Medical Toxicology

Third Edition

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Compositor: Silverchair Science + Communications
Printer: Quebecor World

530 Walnut Street
Philadelphia, PA 19106 USA
LWW.com

Printed in the USA

Library of Congress Cataloging-in-Publication Data

Medical Toxicology / [edited by] Richard C. Dart.– 3rd. ed.
p. ; cm.
Rev. ed. of: Ellenhorn's medical toxicology / [edited by] Matthew J. Ellenhorn ... [et al.]. c1997.
Includes bibliographical references and index.
ISBN 0-7817-2845-2
1. Clinical toxicology. 2. Toxicological emergencies. I. Dart, Richard C. II. Ellenhorn's medical toxicology.
[DNLM: 1. Poisoning--diagnosis. 2. Poisoning--therapy. 3. Toxicology--methods. QV 600 M4888 2003]
RA1218.5M43 2003
615.9–dc22

2003060574

10 9 8 7 6 5 4 3 2 1

SECTION

7

Pharmacokinetics

CHAPTER 79

Principles and Applications of Pharmacokinetics

Michael Mayersohn

This presentation is *not* intended to be a course in mathematics nor, fortunately, does the reader need to be a mathematician to understand and apply the principles of pharmacokinetics. Effort should be expended in understanding the concepts and principles, which, hopefully, is facilitated by the shorthand use of some selected mathematical relationships. The math provides a universal language for developing and discussing the principles. These relationships must make sense (or they are useless), and this occurs if the concepts are understood. That said, it is necessary to use equations to represent the ideas and for calculation purposes. Because one principle or idea draws on those preceding it, try and keep clear "what drives what" (i.e., which is the true *independent* variable and which is the *dependent* variable) and how would a plot of one versus the other appear. Being able to graph one variable against another is important because if one can properly create such a plot, one understands the principle(s) behind the relationship. A graph represents a rapid means of presenting a relationship and often is the starting point for a discussion. By convention, there is only one graphing rule: the dependent variable appears on the y-axis (ordinate) and the independent variable appears on the x-axis (abscissa).

The term *pharmacokinetics* arises from the Greek *pharmacon*, meaning substance (a drug or toxic agent), and *kinetics*, meaning rate process. Pharmacokinetics is the area of study that examines the rates of those processes associated with entry into, disposition through, and exit from the body of a material (i.e., drug or toxin) presented to the body. Further, such study often attempts to relate the pharmacologic response or pharmacodynamic events to the concentration of that substance (or a derivative, such as a metabolite) as a function of time. The latter gives rise to useful pharmacokinetic/pharmacodynamic relationships. By extension, *toxicokinetics* concerns itself with the rate processes associated with a toxic agent (or derivative) entering the body and the consequent concentration and time-related toxicodynamic events. One can contrast pharmacokinetics to pharmacodynamics; the former being what the body does to the drug and the latter representing what the drug does to the body.

The processes that are studied and quantified in pharmacokinetics are often described by the mnemonic *ADME*, *a*bsorption, *d*istribution, *m*etabolism, and *e*xcretion. The three latter processes are associated with *disposition* (i.e., what happens to the drug once in the body, after gaining access to the bloodstream), whereas absorption describes the movement of the drug from the site of application to the bloodstream. In a more general way, these processes may be considered: input (absorption), translocation (distribution), and output (elimination). Critical to our understanding, however, is the ultimate expression of the interaction between the substance and the body, the *biologic outcome*, which is measured as a response or toxic event.

Figure 1 illustrates the important idea of the overlap between the pharmacokinetic events and some corresponding biologic outcome noted as a pharmacodynamic/toxicodynamic event. The driving force for the processes shown is concentration of drug in the blood. For this reason, it is important to understand and characterize the concentration-time profile, as it is critical for all subsequent events (i.e., distribution, elimination, and response). Another important aspect of Figure 1 is that all of the events are occurring at the *same* time, though processes are often sequential. After drug dosing or environmental exposure (on one or multiple occasions), and assuming that the substance is absorbed into the bloodstream, blood concentrations of the substance are achieved. That (driving force) concentration causes movement from the blood to other tissues, including the organs that eliminate the drug (e.g., liver and kidney) as well as the tissues that contain receptors or regions of potential toxicity. Thus, while the drug is being absorbed into the bloodstream, it is simultaneously being distributed to sites of action or toxicity, and it is undergoing elimination. Whereas a response tends to be reversible (increasing or decreasing in some manner related to blood concentration; often directly), elimination processes are almost always irreversible.

A more comprehensive view of the elementary scheme (Fig. 1) is illustrated in Figure 2. The banner cites the basic processes, input-translocation-output, which are further divided into more specific events. Thus, the processes on the left side of the scheme describe the transition steps of disintegration to dissolution to absorption that a solid form of a drug undergoes on ingestion. The dissolution step is often critical because it can rate-limit the overall absorption process, especially for poorly water-soluble

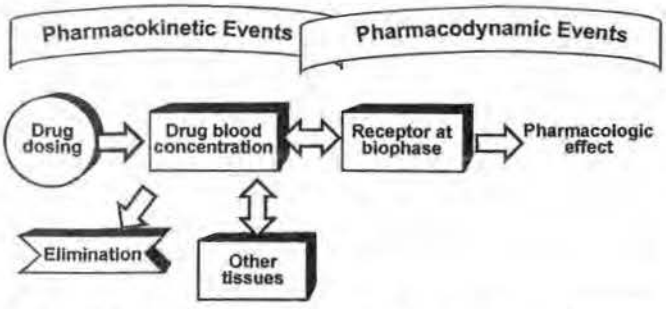


Figure 1. Schematic illustration of the overlap between pharmacokinetic events and biologic outcome noted as pharmacodynamic/toxicodynamic events. Blood concentration is the driving force for all of the events shown. All of the processes are dynamic as they are constantly changing with time. (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

compounds. Absorption, or the process of passing across one or more biologic membranes into the bloodstream, is a function of the permeability of the molecule (which is related to the oil/water partition coefficient of the chemical). As the molecule moves through the intestinal epithelial cells into the bloodstream, it may undergo metabolism (especially by the CYP-450 oxidative system as well as by conjugation reactions) or encounter efflux transporters (P-glycoprotein), which move the compound from the cell back into the gut lumen. Any absorbed drug then moves via the portal circulation into the liver. Because the latter is the major site of metabolism, the compound could undergo further chemical alteration as it passes through the liver. The *first-pass effect*, also known as *presystemic metabolism*, refers to the movement of compound through the gut wall and liver and its metabolic alteration. The first-pass effect can be quite important in modulating the response to a drug. As noted later, it is the magnitude of metabolic clearance that determines the significance of the first-pass effect (see Nonvascular Input: Absorption and Bioavailability. Once past the liver, the compound (and metabolites) gains access to the bloodstream (the *body*).

Numerous other routes of administration (pulmonary, rectal, subcutaneous, intramuscular, dermal, nasal) may provide alternative and perhaps more efficient modes of administration compared to the oral route (Fig. 2). In each instance, just as with oral dosing, the drug must traverse biologic membranes to gain access to the bloodstream. Each route has its own advantages and disadvantages. The absorption process can be completely bypassed by use of a vascular route, such as intravenous administration. The latter involves either bolus (all at once) dosing or infusion over a specified time. In either approach, the entire absorbed dose enters the body.

Once in the bloodstream, the compound has access to all tissues and organs in the body. During this time the drug distributes to the sites of action or toxicity and it undergoes elimination by the primary eliminating organs, the liver and kidney. Metabolites may form during this time and they in turn distribute to tissues and organs, possibly produce an effect or toxicity, and undergo further elimination from the body. The scheme in Figure 2, although appearing somewhat complex, is a considerable simplification of reality.

Recall that all of the events previously described are occurring at the same time. One needs to understand and relate dose to blood concentration, blood concentration to response, and all of these events with time. This is the challenge and the purpose of pharmacokinetics and toxicokinetics.

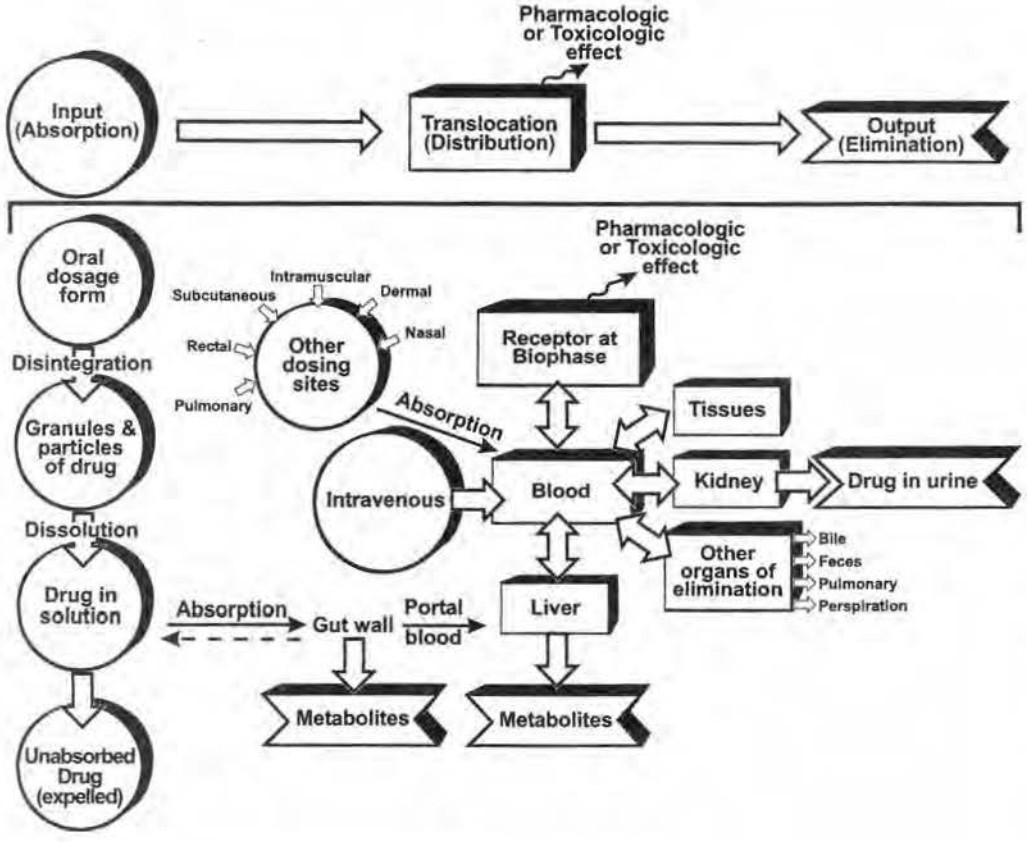


Figure 2. Conceptualized fate of a drug in an animal body after dosing by one or more routes of administration. The left side of the schema represents processes associated with oral absorption (input). The center portion reflects drug movement after gaining access to the body (translocation). The right-hand side of the schema illustrates elimination by various organs (output). (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 1998.)

