S*-Oxidation**		Thioridazine, cimetidine, chlorpromazine
Deamination		Amphetamine, diazepam
Desulfuration		Thiopental

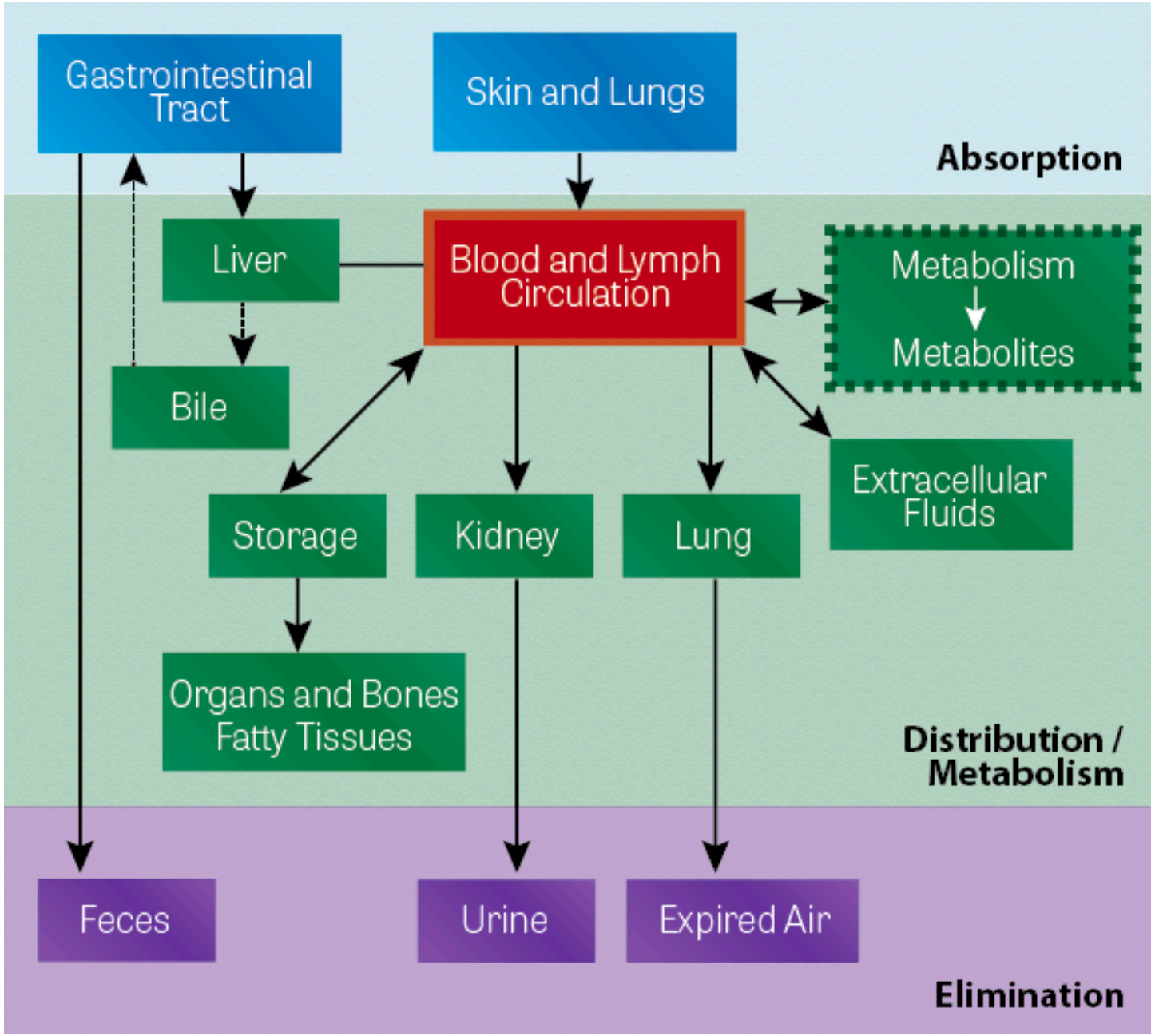
TABLE 4–1 Phase I reactions. (Continued)

Reaction Class	Structural Change	Drug Substrates
Cytochrome P450- dependent oxidations: (continued)		
		Parathion
Dechlorination		Carbon tetrachloride
Cytochrome P450-independent oxidations:	Tidak Bergantung pada enzimCytochrome p450	
Flavin monooxygenase (Ziegler's enzyme)		Chlorpromazine, amitriptyline, benzphetamine
		Desipramine, nortriptyline
		Methimazole, propylthiouracil
Amine oxidases		Phenylethylamine, epinephrine
Dehydrogenations		Ethanol
Reductions		
Azo reductions		Prontosil, tartrazine
Nitro reductions		Nitrobenzene, chloramphenicol, clonazepam, dantrolene
Carbonyl reductions		Metyrapone, methadone, naloxone
Hydrolyses		
Esters		Procaine, succinylcholine, aspirin, clofibrate, methylphenidate
Amides		Procainamide, lidocaine, indomethacin

FASE 2

TABLE 4–3 Phase II reactions.

