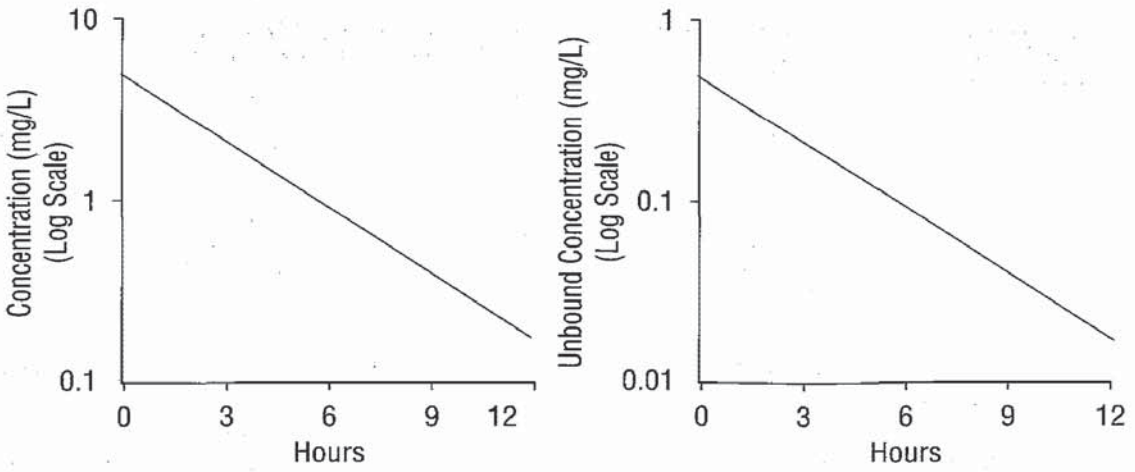

Fig. 10–12.

5. Briefly comment on the validity of each of the following statements.
   a. The equilibrium distribution ratio for a drug between liver and plasma is 50; therefore, its volume of distribution must be at least 75 L in a man weighing 70 kg.
   b. A drug that reaches distribution equilibrium within 30 min, yet whose volume of distribution in a 70-kg man is 200 L, must distribute primarily into highly perfused organs.
6. Using the information in Table 10–8, calculate the time required for the amounts in each of the tissues listed to reach 50% of the equilibrium value for a drug with perfusion rate-limited distribution when the arterial blood concentration is kept constant with time (by giving a bolus and an appropriate infusion). Rank the times and the corresponding tissues.

Table 10–8.

ORGAN	EQUILIBRIUM DISTRIBUTION RATIO	PERFUSION RATE (mL/min/mL of tissue)
Lungs	1	10
Kidneys	4	4
Heart	3	0.6
Liver	15	0.8
Skin	12	0.024

7. Digitoxin has a volume of distribution of 38 L in a 70-kg man and is 97% bound in plasma. Given that the unbound drug distributes evenly throughout total body water, what fraction of drug is unbound in the intercellular fluids?
8. Digoxin has a volume of distribution of about 550 L in a 70-kg subject and is 23% bound in plasma. Using the information provided in problem 7, determine if digoxin is more or less extensively bound in intracellular fluids than digitoxin?
9. Ganeval et al. studied the pharmacokinetics of warfarin in 11 patients with the nephrotic syndrome (daily urinary protein excretion = 10.2 ± 4.5 g; serum creatinine = 105 ± 32 μM) versus 11 controls (no proteinuria; serum creatinine = 96 ± 20 μM). Table 10–9 illustrates the differences in warfarin kinetics in the two populations. No data on differences in weight between the two groups were given. For this problem, both groups averaged 70 kg.