KINETIC PROCESSES

First-Order (Linear) Kinetic Processes

The best place to begin a discussion of pharmacokinetic principles is by first discussing the elimination (or output or loss) process and by making a number of limiting assumptions. To develop a fundamental principle, that of *first-order* or *linear pharmacokinetics*, one first assumes that the drug is given as an intravenous (IV) bolus dose (the entire dose is placed into the bloodstream at one time). Second, one assumes that the drug distributes instantaneously from the blood to the rest of the tissues of the body. That assumption gives rise to the so-called *one-compartment model*. Although the idea of compartments is developed later, for the purpose here, one assumes the simplest possible model (i.e., the one-compartment model).

As long as the body receives doses of the substance that do not exceed the ability of the eliminating processes to handle those doses, one observes a process of elimination referred to as first-order or linear pharmacokinetics. Some important exceptions to this assumption exist (e.g., ethanol), and there are significant pharmacologic and toxicologic implications when they occur. The principle of first-order kinetics, simply stated, is that *the rate of any process is directly related to the concentration or amount of that substance at any given time*. Thus, the driving force for the rate of that process is simply the concentration or amount present at that time. After an IV bolus dose of drug and given the assumptions, the rate of elimination from the body is directly related to the blood concentration or amount present in the body, as shown in equation 1:

$$\text{rate} \propto \text{concentration} \qquad \text{[Eq. 1]}$$

Double the blood concentration (by doubling the dose), and the rate of elimination will double. Halve the concentration (by halving the dose), and the rate will halve. The proportionality sign can be replaced with a constant of proportionality and an equal sign to give

$$\text{rate} = K \cdot \text{concentration} \quad \text{OR} \quad \text{rate} = K \cdot C \qquad \text{[Eq. 2]}$$

in which C is concentration (in blood or plasma or serum), and K is the constant of proportionality. To have a final correct equation, a minus sign needs to be added to one side of the equation to indicate loss or elimination of drug from the body.

$$\text{rate} = -K \cdot C \qquad \text{[Eq. 3]}$$

The sign simply indicates the direction of movement of the substance; in this case, movement out of the body (by elimination) and, therefore, concentrations in the blood are declining with time. The constant of proportionality, K, is referred to as the *apparent overall first-order elimination rate constant*, and it reflects the unchanging relationship between rate and C. Thus,

$$K = \frac{\text{rate}}{C} \qquad \text{[Eq. 4]}$$

Double the concentration, and the rate will double, and K will be unchanged. Halve the concentration, and the rate will be halved and, K will be unchanged. The units of K can be found by substituting the appropriate units for rate and C:

$$K = \frac{\text{rate (concentration/time)}}{\text{C (concentration)}} = \frac{1}{\text{time}} \text{ OR } t^{-1} \qquad \text{[Eq. 5]}$$

The units of a first-order rate constant are always reciprocal time. The meaning of K is described later; however, every compound has a specific average value and range of values for K in a given subject group (or animal species). The problem with the previous rate equations is that they relate concentration and rate rather than what is more useful, concentration and time. To obtain that more useful relationship, it is necessary to integrate equation 3 over the interval, time zero to infinity. Performing that operation gives

$$\int_0^\infty \text{rate} = -\int_0^\infty K \cdot C \cdot dt \qquad \text{[Eq. 6]}$$

$$C = C^0 \cdot e^{-K \cdot t} \qquad \text{[Eq. 7]}$$

Equation 7 is a classic relationship describing an exponential process, in this case a declining exponential. In contrast, microbiologic growth can be described by an identical but positive exponential equation. Blood concentration, C, at any time after an IV bolus dose is equal to an initial (at time zero) blood concentration, C^0, which is multiplied by some number whose value is declining over time. That number is given by the base, e, raised to a negative exponent, which is formed by the product of the first-order elimination rate constant, K, and time (t), after the IV bolus injection. Because the product of K and t increases as time goes on, the base raised to an increasing negative number results in smaller and smaller values, which, when multiplied by C^0, gives decreasing numerical values for blood concentration. Blood concentration is declining exponentially according to the value of K: The larger the value of K, the more rapidly the compound is lost from the body; the smaller the value of K, the slower it is lost from the body. A plot of blood concentration versus time on a linear (Cartesian coordinate) graphic scale results in a curved line whose concentration values decline exponentially. The initial time zero concentration, C^0, is the result of the IV dose being distributed into some apparent space or volume, generally referred to as the *apparent volume of distribution*, V_d. This somewhat confusing term is discussed in Distribution.

Scientists go through almost any contortion to be able to express data in the form of a straight line (which is easy to analyze). It is not surprising, therefore, that equation 7 is most often presented in one of the two following transformations, which are in the form of straight-line equations.

$$\ln C = \ln C^0 - K \cdot t \qquad \text{[Eq. 8]}$$

Equation 8 is obtained by taking the natural logarithm (ln; base e) of both sides of equation 7. Using the more familiar and common logarithmic form (log; base 10), one obtains the following useful equation:

$$\begin{array}{ccccccc} \log C & = & \log C^0 & - & \dfrac{K}{2.3} & \cdot & t \\ \Downarrow & & \Downarrow & & \Downarrow & & \Downarrow \\ Y & = & b & - & m & \cdot & X \end{array} \qquad \text{[Eq. 9]}$$

Thus, as long as all of the assumptions are correct, a plot of log C versus time results in a log-linear straight line whose slope (m) is given by –K/2.3 and whose y-intercept (b) is equal to the time zero concentration, C^0. In contrast to a graphic plot on linear axes, which results in an exponentially curved line, a plot of the same data on a semilogarithmic scale results in a straight line. The latter has far more useful information compared to the linear scale plot. The data are either transformed to logarithmic values and those plotted on a linear scale or, and the more likely method, semilogarithmic graph paper is used in which the numerical values for concentrations are placed onto the logarithmic y-axis. In fact, what is most often done today is to form a data set in a software program (such as EXCEL), and the data are plotted according to the method of choice. The latter approach often gives the choice of selecting between a linear scale or a logarithmic scale on the y-axis.

Semilogarithmic graph paper has also been called *ratio* paper. Semilogarithmic scales are best suited to the plotting of data that

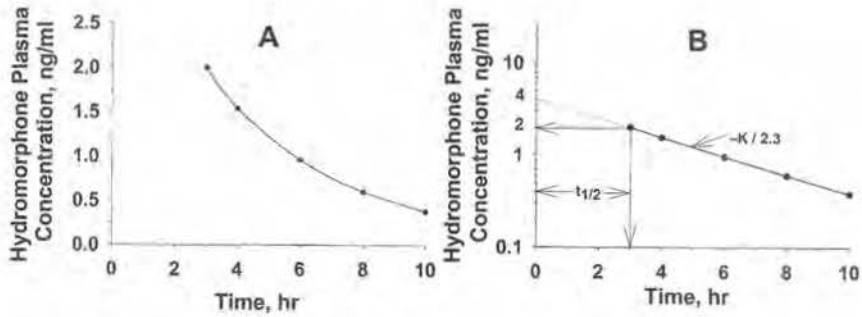


Figure 3. A: Plasma concentration-time profile after an intravenous bolus dose of hydromorphone to normal human subjects. The data are plotted on linear (cartesian) scales, and the resulting curvilinearity is an indication of an exponential decline in concentrations with time. **B:** Graph of the same data illustrated in **(A)** but plotted on a semilogarithmic scale. The data are represented by a single log-linear relationship, consistent with an exponential (i.e., first-order) process to describe drug loss from the body. The initial (hypothetical) time zero concentration of this drug, based on extrapolation of the line back to the y-axis, is approximately 4 ng/ml. The slope of the line is given by –K/2.3. The two arrows indicate the time needed for the hypothetical initial concentration (4 ng/ml) to decline by 50% to a value of 2 mg/L. The corresponding intercept on the x-axis (approximately 3 hours) represents the half-life ($t_{1/2}$) of the drug. Any other pair of concentration values in the ratio of 2:1 gives the same value for half-life. Not all of the data have been replotted for this illustration, as discussed later (see Fig. 12). (Data recovered and replotted from Parab PV, Ritschel WA, Coyle DE, et al. Pharmacokinetics of hydromorphone after intravenous, peroral and rectal administration to human subjects. *Biopharm Drug Dispos* 1988;9:187–199. From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

change in an exponential fashion, such as the concentration-time data obtained in pharmacokinetic investigations. The term *ratio* was used to indicate that numbers in the same ratio to each other are the same distance apart on the logarithmic scale. Thus, the following pairs of numbers, which are in the same ratio (of 5:1), are separated by the same distance: 10/2, 100/20, 600/120, and so forth. Similarly, numbers that represent the same percentage increase or decrease are separated by the same distance on the logarithmic scale. The following pairs of numbers, which represent a 10% decrease, are the same distance apart: 100/90, 10/9, and 20/18. Another characteristic of semilog scales is the number of *cycles* that they represent. Each cycle is an order of magnitude (or a factor) of ten. Two-cycle log axis encompasses a 100-fold range (or two orders of magnitude of ten) from, for example, 1 to 10 to 100 or 0.01 to 0.1 to 1.0.