Type of Conjugation	Endogenous Reactant	Transferase (Location)	Types of Substrates	Examples
Glucuronidation	UDP glucuronic acid (UDPGA)	UDP glucuronosyltransferase (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)	GSH-*S*-transferase (cytosol, microsomes)	Epoxides, arene oxides, nitro groups, hydroxylamines	Acetaminophen, 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
Sulfation	Phosphoadenosyl phosphosulfate (PAPS)	Sulfotransferase (cytosol)	Phenols, alcohols, aromatic amines	Estrone, aniline, phenol, 3- hydroxycoumarin, acetaminophen, methyldopa
Methylation	*S*-Adenosylmethionine (SAM)	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



Absorption, Distribution, Metabolism, and Elimination
(Image Source: NLM)

FASE 1&2

Jenis enzim pada reaksi Fase 1 dan Fase 2

TABLE 6–1 ■ XENOBIOTIC-METABOLIZING ENZYMES

ENZYMES	REACTIONS
Phase 1 enzymes (CYPs, FMOs, EHs)	
Cytochrome P450s (P450 or CYP)	C and O oxidation, dealkylation, others
Flavin-containing monooxygenases (FMOs)	N, S, and P oxidation
Epoxide hydrolases (EHs)	Hydrolysis of epoxides
Phase 2 "transferases"	
Sulfotransferases (SULT)	Addition of sulfate
UDP-glucuronosyltransferases (UGTs)	Addition of glucuronic acid
Glutathione-*S*-transferases (GSTs)	Addition of glutathione
N-Acetyltransferases (NATs)	Addition of acetyl group
Methyltransferases (MTs)	Addition of methyl group
Other enzymes	
Alcohol dehydrogenases	Reduction of alcohols
Aldehyde dehydrogenases	Reduction of aldehydes
NADPH-quinone oxidoreductase (NQO)	Reduction of quinones

mEH and sEH, microsomal and soluble epoxide hydrolase, respectively; NADPH, reduced nicotinamide adenine dinucleotide phosphate; UDP, uridine diphosphate.