Table 10–9. Mean Pharmacokinetic Parameters and Serum Albumin Concentrations in 11 Control and 11 Nephrotic Patients After Oral Administration (8 mg) of Warfarin[a]

PARAMETERS	CONTROL GROUP	NEPHROTIC PATIENTS
V (L)	9.4 ± 2.7	13.7 ± 6.6
Cl (L/hr)	0.20 ± 0.07	0.58 ± 0.26
$t_{1/2}$ (hr)	36 ± 14	18 ± 11
Serum albumin (g/L)	43 ± 5	12.5 ± 6.5

[a]From Ganeval, D., Fischer, A.M., Berre, J., Pertuiset, N., Dautzenberg, M.D., Jungers, P., and Houin, G.: Pharmacokinetics of warfarin in the nephrotic syndrome and effect on vitamin K-dependent clotting factors. Clin. Nephrol., 25:78–80, 1986.

a. Given a fraction unbound of 0.005 in the control group, estimate the value expected in the nephrotic group.
b. Warfarin has a small volume of distribution. Calculate the expected volume of distribution if fu is increased to the value calculated in "a." Hint: determine the value of fu_R in the control group, and assume it is the same in the nephrotic patients.
c. Had the half-life data not been given, could you have predicted the observed shortening of the value in the nephrotic patients? This condition usually suggests induction of metabolism.

11

ELIMINATION

OBJECTIVES

The reader will be able to:

1. Define the following using both words and equations: clearance, blood clearance, unbound clearance, hepatic clearance, biliary clearance, and renal clearance.
2. Calculate the extraction ratio across an eliminating organ given blood clearance and blood flow in that organ.
3. Ascertain from the value of its extraction ratio whether the clearance of a drug by an organ is perfusion rate-limited or is dependent on its binding to plasma proteins.
4. Calculate the maximum oral bioavailability of a drug given either its hepatic extraction ratio or the appropriate information to estimate this value.
5. Determine the biliary clearance of a drug from its bile-to-plasma concentration ratio and the bile flow.
6. Describe the role that biliary secretion can play in drug disposition.
7. Describe where filtration, secretion, and reabsorption of drugs occur within the nephron.
8. State the average value of glomerular filtration rate.
9. Given renal clearance and binding data, determine if a drug is predominantly reabsorbed from or secreted into the renal tubule.
10. Anticipate those drugs for which a change in either urine pH or urine flow may alter the value of their renal clearance.
11. Ascertain the relative contribution of the renal and extrarenal routes to total elimination from their respective clearance values.
12. Explain the statement, "Half-life depends upon clearance and volume of distribution."

This chapter is concerned with elimination processes and particularly with the concept of clearance. In Chap. 3, 6, and 7, the methods of quantifying clearance were presented. Here its physiologic meaning is given.

ELIMINATION

Elimination occurs by excretion and metabolism. Some drugs are excreted via the bile. Others, particularly volatile substances, are excreted in the breath. For most drugs, however, excretion occurs predominantly via the kidneys.

Metabolism is the major mechanism for elimination of drugs from the body. Some drugs are eliminated almost entirely unchanged by the kidneys, but these drugs are relatively few.

The most common routes of drug metabolism are oxidation, reduction, hydrolysis, and conjugation. Frequently, a drug simultaneously undergoes metabolism by several competing pathways. The fraction going to each metabolite depends on the relative rates of each of the parallel pathways. Metabolites may undergo further metabolism. For example, oxidation, reduction, and hydrolysis are often followed by a conjugation reaction. These reactions occur in series or are said to be *sequential*. Because they often occur first, oxidation, reduction and hydrolysis are commonly referred to as Phase I reactions, and conjugations as a Phase II reactions.

Generally, the liver is the major and sometimes only, site of drug metabolism. Occasionally, however, a drug is extensively metabolized in one or more other tissues, such as the kidneys, skin, lungs, blood, and gastrointestinal wall. Nitroglycerin is such an example.

Table 11–1 illustrates patterns of biotransformation (metabolism) of representative drugs. The pathways of metabolism are classified by chemical alteration. Several of the transformations occur in the endoplasmic reticulum of the liver and of certain other tissues. On homogenizing these tissues, the endoplasmic reticulum is disrupted with the formation of small vesicles called *microsomes*. For this reason, metabolizing enzymes of the endoplasmic reticulum are called *microsomal enzymes*. Drug metabolism, therefore, may be classified as microsomal and nonmicrosomal.