K, the apparent overall first-order elimination rate constant, represents a fractional rate of loss of drug from the body. Thus, for example, if a drug has a value of K of 0.1 $hour^{-1}$ (or 0.1/hour), it is *approximately* correct to say that at the end of any hour *approximately* 10% of drug that was there at the beginning of the hour has now been eliminated. For example, at time zero after giving an IV bolus dose of drug the plasma concentration is 100 mg/L. One hour later, the body has lost *approximately* 10% of 100 mg/L, giving a concentration of 90 mg/L at 1 hour. One hour after that (at 2 hours), another 10% has been lost and the plasma concentration at 2 hours is now *approximately* 81 mg/L. At 3 hours, the concentration is *approximately* 73 mg/L; at 4 hours, *approximately* 67 mg/L; and so forth. If the rate constant had a value of 0.05 $year^{-1}$ (0.05/year), *approximately* 5% of the drug present at the beginning of the year would be lost by the end of that year. There is a more useful and simpler way to express drug loss from the body and it involves the idea of *half-life*, $t_{1/2}$; a term commonly used in many disciplines (i.e., radioactive decay in physics and *in vitro* degradation reactions in chemistry).

Figure 3 illustrates two plasma concentration-time graphs of hydromorphone after IV bolus dosing to a group of normal human subjects (1). For a reason that is explained in Disposition: Models, not all of the data have been replotted in these graphs. The graph on the left (Fig. 3A) is plotted on linear (cartesian) coordinate axes. The data and the corresponding line are curvilinear, consistent with exponential decline in concentration with time. In contrast, the graph on the right (Fig. 3B) is a plot of the same data on semilog axes. This graph, unlike the one using a linear scale, contains useful information and is the starting point for any pharmacokinetic data analysis. It is absolutely essential to plot a data set before beginning any analysis to visualize the behavior of the drug and the system. There are several points that need to be made about Figure 3B. The data are represented by a single, log-linear line, which is expected for any simple (i.e., single) exponential, first-order kinetic process. There is no curvilinearity in the graph for the data plotted, which is consistent with the assumption of instantaneous distribution from the blood to all body tissues (i.e., a one-compartment model). The slope of the line is given by –K/2.3, from which one can estimate the value for the apparent overall first-order elimination rate constant, K. The intercept on the y-axis represents the (hypothetical) time zero plasma concentration, which is never actually measured (it is always estimated by extrapolation of the straight line back to the y-axis).

An important concept illustrated on the semilog graph is the useful and practical idea of a $t_{1/2}$. Unlike a value for K, it is easy to understand the concept of a $t_{1/2}$. By definition, $t_{1/2}$ is the time necessary for any given value of concentration to decline by one-half or by 50%. This is illustrated in Figure 3B by the horizontal arrow indicating where a plasma concentration value of 2 ng/ml is seen on the line and the vertical arrow that indicates the time at which that concentration is achieved. Because the drug level declined 50% (4 to 2 ng/ml) at the 3-hour time point, 3 hours is the value for $t_{1/2}$ for hydromorphone. However, any other pair of concentration values in the ratio of 2:1 could have been used (e.g., 2 to 1 ng/ml) and the same value for $t_{1/2}$ would have been obtained.

Although it does not have meaning at this point, it is good practice to refer to $t_{1/2}$ as the *terminal* $t_{1/2}$. In fact, although a variety of different words are used to qualify the term $t_{1/2}$, including *biologic*, *elimination*, and *disposition*, the one term that is always correct is terminal $t_{1/2}$. *Biologic* $t_{1/2}$ is not a good expression because it can be confused with the decline in pharmacody-

namic activity rather than characterization of drug loss from the body. *Elimination* $t_{1/2}$, although commonly used, is only correct when dealing with a one-compartment model, as discussed later. *Disposition* $t_{1/2}$ is often a correct usage; however, it may be incorrect when characterizing plasma concentration-time data after nonvascular dosing (e.g., oral route).

$t_{1/2}$ and K are related. Taking equation 9 and specifying that C is one-half of the starting value, C^0 (which by definition occurs after one $t_{1/2}$) and rearranging,

$$\log C^0 - \log C = \frac{K \cdot t}{2.3}$$

$$\log C^0 - \log[0.5C^0] = \frac{K \cdot t_{1/2}}{2.3}$$

$$\log\left[\frac{C^0}{0.5C^0}\right] = \frac{K \cdot t_{1/2}}{2.3} \qquad \text{[Eq. 10]}$$

$$\log[2] = \frac{K \cdot t_{1/2}}{2.3}$$

$$t_{1/2} = \frac{[0.3010] \cdot [2.3]}{K}$$

$$t_{1/2} = \frac{0.693}{K}$$

$t_{1/2}$ and K are inversely related; the greater the K, the smaller the $t_{1/2}$, and the smaller the K, the greater the $t_{1/2}$. Furthermore, notice that $t_{1/2}$ (and K) is *independent* of dose or plasma concentration. This is what is meant by dose-*independent* pharmacokinetics; the parameters describing the disposition of a drug are *not* dependent on dose (this statement also applies to other pharmacokinetic parameters, such as apparent volume of distribution and clearance). In the example cited in Figure 3B, the terminal $t_{1/2}$ value of approximately 3 hours for hydromorphone has a terminal rate constant of 0.693/3 hours, or 0.231 $hour^{-1}$.

In contrast to the parameters being *independent* of dose, plasma concentration does *depend* on dose; double the dose and plasma concentrations will double, with no change in $t_{1/2}$. These two statements are illustrated in Figure 4. In Figure 4A, three different IV bolus doses have been administered: dose D, dose 2D, and dose 5D. A plot of the concentration-time data on semilog axes gives lines that are parallel to each other, because there is only one value for K or $t_{1/2}$ for that drug. However, the lines intercept the y-axis giving time zero concentrations in the same ratio as the doses: concentration of one unit, concentration of two units, and concentration of five units. As noted above, and as shown in Figure 4B, a plot of $t_{1/2}$ (or K) as a function of dose gives a flat line; there is no dependence of $t_{1/2}$ on dose.

Whereas $t_{1/2}$ is *independent* of dose, the resulting plasma concentrations (as noted in Fig. 4A) are directly *dependent* on dose, as shown in Figure 5A. This is often referred to as dose-proportionality. The idea illustrated in Figure 4A can also be represented by the principle of *superposition*, which states that because doubling the dose results in doubling of plasma concentration, a plot of concentration/dose should give rise to one line that represents the superposition of all concentration and dose pairs. This principle is illustrated in Figure 5B.

One of the most important aspects of first-order or linear kinetics is that everything about the disposition or behavior of a drug is predictable, as can be surmised from the relationships illustrated in Figures 4 and 5. Because parameters remain constant with dose and because concentrations are directly dependent on dose, one is able to predict a concentration-time profile for any given IV dose. In such a linear system, doubling the input results in an exact doubling of the output (e.g., double the dose, double the plasma concentration). When first-order kinetic principles do not apply, all predictability is gone and one faces significant problems in, for example, drug dosing and extrapolating from a subtoxic dose to a toxic dose.

Non–First-Order (Nonlinear) Kinetic Processes

Many physical and biologic processes cannot be simply characterized by first-order kinetic or linear systems behavior. In fact, the world is a nonlinear one in which doubling the input often results in something other than a doubling of the output (less than or more than double the output). The assumption is often made that the system (e.g., the body) behaves in a linear way, or at least that approximation is believed to be correct. In fact, it is true that many of the drugs and toxins that are dealt with behave in a linear manner, at least at medically relevant doses. But, this may not be a reasonable approximation for some doses or levels of exposure, especially at the high end of the range in which the toxicologist becomes involved. All pharmacokinetic processes (absorption, distribution, elimination) may exhibit nonlinear behavior, and there are drug and toxin examples of such behavior for each of those processes.

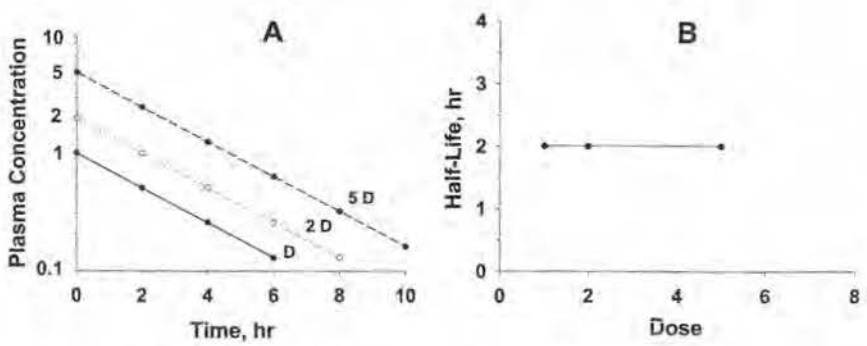


Figure 4. A: Hypothetical semilog plasma concentration-time plots for a drug given at increasing doses of D, 2D, and 5D. Note that the lines are parallel (same slope and, therefore, the same K and half-life), and the intercepts on the y-axis (initial time zero concentrations) are in the same ratio as the doses (1:2:5). These same ratios apply to concentrations resulting from those doses at any given time. **B:** The results of the data in **A** in terms of half-life and its relationship to dose are illustrated in this graph. Note that the half-life is *independent* of dose (or concentration). This behavior is referred to as *dose-independent* pharmacokinetics, which is a characteristic of first-order processes. (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

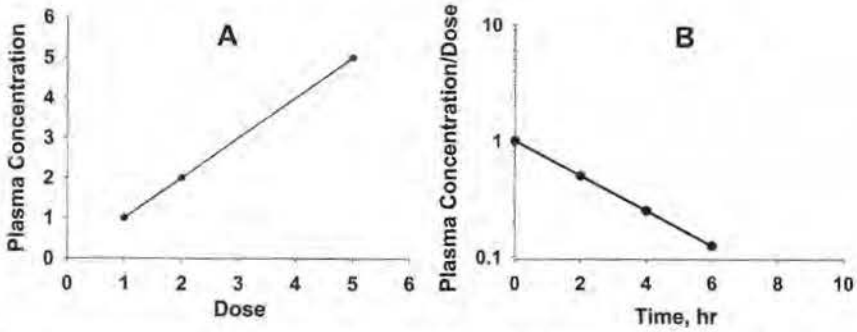


Figure 5. A: The relationship between plasma concentration and dose at any time after an IV bolus dose for the hypothetical drug illustrated in Figure 4A. The points noted are for doses D, 2D, and 5D, and the concentrations are for those seen at time zero. This behavior is often referred to as illustrating *dose-proportionality*. **B:** The concentrations resulting from any given dose are divided by that dose and plotted on semilog axes as a function of dose. This graph illustrates the principle of *superposition* as well as dose-proportionality. (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

The nonlinear behavior of interest for chemicals and drugs involves the output or elimination process, especially metabolism and urinary excretion. There are some, but few, examples of drugs or toxins that undergo non–first-order or nonlinear elimination. Dosing or exposure to such a compound results in plasma concentrations that exceed the ability of the eliminating organ to efficiently remove that substance. That is, the elimination process is *not able to keep up with* or is *swamped* by the amount of substance that is being presented to it for processing. The latter statement is in contrast with first-order kinetics in which there is a direct relationship between the amount of substance presented and the rate of its being processed (recall: rate ∝ concentration).