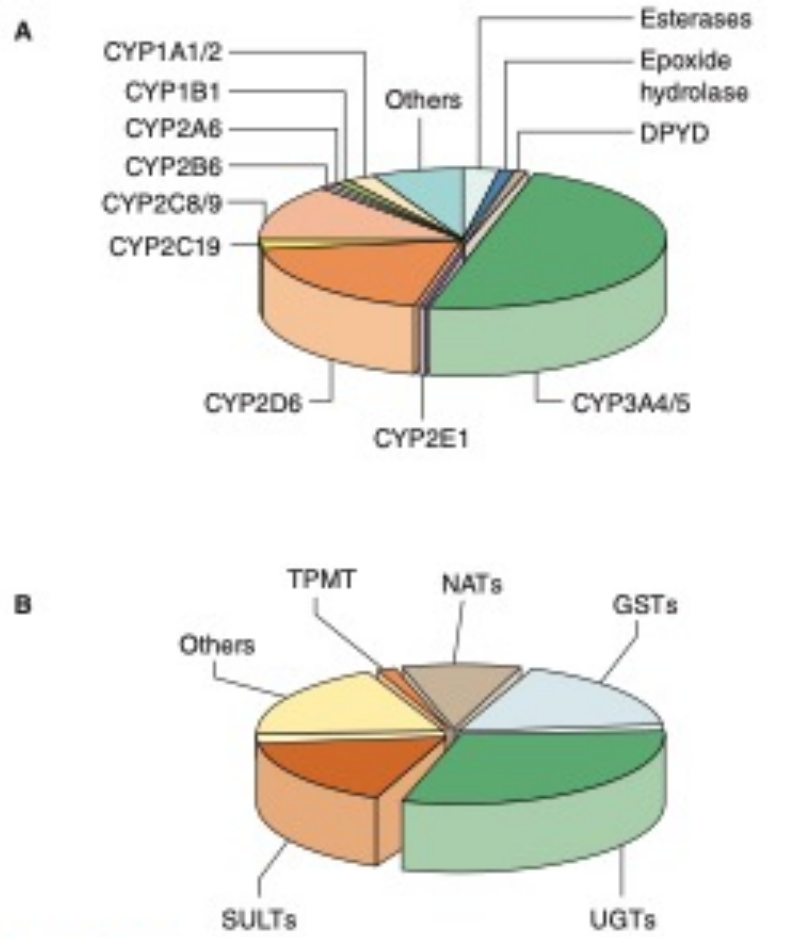


FIGURE 4–4 Relative contributions of various cytochrome P450 isoforms (**A**) and different phase II pathways (**B**) to metabolism of drugs in clinical use. Many drugs are metabolized by two or more of these pathways. Note that two pathways, CYP3A4/5 and UGT, are involved in the metabolism of more than 75% of drugs in use. DPYD, dihydropyrimidine dehydrogenase; GST, glutathione-*S*-transferase; NAT, *N*-acetyltransferase; SULT, sulfotransferase; TPMT, thiopurine methyltransferase; UGT, UDP-glucuronosyltransferase. (Reproduced, with permission, from Brunton LL, Chabner BA, Knollman BC: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th ed. McGraw-Hill, 2011. Copyright © The McGraw-Hill Companies, Inc.)

BIOAVAILABILITAS

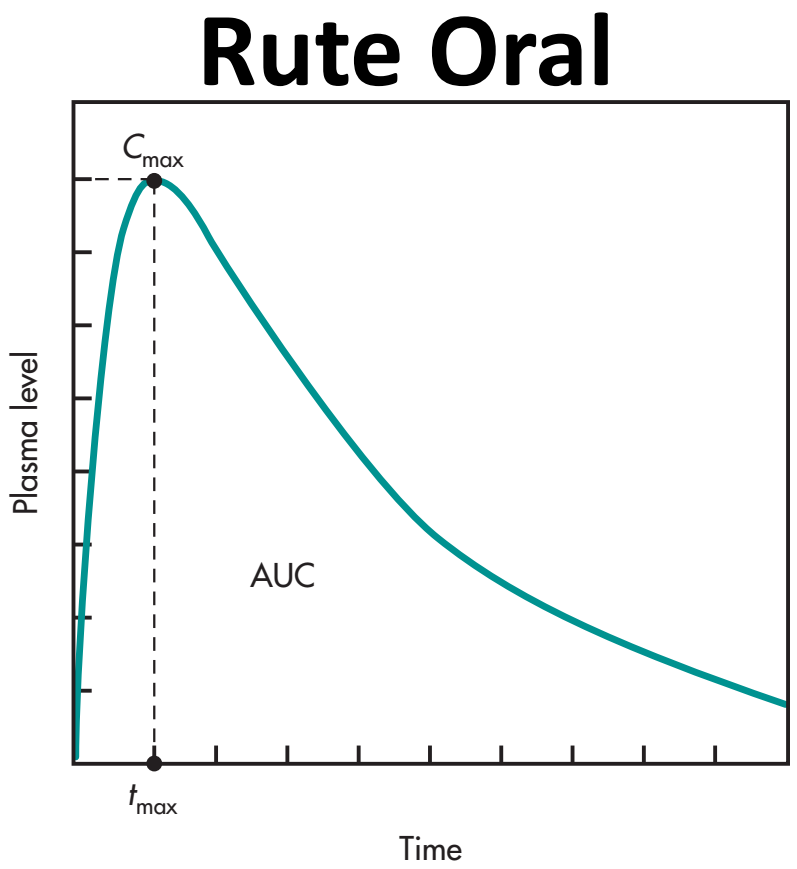


FIGURE 8-8 Typical plasma level–time curve for a drug given in a single oral dose.

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

Route	Biovailability (%)	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 important
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

$$F = \frac{\text{Quantity of drug reaching systemic circulation}}{\text{Quantity of drug administered}}$$

where $0 < F \leq 1$.