Table 11–1. Patterns of Biotransformation[a] of Representative Drugs[b]

PRODRUG	DRUG	ACTIVE METABOLITE	INACTIVE METABOLITE[c]
	Acetylsalicylic acid	Salicylic acid (H)	Salicyl (acid) glucuronide (C); Salicyl (phenolic) glucuronide (C); Salicyluric acid (C); Gentisic acid (O)
	Glutethimide	Hydroxyglutethimide (O)	Hydroxyglutethimide glucuronide (C)
	Morphine	Morphine-6-glucuronide (C)	Morphine-3-glucuronide (C)
	Phenytoin		p-Hydroxyphenytoin (O)
	Prednisone	Prednisolone (R)	
	Succinylcholine		Succinylmonocholine (H)
	Theophylline		1-Methylxanthine (O); 1,3-Dimethyluric acid (O)

[a]Classification: (O), oxidation; (R), reduction; (H), hydrolysis; (C), conjugation.
[b]For some drugs only representative metabolic pathways are indicated.
[c]Inactive at concentrations obtained following the therapeutic administration of the parent drug.

The major enzymes responsible for the oxidation and reduction of drugs belong to the superfamily of cytochrome P450 enzymes. The isozymes of this family display a relatively high degree of structural specificity; a drug is often a good substrate for one enzyme but not another (see also Chap. 14).

The consequences of drug metabolism are manifold. Biotransformation provides a mechanism for ridding the body of undesirable foreign compounds and drugs; it also provides a means of producing active compounds. Numerous examples are now recognized in which the administered drug is really an inactive prodrug, which is converted into a pharmacologically active species. Often both the drug and its metabolite(s) are active. The duration and intensity of the responses vary with the time courses of these substances in the body. The pharmacokinetics of active metabolites, as well as that of the compound administered, is therefore of therapeutic concern. The common pathways of biotransformation and the kinetics of metabolites are presented in Chap. 21, Metabolite Kinetics. The elimination processes are emphasized here.

CONCEPT OF CLEARANCE

Of the concepts in pharmacokinetics, *clearance* has the greatest potential for clinical applications. It is also the most useful parameter for the evaluation of an elimination mechanism.

Loss Across an Organ of Elimination

Recall from Chap. 3 that clearance is defined as the proportionality factor relating rate of drug elimination to the plasma (drug) concentration. That is, rate of elimination $= CL \cdot C$. Clearance may be viewed in another way, namely from the loss of drug across an organ of elimination. This latter physiologic approach has a number of advantages, particularly in predicting and in evaluating the effects of changes in blood flow, plasma protein binding, enzyme activity, or secretory activity on the elimination of a drug. Fig. 11–1 summarizes the various ways of viewing mass balance across an eliminating organ. In this scheme, drug in the eliminating organ is assumed to have reached distribution equilibrium; thus, the sole reason for any difference between the arterial and venous concentrations is elimination. For all but the earliest moments, this assumption is reasonable for the kidneys and the liver, which are among the most highly perfused and hence most rapidly equilibrating organs in the body.

The rate of presentation of a drug to an organ of elimination is the product of blood flow, Q, and concentration in blood entering the arterial side, C_A, that is, $Q \cdot C_A$. Similarly, the rate at which drug leaves on the venous side is $Q \cdot C_V$, where C_V is the concentration in the returning venous blood. The difference between these rates is the rate of drug extraction (elimination) by the organ,

$$\text{Rate of extraction} = Q(C_A - C_V) \qquad 1$$

If the rate of drug extraction is related to the rate at which it is presented to the organ, $Q \cdot C_A$, a useful parameter, the *extraction ratio*, E, is derived:

$$E = \frac{\text{Rate of extraction}}{\text{Rate of presentation}} = \frac{(C_A - C_V)}{C_A} \qquad 2$$

The extraction ratio lies between zero, where no drug is eliminated, and 1, where no drug escapes past the organ.

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