The most fundamental difference between first-order kinetics and non–first-order (nonlinear) kinetics is illustrated by the relationship between the rate of a given process (e.g., metabolism) and plasma concentration, the driving force for the process. The most useful relationship for the latter process is best expressed in the form of the classical enzyme kinetics equation of Michaelis and Menten. The Michaelis-Menten enzyme kinetic equation expresses the relationship between the rate of enzyme-catalyzed substrate metabolism to the concentration of substrate,

$$\text{rate (or, v)} = \frac{V_{max} \cdot C}{k_{mm} + C} \qquad \text{[Eq. 11]}$$

in which rate (or v for velocity) is a function of a maximal rate (V_{max}), plasma concentration (C), and the Michaelis constant k_{mm}.* The Michaelis constant is equal to the concentration associated with one-half the maximal rate, V_{max} (units of k_{mm} are those of concentration). Equation 11 is in the form of a hyperbola—a relationship commonly noted in biologic systems as a consequence of some nonlinear behavior (e.g., pharmacologic effect versus plasma concentration or receptor or protein binding as a function of concentration). The best way to analyze this relationship is to consider low and high plasma concentrations to simplify the equation by making appropriate approximations.

At low concentrations (i.e., $C << k_{mm}$), C can be ignored in the denominator of equation 11,

$$\text{rate (or, v)} = \frac{V_{max} \cdot C}{k_{mm} + C} \cong \frac{V_{max} \cdot C}{k_{mm}} = \left(\frac{V_{max}}{k_{mm}}\right) \cdot C \qquad \text{[Eq. 12]}$$

This approximation results in the relationship noted in equation 12, which indicates that at low concentrations, rate is directly proportional to concentration, as would occur for a first-order process. The ratio of the two constants, V_{max} to k_{mm}, is itself a constant, as it is in a first-order process. Thus, at low concentrations, the system behaves according to first-order kinetic principles. The ratio of V_{max} to k_{mm} is a first-order rate constant, and it has also been referred to as *intrinsic clearance*, as is discussed later in the Clearance section. The units of these two terms differ (time^{-1} for a first-order rate constant and volume/time for clearance).

In contrast, at higher concentrations (i.e., $C >> k_{mm}$), k_{mm} is ignored in the denominator of equation 11,

$$\text{rate (or, v)} = \frac{V_{max} \cdot C}{k_{mm} + C} \cong \frac{V_{max} \cdot C}{C} = V_{max} \qquad \text{[Eq. 13]}$$

This approximation results in the relationship shown in equation 13, which indicates that rate becomes a constant, no matter how much concentration increases (or, no matter how the dose increases). At the extreme, this would represent *zero-order kinetics*, but, with few exceptions, true zero-order behavior is rarely actually seen. Instead, *mixed kinetics* is more likely seen—behavior somewhere in between first-order and zero-order kinetics. In a zero-order kinetic process, the rate does not depend on concentration (which is raised to a power of zero, resulting in a constant). Rather, the rate depends on some other factor.

A comparison of this basic behavior (rate vs. concentration) for a linear first-order process and for a nonlinear (Michaelis-Menten) process is illustrated in Figure 6. The graph on the left (Fig. 6A) indicates a direct, linear relationship between rate and concentration for any compound that undergoes first-order elimination. The hypothetical graph shown is for ethanol metabolic rate in humans assuming that ethanol was metabolized according to a first-order process (i.e., using the ratio of V_{max} to k_{mm}, as noted in equation 12). The slope of the line is the first-order rate constant for metabolism or metabolic clearance, depending on units. The graph on the right (Fig. 6B) is a plot of ethanol metabolic rate versus ethanol plasma concentration in humans. This graph is a typical representation of nonlinear elimination, which is characterized by a hyperbolic Michaelis-Menten relationship. Notice that the rate is not directly proportional to concentration, except at low concentrations as shown in the inset graph (i.e., at concentrations much less than the k_{mm} value; in this case, approximately 0.06 g/L). The arrow along the x-axis points to the Michaelis constant (approximately 0.06 g/L), which corresponds to one-half V_{max} (approximately 4.5 g/hour, as shown on the y-axis; V_{max} is approximately 9 g/hour). Aver-

*The Michaelis constant is often given the symbol k_m, but it is easily confused with a rate constant, such as a first-order metabolic rate constant. To avoid that confusion, the symbol k_{mm} is used here.

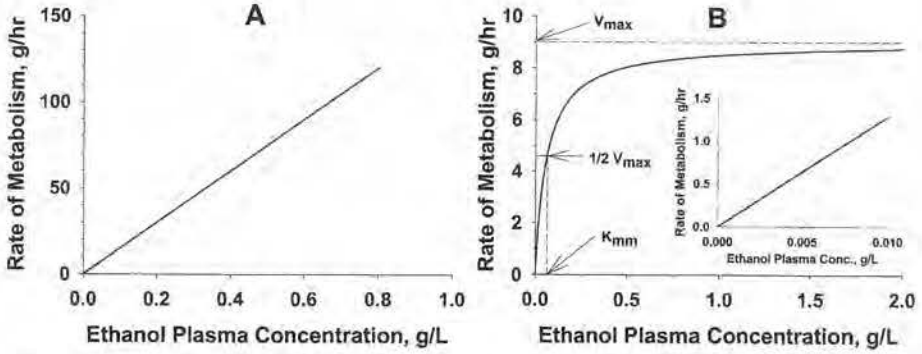


Figure 6. **A:** Hypothetical rate of ethanol metabolism as a function of plasma concentration if ethanol were eliminated by a first-order process. The direct, linear relationship is characteristic of first-order kinetics. The slope of the line is either a first-order rate constant of metabolism or metabolic clearance, depending on units. **B:** Rate of ethanol metabolism as a function of plasma concentration based on the average values of V_{max} (approximately 9 g/hour) and k_{mm} (approximately 0.06 g/L) in humans. The hyperbolic relationship is characteristic of nonlinear or Michaelis-Menten enzyme kinetics. The maximal rate, V_{max}, is the extrapolation on the y-axis of the asymptote of the line (as predicted by equation 13), and k_{mm} is the concentration value on the x-axis corresponding to one-half of V_{max}. Mixed order kinetics is observed over much of the concentration range. The inset graph illustrates the direct, linear relationship between rate and concentration at low concentrations of ethanol (as predicted by equation 12). That line is extended to higher concentrations, assuming first-order kinetics, in **(A)**. (From M. Mayersohn, *unpublished,* with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

age values in human subjects for V_{max} and k_{mm} have been used in generating the data for these plots.

The consequences of the rate versus concentration relationship for a nonlinear process are extremely important, and there are several significant clinical and toxicologic implications. At low concentrations ($C << k_{mm}$), in which first-order kinetics applies, the apparent elimination rate constant is a constant, such that as concentrations increase so do the corresponding rates, as noted on the left side of equation 14. In contrast, as concentrations increase ($C>>k_{mm}$), rate does not keep up with concentration and the value for K decreases, as noted on the right side of equation 14.

$$C \ll k_{mm}: \vec{K} = \frac{\text{rate}\uparrow}{C\uparrow} \qquad C \gg k_{mm}: K\downarrow = \frac{\overrightarrow{\text{rate}}}{C\uparrow} \qquad \text{[Eq. 14]}$$

If the value of K decreases as concentration (or dose) increases, then the $t_{1/2}$ increases. The $t_{1/2}$ is longest at the highest concentrations and then decreases in value as concentrations decrease with time until, finally, a constant terminal $t_{1/2}$ is seen at lower concentrations (i.e., $C << k_{mm}$).

The behavior just described is illustrated for ethanol in one human subject in Figure 7 (2) and for the solvent dioxane in rats in Figures 8 and 9 (3). The ethanol blood concentration-time data (2) shown in the large graph is plotted on a linear (y-axis) scale. Most of the data have the appearance of a straight line with curvature at later times when low concentrations are seen. This *hockey-stick* shape occurs when high concentrations exceed k_{mm} and the resulting rate of decline is approximately a constant (i.e., zero-order). This gives rise to a linear concentration-time relationship. At later times (low ethanol concentrations; $C << k_{mm}$), the line begins to curve, representing return to an exponential process. In contrast, the semilog plot shown in the inset graph has a line that is continually changing slope until it becomes approximately log-linear at later times (low concentrations; return to first-order kinetics).