BIOAVAILA-BILITAS

Rute IV

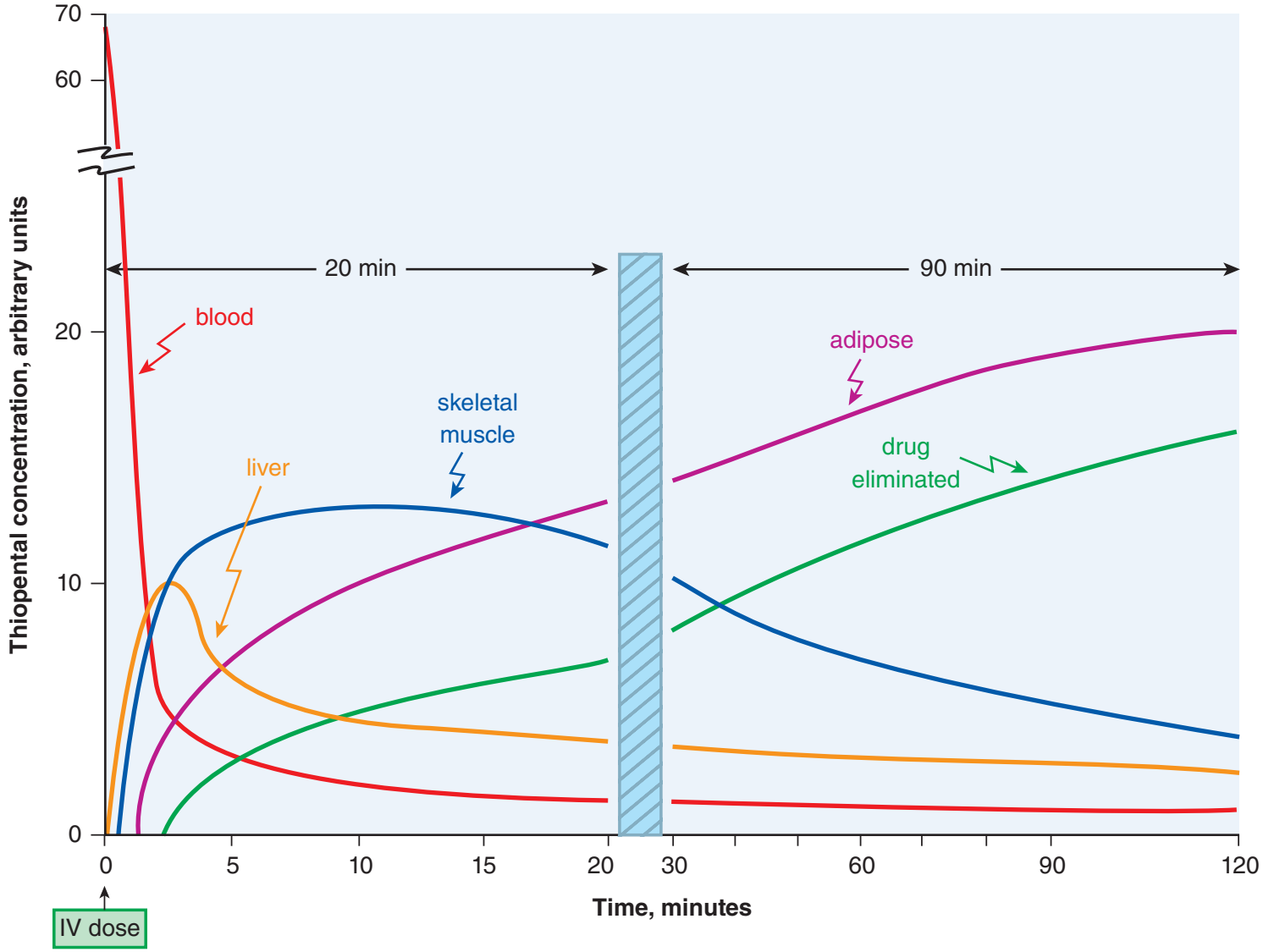


Figure 2–4 *Redistribution.* Curves depict the distribution of the barbiturate anesthetic thiopental into different body compartments following a single rapid intravenous dose. Note breaks and changes of scale on both axes. The drug level at thiopental's site of action in the brain closely mirrors the plasma level of the drug. The rate of accumulation in the various body compartments depends on regional blood flow; the extent of accumulation reflects the differing capacities of the compartments and the steady but slow effect of elimination to reduce the amount of drug available. Emergence from the anesthetic influence of this single dose of thiopental relies on redistribution, not on metabolism. The drug will partition out of tissue depots as metabolism and elimination take their course. Depletion of compartments will follow the same order as accumulation, as a function of their perfusion.

ELIMINASI DAN EKSKRESI

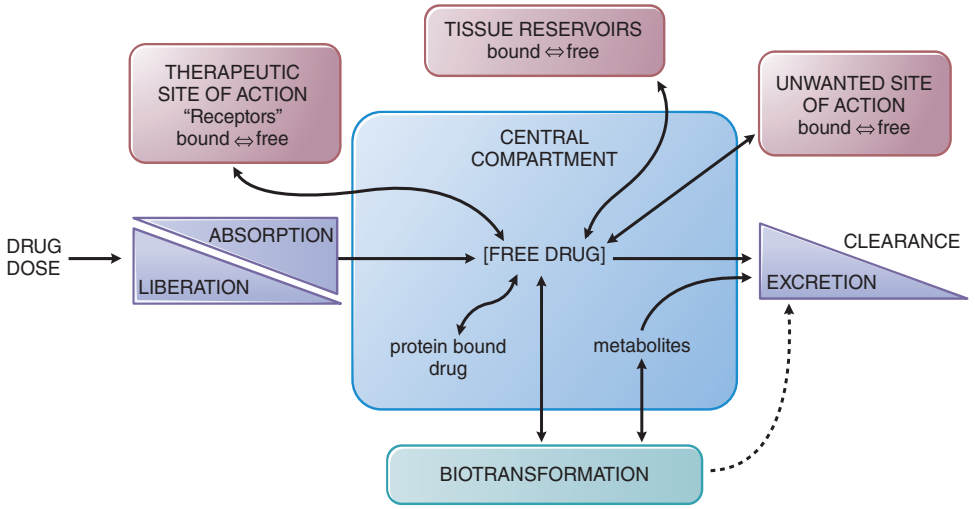


Figure 2–1 *The interrelationship of the absorption, distribution, binding, metabolism, and excretion of a drug and its concentration at its sites of action.* Possible distribution and binding of metabolites in relation to their potential actions at receptors are not depicted.

Excretion of Drugs

Drugs are eliminated from the body either unchanged or as metabolites. Excretory organs, the lung excluded, eliminate polar compounds more efficiently than substances with high lipid solubility. Thus, lipid-soluble drugs are not readily eliminated until they are metabolized to more polar compounds. The kidney is the most important organ for excreting drugs and their metabolites. Renal excretion of unchanged drug is a major route of elimination for 25%–30% of drugs administered to humans. Substances excreted in the feces are principally unabsorbed orally ingested drugs or drug metabolites either excreted in the bile or secreted directly into the intestinal tract and not reabsorbed. Excretion of drugs in breast milk is important not because of the amounts eliminated (which are small) but because the excreted drugs may affect the nursing infant (also small, and with poorly developed capacity to metabolize xenobiotics). Excretion from the lung is important mainly for the elimination of anesthetic gases (see Chapter 21).

Renal Excretion

Excretion of drugs and metabolites in the urine involves three distinct processes: glomerular filtration, active tubular secretion, and passive tubular reabsorption (Figure 2–5). The amount of drug entering the tubular lumen by filtration depends on the glomerular filtration rate and the extent of plasma binding of the drug; only unbound drug is filtered. In the proximal renal tubule, active, carrier-mediated tubular secretion also may add drug to the tubular fluid (see Chapters 5 and 25). Drug from the tubular lumen may be reabsorbed back into the systemic circulation. In the renal tubules, especially on the distal side, the nonionized forms of weak acids and bases undergo net passive reabsorption. Because the tubular cells are less permeable to the ionized forms of weak electrolytes, passive reabsorption of these substances depends on the pH. When the tubular urine is made more alkaline, weak acids are largely ionized and are excreted more rapidly and to a greater extent; conversely, acidification of the urine will reduce fractional ionization and excretion of weak acids. Effects of changing urine pH are opposite for weak bases. In the treatment of drug poisoning, the excretion of some drugs can be hastened by appropriate alkalinization or acidification of the urine (see Figure 2–3 and Chapter 4).

In neonates, renal function is low compared with body mass but matures rapidly within the first few months after birth. During adulthood, there is a slow decline in renal function, about 1% per year, so that in elderly patients a substantial degree of functional impairment may be present, and medication adjustments are often needed.

Biliary and Fecal Excretion

Transporters present in the canalicular membrane of the hepatocyte (see Figure 5–6) actively secrete drugs and metabolites into bile. Ultimately, drugs and metabolites present in bile are released into the GI tract during the digestive process. Subsequently, the drugs and metabolites can be reabsorbed into the body from the intestine, which, in the case of conjugated metabolites such as glucuronides, may require enzymatic hydrolysis

Excretion by Other Routes

Excretion of drugs into sweat, saliva, and tears is quantitatively unimportant. Because milk is more acidic than plasma, basic compounds may be slightly concentrated in this fluid; conversely, the concentration of acidic compounds in the milk is lower than in plasma. Nonelectrolytes (e.g., ethanol and urea) readily enter breast milk and reach the same concentration as in plasma, independent of the pH of the milk (Rowe et al., 2015). Breast milk can also contain heavy metals from environmental exposures. The administration of drugs to breastfeeding women carries the general caution that the suckling infant will be exposed to some extent to the medication or its metabolites. Although excretion into hair and skin is quantitatively unimportant, sensitive methods of detection of drugs in these tissues have forensic significance.

Added together, these separate clearances equal total systemic clearance:

$$CL_{kidney} = \frac{\text{Rate of elimination}_{kidney}}{C} \quad (3a)$$

$$CL_{liver} = \frac{\text{Rate of elimination}_{liver}}{C} \quad (3b)$$

$$CL_{other} = \frac{\text{Rate of elimination}_{other}}{C} \quad (3c)$$

$$CL_{systemic} = CL_{kidney} + CL_{liver} + CL_{other} \quad (3d)$$

"Other" tissues of elimination could include the lungs and additional sites of metabolism, eg, blood or muscle.