The dioxane concentration-time data obtained in rats and shown in Figure 8 are a dramatic example of nonlinear elimination (3). The lowest intravenous dose (3 mg/kg) results in a log-linear decline in concentrations, whereas the two larger doses (100 and 1000 mg/kg) show dramatic curvilinearity, until the terminal log-linear phases are achieved. Notice that the ultimate terminal log-linear lines for all doses are parallel, as they must be for this type of saturable process. The inset graph plots plasma concentration divided by dose as a function of time for the data shown in the large graph. This type of plot illustrates whether the principle of superposition applies. If the lines superimpose at all doses (as noted in Fig. 5B), then first-order, linear kinetics apply. If this does not occur, then there is deviation from linearity and some non–first-order, nonlinear process(es) is being evidenced. The inset graph illustrates that

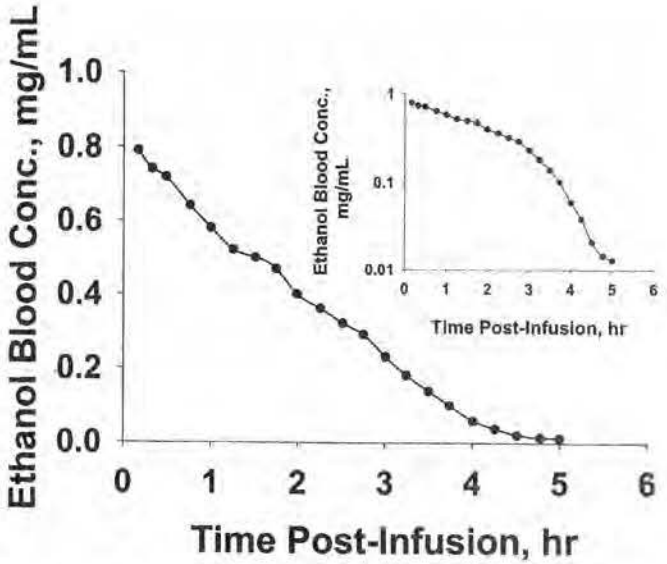


Figure 7. Ethanol blood concentrations as a function of time in one human subject given a 2-hour constant rate intravenous infusion of ethanol (720 ml of 8% v/v ethanol in normal saline). Only the postinfusion data are plotted (i.e., data after the end of the 2-hour infusion; first value deleted). Note that this is a linear scale, and a straight line is obtained until approximately 4 hours after the end of the infusion. The inset graph is a semilogarithmic plot of the same data. Note that a curvilinear line is seen whose slope changes with time until it becomes log-linear only at later times at low concentrations. (Based on data recovered from Wilkinson PK, Sedman AJ, Sakmar E, et al. Blood ethanol concentrations during and following constant-rate intravenous infusion of alcohol. *Clin Pharmacol Ther* 1976;19:213–223. From M. Mayersohn, *unpublished,* with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

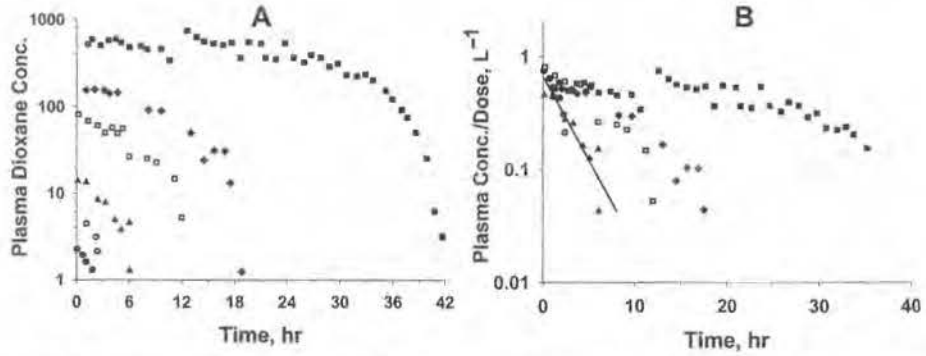


Figure 8. A: Semilogarithmic plot of dioxane plasma concentrations as a function of time after the administration of three different intravenous doses to rats. Note that the lowest dose (3 mg/kg) provides a log-linear straight line suggesting first-order kinetics. In contrast, the two higher doses (100 and 1000 mg/kg) result in a typical curvilinear relationship characteristic of a nonlinear saturable process. **B:** Plasma concentrations (for six different doses) divided by dose as a function of time. The principle of superposition (see Fig. 5B) predicts that the resulting data fall onto one line if disposition is described by first-order kinetics. The solid regression line shown represents data from the three smallest doses of dioxane (i.e., 3, 10, and 30 mg/kg). The principle of superposition is violated for all of the larger doses (i.e., 100, 300, and 1000 mg/kg), indicating that some nonlinear, non–first-order process is occurring. Dose key (mg/kg): 3 (●); 10 (○); 30 (▲); 100 (□); 300 (◆); 1000 (■). (Based on data recovered from Young JD, Braun WH, Gehring PJ. The dose-dependent fate of 1,4-dioxane in rats. *J Environ Pathol Toxicol* 1978;2:263–282. From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

linearity applies for the three lowest doses, as expressed by the solid linear regression line. For all other (larger) doses, however, it is clear that dioxane disposition is nonlinear.

The biologic implications of this nonlinear behavior can be appreciated from the graphs illustrated in Figure 9. The general shapes of the relationships shown apply to any first-order (dashed lines) and saturable nonlinear (solid lines) elimination processes; however, the graphs illustrate dioxane behavior in rats. Graph A is a plot of the initial *clearance* of dioxane based on parameter values reported in the literature (3). Because clearance is a measure of the efficiency of elimination (discussed under Clearance Concepts), efficiency decreases with increasing dose, unlike what would be found for a first-order process (dashed line). The apparent $t_{1/2}$ of dioxane is illustrated in graph B and, consistent with the idea of reduced efficiency of removal from the body, the compound stays in the body for a longer and longer time as the dose increases (unlike the behavior of a first-order process; dashed line). Graph C examines what is being referred to as *exposure* as a function of dose. Exposure is related to and often measured by the *area under the plasma concentration-time curve* (AUC), a useful concept that is discussed under Clearance Concepts. For a first-order kinetic process, the greater the dose, the greater the exposure (dashed line); however, exposure increases out of proportion to dose when elimination is saturable. A conse-

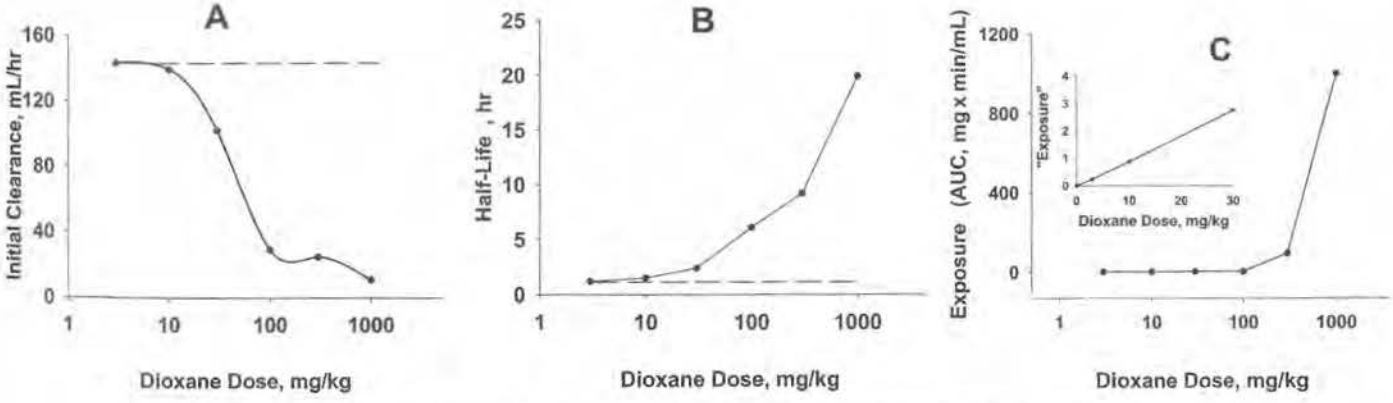


Figure 9. A: Initial clearance of dioxane as a function of IV dose given to rats. (The initial clearance was calculated using the parameter values provided in Young JD, Braun WH, Gehring PJ. The dose-dependent fate of 1,4-dioxane in rats. *J Environ Pathol Toxicol* 1978;2:263–282.) Note that clearance, an expression of efficiency of elimination (rate/concentration), decreases as the dose rises. In contrast, clearance is independent of dose for a first-order process (*dashed line*). **B:** Apparent *half-life* of dioxane as a function of IV dose given to rats. The value of *half-life* is based on the initial clearance and apparent volume of distribution. (From Young JD, Braun WH, Gehring PJ. The dose-dependent fate of 1,4-dioxane in rats. *J Environ Pathol Toxicol* 1978;2:263–282, with permission.) Note that *half-life* increases as dose increases. In contrast, half-life is independent of dose for a first-order process (*dashed line*). **C:** *Exposure* to dioxane as a function of IV dose given to rats. *Exposure* is measured as the total area under the dioxane plasma concentration-time curve for each dose. Note that *exposure* increases out of proportion to dose, whereas a linear relationship is expected for a first-order process (*dashed line*). (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

quence of this behavior is that plasma concentrations on multiple dosing or continued exposure, increase out of proportion to dose (a direct, linear relationship is expected for a first-order process). Furthermore, and of considerable significance, one would expect an abrupt change in the response (or toxicity)-dose relationship at doses above saturation. The graphs illustrated in Figure 9, each representing an important clinical or toxicologic biologic measure, indicate that for a saturable elimination process one does not expect a proportional and predictable relationship with dose. This is in dramatic contrast with a linear, first-order process.

Substrate saturation of enzymatic activity occurs as the result of one of the following conditions: the substrate k_{mm} is small and smaller than plasma concentrations obtained from typical dosing or exposure (e.g., phenytoin); the substrate is ingested in large doses, resulting in plasma concentrations that exceed k_{mm} (e.g., ethanol, salicylates). The latter possibility is especially relevant to the ingestion of a drug overdose or environmental over-exposure and, therefore, is a particularly important consideration in medical toxicology.

There are numerous other mechanisms that may be responsible for nonlinear metabolic behavior, including depletion of metabolic cofactors (e.g., acetaminophen metabolism), reduction in liver blood flow, enzyme induction or inhibition, and substrate-induced hepatic toxicity affecting the previous parameters. Several of these mechanisms suggest that a more inclusive definition of linearity would consider temporal effects. Thus, a *linear system* is one that is both dose and time invariant; the output (or response) is directly related to dose (input) and that relationship remains unchanged at all times. A *nonlinear system* is one that violates either dose or time invariance or both.

Although hepatic metabolism has received the greatest attention with respect to nonlinearity, any route of elimination may undergo nonlinear behavior. For example, the renal excretion of compounds that undergo active tubular secretion (e.g., penicillin) or reabsorption (e.g., nutrients as vitamins, monosaccharides, amino acids) involve transport systems that may be saturated by substrate or inhibited by structurally related compounds. The Michaelis-Menten relationship noted previously applies in an identical fashion to these saturable transport processes, as discussed under Clearance Concepts. Other mechanisms that may result in nonlinear renal excretion include alterations in urine pH (e.g., phencyclidine, methamphetamine) and urine flow (e.g., theophylline) as well as substrate-induced renal toxicity affecting the previous parameters.

DISPOSITION: MODELS

One of the most important functions of any scientific discipline is to make quantitative predictions. This is certainly true in pharmacokinetics, in which one might ask, How does a change in body function or dose affect drug disposition and response? A fairly general approach that is used to make such predictions is through the use of *models*. A model is a hypothetical construct that appears to work in a way similar to that of the system under study—in this case, the human body. A model (any model) only does so, of course, in a limited way. In fact, it is important to bear in mind that "all models are wrong; some models are useful." Useful is often good enough. The human biologic model, which gives rise to a corresponding mathematical model, is usually an abstract notion of how the system is conceived to behave. To create such a model it is necessary to make numerous simplifying assumptions; after all, this is a model and not a duplicate of the system. The correctness of the model predictions is only as good as the quality of the assumptions that have gone into creating the model.

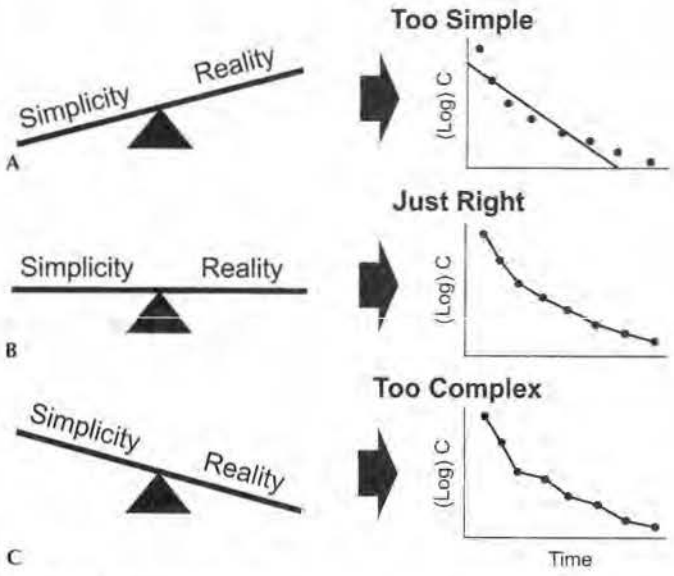


Figure 10. Illustration of the balance needed between simplicity of the model and reality as judged by the plasma concentration-time data. **A:** The model is too simple, as the model-predicted line provides a poor depiction of the actual data. **B:** A reasonable model results in an excellent model-predicted line as it provides a good description of the actual data. A good balance between simplicity and reality is achieved. **C:** The model is unnecessarily complex, resulting in a complicated model equation that exactly connects all of the data points. (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

All models must balance two opposing needs: simplicity and reality. The model must be simple or it cannot be used in a practical way; we must be able to understand it and write sufficiently simple equations to describe it. The K.I.S.S. principle (*k*eep *i*t *s*imple, *s*tupid) or the rule of parsimony, embodied in the older concept referred to as *Ockham's razor*,* states that the model should be no more complicated than it need be to meet its function, in this case, describing the data. However, if the model is too simple, it does not explain reality (i.e., the data). The simplicity of a model must be balanced by the need of the model to describe the data: If it does not do so, it is useless for predictive purposes. It must also be emphasized, however, that a model can never be any better than the quality of the experimental data that goes into its creation; the experiment and the quality of the data need to be emphasized. In practice, the *best* model is chosen on the basis of statistical comparisons, a discussion of which is beyond the scope of this chapter.

Figure 10 illustrates this idea of balance between simplicity and reality. The model-predicted line in Figure 10A does a poor job in describing the plasma concentration-time data. In this instance the model is too simple, as it does not reflect reality; simplicity is over-weighted. In contrast, the model-predicted line in Figure 10B does a nice job in describing the data. There is a good balance here between simplicity and reality. An unnecessarily complex model and complicated equation results in the predicted line shown in Figure 10C; simplicity is underweighted.

*Ockham's razor, after William of Ockham (b. 1280 England). "Entia non sunt multiplicanda praeter necessitate"; entities should not be multiplied unnecessarily. Thus, simpler is better. When competing theories lead to the same result, the least complicated is preferred. The simplest most parsimonious explanation for a phenomenon is likely to be the correct one. When seeking to explain a phenomenon, start with the simplest theory. This is opposite a "Rube Goldberg," which uses the most complex methods for completing a task. The *razor* probably represents cutting out the unnecessary details. Einstein takes it one step further: "Everything should be made as simple as possible, but not simpler."

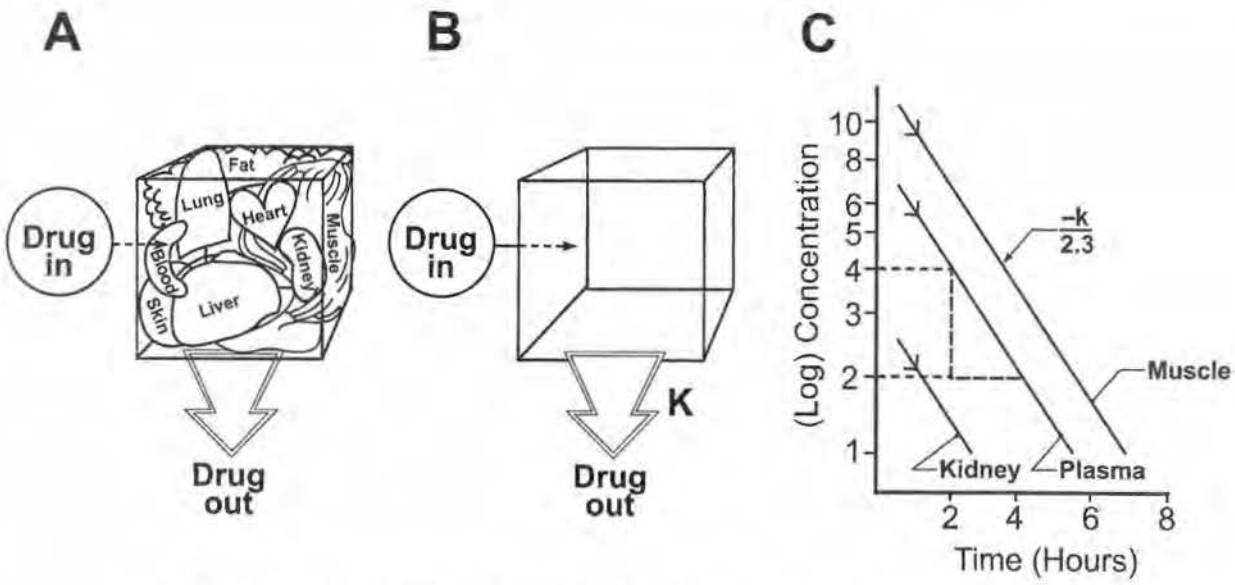


Figure 11. **A:** A one-compartment open model illustrated from an *anatomic* view. All body tissues and organs are *lumped* together in this single *body* box. Blood connects to all regions. **B:** The one-compartment open model as it is generally presented. K is the apparent overall first-order terminal rate constant. **C:** Semilog concentrations of the drug measured in several tissues after an IV bolus dose. Note that the lines are log-linear at all times after dosing (instantaneous distribution), they are parallel (kinetic homogeneity), but they do not superimpose (lack of concentrational homogeneity). (From Mayersohn M. Toxicokinetics: Measurement of disposition half-life, clearance and residence times. In: Maines M, ed. *Current protocols in toxicology*. New York: John Wiley and Sons, 2000:5.3.3, with permission of Saguaro Technical Press, Inc, 2002, Tucson, AZ.)

Although several approaches are commonly used to analyze data to obtain pharmacokinetic information about a substance, a classic method of data analysis has been referred to as *compartmental modeling*. This approach to modeling visualizes one or more compartments or regions connected together to represent (but are not equivalent to) body tissues. These models are strictly hypothetical and seldom bear any resemblance to physiologic reality, in the sense that real body organs, tissues, or fluids are not actually represented. In contrast, a nonabstract, physiologically meaningful approach exists and is referred to as *physiologically based pharmacokinetic modeling*.

A *compartment* represents body tissues or organs that are lumped together because they behave in the same manner with respect to drug distribution. Thus, body tissues could be lumped together and distinguished from each other as a result of blood flow (well- or poorly perfused) or because they are lean tissues or because they are fatty tissues. The simplest possible model, the *one-compartment open model*, rests on the assumption that all body regions behave the same with regard to drug distribution and this occurs as a result of *instantaneous distribution* to all body regions. Administer an IV bolus dose and the drug instantaneously distributes from the blood to all tissues in the body. Of course, this cannot happen; drug must move at a finite rate from the blood to body tissues, but if this occurs so fast that distribution cannot be accurately measured, then, for practical purposes, distribution is instantaneous. This model and the concentration-time data that it would reflect are illustrated in Figure 11. The data that give rise to this simple model are plotted on semilog axes in Figure 11C. Because the data can be described by a log-linear line, elimination occurs according to first-order kinetics. Because the line is uniformly log-linear at all times (essentially going back to the y-axis), distribution from the blood to all tissues must have occurred rapidly (instantaneously). At least there are no sufficiently early samples taken soon after the IV dose to suggest otherwise. This log-linear line can be described by a single exponential function (i.e., $C = C^0 \cdot e^{-K \cdot t}$) as a result of first-order elimination kinetics and because of instantaneous distribution. Note that the concentration-time lines for different tissues are parallel, indicating that all tissues behave the same kinetically (i.e., *kinetic homogeneity*). The slopes of these lines are identical, and, therefore, values for K and $t_{1/2}$ are the same; there is only one $t_{1/2}$ value for the drug in the body. However, the lines are *not* superimposable. The latter, indicating a lack of concentrational homogeneity, is to be expected as a result of differences in drug binding to different tissues. In the instance shown, muscle tissue, which has higher concentrations than plasma, must bind the drug more than plasma proteins. Plasma concentrations are greater than those in the kidney, suggesting that plasma protein binding must be greater than binding to kidney tissue. This relative ranking of concentrations for the tissues noted is arbitrary and should not be generalized. It is important to recognize that in virtually all experiments it is the *total* concentration of drug that is assayed (i.e., bound and unbound) and plotted. As noted later, the *unbound* concentrations are expected to be identical in all tissues.