The two major sites of drug elimination are the kidneys and the liver. Clearance of unchanged drug in the urine represents renal clearance. Within the liver, drug elimination occurs via biotransformation of parent drug to one or more metabolites, or excretion of unchanged drug into the bile, or both. The pathways of biotransformation are discussed in Chapter 4. For most drugs, clearance is constant over the concentration range encountered in clinical settings, ie, elimination is not saturable, and the rate of drug elimination is directly proportional to concentration (rearranging equation [2]):

$$\text{Rate of elimination} = CL \times C \quad (4)$$

ELIMINASI DAN EKSKRESI

Clearance of a drug is its rate of elimination by all routes normalized to the concentration of drug *C* in some biological fluid where measurement can be made:

$$CL = \text{Rate of elimination}/C \qquad \text{(Equation 2–5)}$$

Thus, when clearance is constant, the rate of drug elimination is directly proportional to drug concentration. Clearance indicates the volume of

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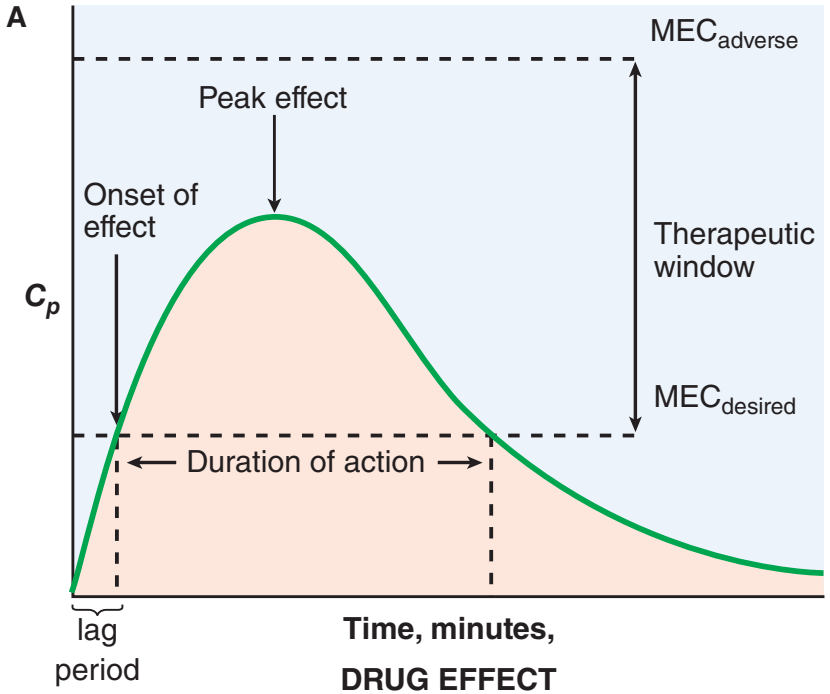