The hydromorphone data illustrated in Figure 3B would be interpreted as reflecting first-order kinetics and a one-compartment model, at least for the data plotted. Of course, it is not known what happens before the 3-hour sample. Actually, that is not true; the author of this chapter intentionally deleted the concentration values before 3 hours to illustrate the behavior that was discussed at that point. The complete data set, shown in Figure 12, now indicates a concentration-time curve not consistent with a one-compartment model; the data are behaving in a more complex manner. The display of data, such as that noted in Figure 12, is inconsistent with instantaneous distribution and, therefore, cannot be described by a simple one-compartment model. The initial rapid decline in plasma concentrations that occurs during the first 1 to 2 hours after dosing may be explained by the drug distributing out of the bloodstream and diffusing into other tissues of the body. This movement, unlike the idea of instantaneous distribution, occurs at a measurable rate. This early phase is sometimes referred to as the *distribution phase*, but it is important to keep in mind that elimination also occurs during this phase as

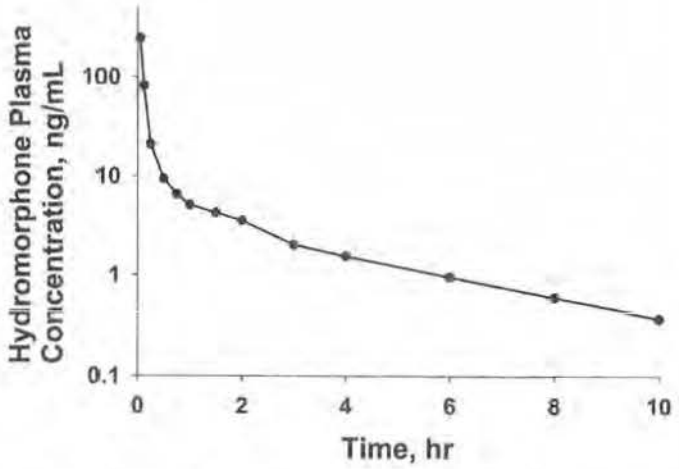


Figure 12. Hydromorphone plasma concentration-time data after an intravenous bolus dose to normal human subjects. The entire data set, which is plotted here, was presented as truncated data shown in Figure 3. The entire data set indicates that drug disposition can be described by a multi-compartment model, rather than by a one-compartment model suggested by the truncated data. Because the terminal data are the same for both plots, the terminal half-life is identical whether all of the data are plotted. (Data recovered and replotted from Parab PV, Ritschel WA, Coyle DE, et al. Pharmacokinetics of hydromorphone after intravenous, peroral and rectal administration to human subjects. *Biopharm Drug Dispos* 1988;9:187–199. From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

well as later times. Once distribution is complete, when there is a type of equilibrium in concentrations between the blood and all other tissues, concentrations in plasma (as well as all other tissues) decline more slowly and these data constitute the *terminal phase*. The latter is sometimes referred to as the elimination phase, but this is not a correct term because the slope of the terminal data depends as much on distribution as it does on elimination. The term noted previously, terminal rate constant or terminal $t_{1/2}$, now has some meaning, as it really does not apply to a one-compartment model (because there is only one phase).

There is need to apply a more complex model, to explain the behavior of the data. Such models require conceiving of the body to be made up of more than one compartment. These *multicompartmental* models require additional compartments consistent with the behavior of the data (e.g., two- or three-compartments). The ultimate selection of the model depends on a statistical comparison of possible choices based on nonlinear regression analysis of the data. Numerous software programs perform the fitting of the data necessary to choose the best model (e.g., WinNonlin, SAAM II, MatLab), but such a discussion is beyond this presentation. A good introduction to nonlinear regression is presented by Motulsky and Ransnas (4).

Reliable parameter values to describe disposition of a drug and the quality of the resulting model depends on experimental design issues, especially analytical parameters (sensitivity, selectivity, reproducibility); frequency; number of samples; and duration of sampling. There is nothing arbitrary about the sampling scheme; it must be designed in accordance with what is known about the disposition of the drug to optimize information about disposition.

The hydromorphone data in Figure 12 suggest that the disposition of the drug can be described by multicompartmental behavior and by, at least, a two-compartment model. A two-compartment (open) model is depicted in Figure 13. Those organs and tissues that receive the drug rapidly are lumped together (*A*, on the left) to form one region or compartment. In this instance those organs include, in addition to blood, the heart, lung, kidney, and liver. In contrast, those regions to which the drug distributes slowly are also lumped together to form another region or compartment (*A*, on the right). The regions depicted are (arbitrarily) the skin, muscle, and fat. As noted in the middle figure, compartment 1 or the *central compartment* is made up of those tissues that receive the drug rapidly. In contrast, the attached compartment 2 or *peripheral compartment* contains tissues that receive drug at a measurable rate. Drug is eliminated from compartment 1 (which contains the major organs of elimination, liver and kidney). Connecting the two compartments are two first-order *micro-rate constants*.

The relationship that is used to describe this profile is in the form of a multiexponential equation: one exponent for each compartment, after IV bolus dosing. The two most commonly used expressions are

$$C = A \cdot e^{-\alpha \cdot t} + B \cdot e^{-\beta \cdot t} \text{ OR } C = A_1 \cdot e^{-\lambda_1 \cdot t} + A_2 \cdot e^{-\lambda_2 \cdot t} \quad \text{[Eq. 15]}$$

The rate constants (α and β or λ_1 and λ_2), which are first-order, have units of reciprocal time. These rate constants are often referred to as *hybrid rate constants*, because they depend on all of the other micro-rate constants in the model, as noted in Figure 13. The terminal $t_{1/2}$ and rate constant, which has a number of symbols (K, β, λ_N, or λ_Z), is as much affected by distribution as elimination of the drug. The coefficients (A and B or A_1 and A_2), which represent intercepts on the y-axis, have units of concentration.

Figure 13C presents a semilog plot of concentrations in plasma and in two other tissues, one in compartment 1 (kidney) and the other in compartment 2 (muscle), as a function of time after an IV bolus dose of drug. The curvilinearity noted in the plasma data is an indication of the need to describe the data according to multicompartmental behavior and, in this instance, by a two-compartment model. The tissues, which are in rapid equilibrium with the blood (and are present in compartment 1), such as the kidney, have a concentration-time curve identical with that of plasma. In contrast, concentrations initially increase in those tissues that receive the drug at a measurable rate (and are present in compartment 2), such as the muscle tissue, and then decline once a type of equilibrium is achieved with plasma concentration. Once the *post–distributive phase* is reached, concentrations in all tissues decline in parallel according to the terminal $t_{1/2}$. However, as noted previously, tissue concentrations do not superimpose due to differences in drug binding to those tissues.

Other, more complex multicompartment models may be necessary to describe the disposition of certain compounds. The necessity to use such models is a consequence of the distribution properties of those compounds. Thus, in addition to its distribution to two other lumped regions, a third compartment may be needed if a tissue, such as adipose, slowly accumulates a lipid-soluble compound. These models are always presented as *mammillary models*, meaning that all compartments feed off or are connected to the central compartment. Furthermore, it has been assumed that all elimination of drug occurs from the central compartment. This may not be the case, for example, if drug is broken down chemically or enzymatically in a tissue that forms part of the peripheral compartment. Such complications have been intentionally avoided here.

Plasma concentration-time data may be analyzed with use of compartmental models, as previously noted. This *parametric* approach requires fitting the data to the best possible model, from which the parameters of the model equation are obtained. Further treatment of those parameters permits the calculation of all disposition characteristics of the drug under study. In contrast, a *noncompartmental* or *nonparametric* approach can also be applied to the same plasma concentration-time data set. In this