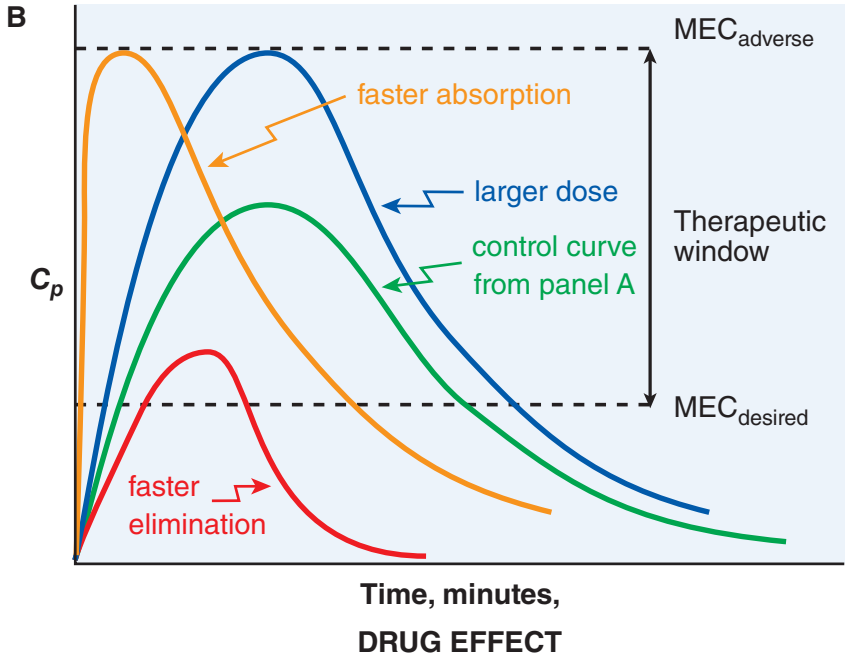

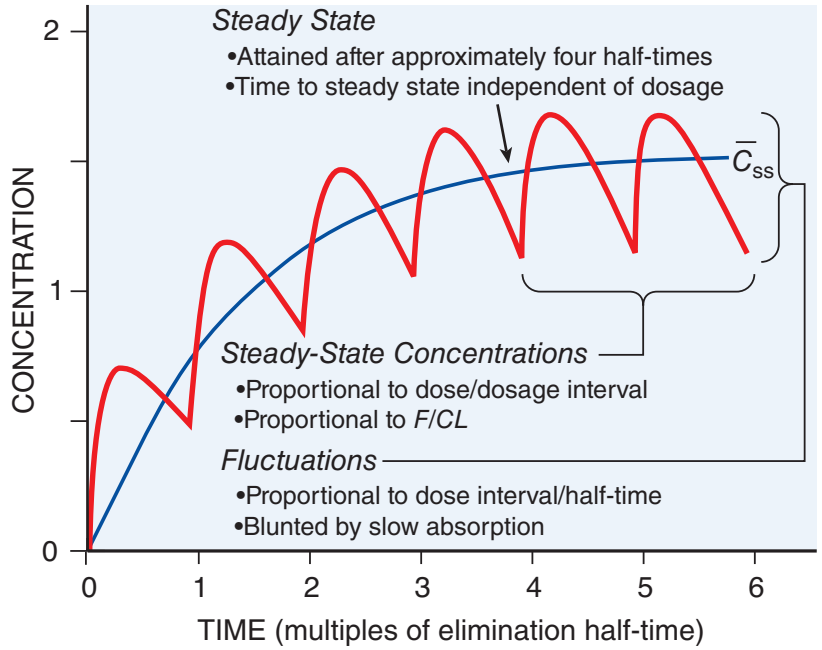

Figure 2–7 *Fundamental pharmacokinetic relationships for repeated administration of drugs.* The red line is the pattern of drug accumulation during repeated administration of a drug at intervals equal to its elimination half-time. With instantaneous absorption, each dose would add 1 concentration unit to C_p at the time of administration, and then half of that would be eliminated prior to administration of the next dose, resulting in the oscillation of C_p between 1 and 2 after four or five elimination half-times. However, this more realistic simulation uses a rate of drug absorption that is not instantaneous but is 10 times as rapid as elimination; drug is eliminated throughout the absorption process, blunting the maximal blood level achieved after each dose. With repeated administration, C_p achieves steady state, oscillating around the blue line at 1.5 units. The blue line depicts the pattern during administration of equivalent dosage by continuous intravenous infusion. Curves are based on the one-compartment model. Average drug concentration at steady state $\bar{C}_{ss}$ is:

Distribution

Volume of Distribution

The volume of distribution V relates the amount of drug in the body to the concentration of drug C in the blood or plasma, depending on the fluid measured. This volume does not necessarily refer to an identifiable physiological volume but rather to the fluid volume that would be required to contain all of the drug in the body at the same concentration measured in the blood or plasma:

$$\text{Amount of drug in body}/V = C$$

or

$$V = \text{Amount of drug in body}/C \qquad \text{(Equation 2–11)}$$

View V as an imaginary volume because for many drugs V exceeds the known volume of any and all body compartments (Box 2–1). For example, the value of V for the highly lipophilic antimalarial chloroquine is some 15,000 L, whereas the volume of total-body water is about 42 L in a 70-kg male.

Loading Dose

When the time to reach steady state is appreciable, as it is for drugs with long half-lives, it may be desirable to administer a loading dose that promptly raises the concentration of drug in plasma to the target concentration. In theory, only the amount of the loading dose need be computed—not the rate of its administration—and, to a first approximation, this is so. The volume of distribution is the proportionality factor that relates the total amount of drug in the body to the concentration; if a loading dose is to achieve the target concentration, then from equation (1):

$$\begin{aligned}\text{Loading dose} &= \text{Amount in the body immediately following the loading dose} \\ &= V \times TC \qquad (12)\end{aligned}$$

Maintenance Dose

In most clinical situations, drugs are administered in such a way as to maintain a steady state of drug in the body, ie, just enough drug is given in each dose to replace the drug eliminated since the preceding dose. Thus, calculation of the appropriate maintenance dose is a primary goal. Clearance is the most important pharmacokinetic term to be considered in defining a rational steady-state drug dosage regimen. At steady state, the dosing rate ("rate in") must equal the rate of elimination ("rate out"). Substitution of the target concentration (TC) for concentration (C) in equation (4) predicts the maintenance dosing rate:

$$\begin{aligned}\text{Dosing rate}_{ss} &= \text{Rate of elimination}_{ss} \\ &= CL \times TC \qquad (9)\end{aligned}$$

Thus, if the desired target concentration is known, the clearance in that patient will determine the dosing rate. If the drug is given by a route that has a bioavailability less than 100%, then the dosing rate predicted by equation (9) must be modified. For oral dosing:

$$\text{Dosing rate}_{oral} = \frac{\text{Dosing rate}}{F_{oral}} \qquad (10)$$

If intermittent doses are given, the maintenance dose is calculated from:

$$\text{Maintenance dose} = \text{Dosing rate} \times \text{Dosing interval} \qquad (11)$$

Example: Maintenance Dose Calculations

A target plasma theophylline concentration of 10 mg/L is desired to relieve acute bronchial asthma in a patient. If the patient is a nonsmoker and otherwise normal except for asthma, we may use the mean clearance given in Table 3–1, ie, 2.8 L/h/70 kg. Since the drug will be given as an intravenous infusion, F = 1.

$$\begin{aligned}\text{Dosing rate} &= \text{CL} \times \text{TC} \\ &= 2.8\ \text{L/h/70 kg} \times 10\ \text{mg/L} \\ &= 28\ \text{mg/h/70 kg}\end{aligned}$$

Therefore, in this patient, the infusion rate would be 28 mg/h/70 kg.

If the asthma attack is relieved, the clinician might want to maintain this plasma level using oral theophylline, which might be given every 12 hours using an extended-release formulation to approximate a continuous intravenous infusion. According to Table 3–1, F_{oral} is 0.96. When the dosing interval is 12 hours, the size of each maintenance dose would be:

$$\begin{aligned}\text{Maintenance dose} &= \frac{\text{Dosing rate}}{F} \times \text{Dosing interval} \\ &= \frac{28\ \text{mg/h}}{0.96} \times 12\ \text{hours} \\ &= 350\ \text{mg}\end{aligned}$$

A tablet or capsule size close to the ideal dose of 350 mg would then be prescribed at 12-hourly intervals. If an 8-hour dosing interval was used, the ideal dose would be 233 mg; and if the drug was given once a day, the dose would be 700 mg. In practice, F could be omitted from the calculation since it is so close to 1.

ADJUSTMENT OF DOSAGE WHEN ELIMINATION IS ALTERED BY DISEASE

Renal disease or reduced cardiac output often reduces the clearance of drugs that depend on renal elimination. Alteration of clearance by liver disease is less common but may also occur. Impairment of hepatic clearance occurs (for high extraction drugs) when liver blood flow is reduced, as in heart failure, and in severe cirrhosis and other forms of liver failure. Because it is important in the elimination of drugs, assessing renal function is important in estimating dosage in patients. The most important renal variable in drug elimination is glomerular filtration rate (GFR), and creatinine clearance (CL_{cr}) is a convenient approximation of GFR. The dosage in a patient with renal impairment may be corrected by multiplying the average dosage for a normal person times the ratio of the patient's altered creatinine clearance (CL_{cr}) to normal creatinine clearance (approximately 100 mL/min, or 6 L/h in a young adult).

$$\text{Corrected dosage} = \text{Average dosage} \times \frac{\text{Patient's } CL_{cr}}{100 \text{ mL/min}} \quad (6)$$

This simplified approach ignores nonrenal routes of clearance that may be significant. If a drug is cleared partly by the kidney and partly by other routes, Equation 6 should be applied to the part of the dose that is eliminated by the kidney. For example, if a drug is 50% cleared by the kidney and 50% by the liver and the normal dosage is 200 mg/d, the hepatic and renal elimination rates are each 100 mg/d. Therefore, the corrected dosage in a patient with a creatinine clearance of 20 mL/min will be:

$$\begin{aligned}\text{Dosage} &= 100 \text{ mg/d (liver)} + 100 \text{ mg/d} \\ &\quad \times \frac{20 \text{ mL/min}}{100 \text{ mL/min}} \text{ (kidney)} \quad (7) \\ \text{Dosage} &= 100 \text{ mg/d} + 20 \text{ mg/d} = 120 \text{ mg/d}\end{aligned}$$

Renal function is altered by many diseases and is often decreased in older patients. CL_{cr} can be measured directly, but this requires careful measurement of both serum creatinine concentration and a timed total urine creatinine. A common shortcut that requires only the serum (or plasma) creatinine measurement (S_{cr}) is the use of an equation. One such equation in common use is the Cockcroft-Gault equation:

$$CL_{cr}\ (\text{mL/min}) = \frac{(140 - \text{Age}) \times \text{body weight (kg)}}{72 \times S_{cr}} \quad (8)$$

The result is multiplied by 0.85 for females. A similar equation for GFR is the MDRD equation:

$$\begin{aligned}&\text{GFR (mL/min/1.73 m}^2\text{ body surface area)} \\ &= \frac{175 \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})}{S_{cr}^{1.154} \times \text{Age}^{0.203}} \quad (9)\end{aligned}$$