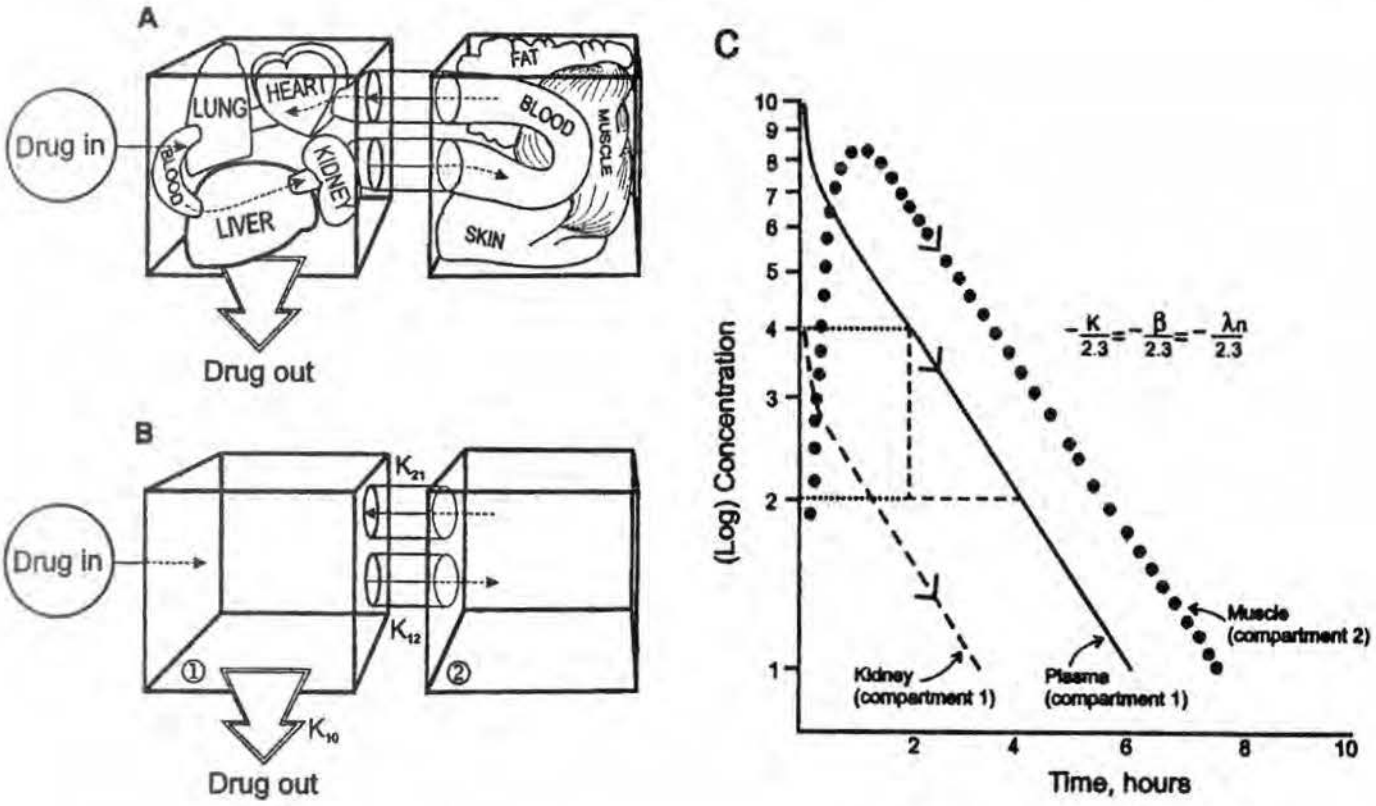


Figure 13. A: An *anatomic* view of a two-compartment open model. Organs and tissues that rapidly receive drug are lumped together in one compartment (*left*), whereas other regions that receive the drug more slowly due to a measurable distribution process are lumped together to form another compartment (*right*). **B:** A conventional scheme used to present a two-compartment open model. Drug enters into the first or central compartment where there is rapid equilibration with blood. Drug is eliminated from this compartment by a first-order rate constant (noted as k_{10} or k_{el}). The second or peripheral compartment into which drug distributes from blood at a measurable rate is connected to the first compartment by first-order micro-rate constants, k_{12} and k_{21}. **C:** The (log) concentration-time, which leads to the necessity for using a multi-compartment model, in this instance, a two-compartment model. Drug has been given as an intravenous bolus. Note that the plasma concentration-time is curvilinear, denoting multi-compartmental behavior. Other tissues associated with the plasma or compartment 1 (e.g., kidney) have lines parallel with the plasma line at all times. Regions contained in compartment 2 (e.g., muscle) have a rising (due to distribution) and then declining concentration-time profile. All of the terminal lines become parallel, giving a single terminal rate constant and half-life, but the concentrations do not superimpose (due to differences in drug binding). The terminal (hybrid) rate constant has a number of symbols, all having the same meaning: K, β, λ_n, or λ_z. (From Mayersohn M. Toxicokinetics: Measurement of disposition half-life, clearance and residence times. In: Maines M, ed. *Current protocols in toxicology*. New York: John Wiley and Sons, 2000:5.35, with permission of Saguaro Technical Press, Inc, 2002, Tucson, AZ.)

instance, however, it is not necessary to fit the data according to a compartmental model, but rather the useful parameters describing the disposition properties of the drug can be obtained from analysis of the terminal data in conjunction with area analyses. Both approaches provide virtually equivalent parameter values. The disposition parameters of drugs that are of greatest interest are terminal $t_{1/2}$ and rate constant, apparent volume of distribution, and clearance. Other parameters, however, may also be determined such as mean residence time, steady state volume of distribution, and others. These are noted where appropriate. The general type of analysis that may be applied to the curves concerned with here has been given the acronym SHAM, which stands for *s*lope, *h*eight, *a*rea, and *m*oment (5). Consider a plasma concentration-time curve: *slope* gives an estimate of rate constant and $t_{1/2}$; *height* is related to apparent volumes; *area* gives an estimate of exposure from which clearance is calculated; *moments* give rise to residence times. Although many of these calculations are cited later, Table 1 compares the compartmental and noncompartmental approaches for estimation of $t_{1/2}$, apparent volume, and clearance after an IV bolus dose.

Although the previous two methods of analysis are commonly used in characterizing drug disposition, and they are practical methods of data calculation, they are sometimes criticized on the basis of lack of physiologic reality, a charge especially levied against the compartmental approach. In stark contrast to these methods of analysis is an approach referred to as *physiologically based pharmacokinetic models*. As its name implies, it is an attempt to ground the analysis in physiologic reality, and, as all methods of analysis, it has advantages and disadvantages. The prime advantage to this model is that disposition of a drug or chemical is based on real measurements (e.g., concentrations in numerous tissues with time, tissue weights, tissue blood flows, and so forth), as depicted in Figure 14. Each *compartment* is actually a real body organ, tissue, or region that can be removed, weighed, and drug or chemical content determined by assay. Connecting each of these real physiologic areas are real, measurable blood flows (indicated by the arrows), not artificial

TABLE 1. Comparison of compartmental and noncompartmental determination of parameters of disposition

Parameter	Compartmental analysis	Noncompartmental analysis
Half-life, $t_{1/2}$:	From curve fitting: $C = A_1 \cdot e^{-\lambda_1 \cdot t} + A_2 \cdot e^{-\lambda_2 \cdot t}$	From the terminal line:
	$t_{1/2} = \frac{0.693}{\lambda_2}$	$t_{1/2} = \frac{0.693}{\lambda_2}$
Apparent volume, V_d:	From curve fitting: $V_d = \frac{\text{IV dose}}{\lambda_2 \cdot \sum_{i=1}^{2} \frac{A_i}{\lambda_i}}$	From terminal line and $(AUC)_0^\infty$:
	$= \frac{\text{IV dose}}{\lambda_2 \cdot (AUC)_0^\infty}$	$V_d = \frac{\text{IV dose}}{\lambda_2 \cdot (AUC)_0^\infty}$
Clearance, CL_s:	From curve fitting: $CL_s = \frac{\text{IV dose}}{\sum_{i=1}^{2} \frac{A_i}{\lambda_i}}$	From $(AUC)_0^\infty$:
	$= \frac{\text{IV dose}}{(AUC)_0^\infty}$	$CL_s = \frac{\text{IV dose}}{(AUC)_0^\infty}$

intercompartmental transfer rate constants. Furthermore, perhaps the most intriguing and useful aspect of this model is that, although it may be experimentally characterized in the mouse or rat, it has the potential to be scaled up to humans. It is this quality that has most attracted researchers in the area of toxicology and risk-assessment.

The disadvantage to this type of modeling is the large number of experiments and extensive amount of data that must be amassed to thoroughly characterize the drug or chemical in the animal species under study. Scaling up to humans becomes that much more of a challenge. It is well beyond the purpose of this chapter to provide an adequate working presentation of physiologically based pharmacokinetic models, and the reader is referred to several recent publications (6,7).

DISTRIBUTION

Distribution or translocation is the process of a molecule moving from the blood to other areas of the body. The blood acts as the primary communicating system of the body, and this movement of drug or chemical to the receptor(s) at the site of action is essential for production of a desired response or, at higher doses, an exaggerated response that may appear as toxicity. All other processes are irrelevant unless this desired event occurs. The other side to this story, however, is the movement of drug or chemical to other areas of the body not associated with a desired response, but which can give rise to undesired, adverse, or toxic events. The occurrence of these desired and undesired effects is the *ying and yang* of drug therapy, analogous to a two-sided sword, and only in rare cases is this not the prevailing rule.

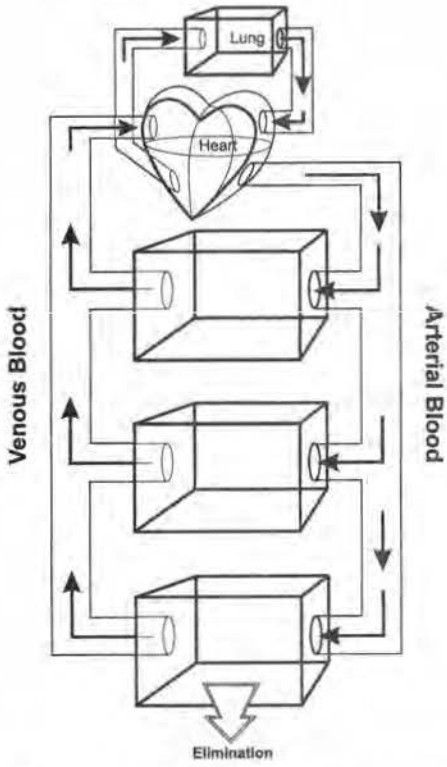


Figure 14. A schematic representation of a simple physiologically based pharmacokinetic model (PB/PK). This model is limited to the heart, lung, and three other organs/tissues, one of which is an eliminating organ (e.g., liver, kidney). The arrows indicate blood flow either entering (arterial) or exiting (venous) the organs (with the exception of the lung, which receives venous flow). The PB/PK model uses real values for blood flows, organ weights, drug partition from blood to tissue, and other potentially important parameters (e.g., binding, V_{max}, k_{mm}, and so forth). The experimental data involve quantitation of the drug (and, perhaps, metabolites) in all tissues/organs of the model as a function of time after dosing or exposure. (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

The distribution process has two components, how fast and how much? The former, how fast, affects the onset of a response and the resulting compartmental model. Thus, rapid-acting IV general anesthetics (e.g., thiopental) distribute quickly from the blood to the brain and result in a fast onset of anesthesia. That rapid movement has a parallel, slower component that describes distribution to other tissues (e.g., adipose tissue) resulting in multicompartmental behavior.

The rate of distribution is a complex function of the physical-chemical properties of the drug molecule, the properties of the tissue and blood flow to that tissue. There are two possible rate-limiting steps to drug distribution from blood to any given organ or tissue: blood flow and permeability. Blood flow is the limiting step for the majority of compounds and for the majority of body regions. The compound needs to have a moderate molecular weight (most drugs are small organic molecules) and a reasonable oil-to-water partition coefficient ($K_{O/W}$), which provides sufficient ability to traverse cell membranes. It has been shown (8) that the $t_{1/2}$ for tissue distribution (or redistribution) is a direct function of the tissue to blood partition coefficient ($K_{Tissue/Blood}$) and inversely related to blood perfusion rate (Q_{Tissue}) per tissue volume (V_{Tissue}), Q_{Tissue}/V_{Tissue}.

$$t_{1/2} \text{ for tissue equilibration} = \frac{0.693 \cdot K_{Tissue/Blood}}{Q_{Tissue}/V_{Tissue}} \quad \text{[Eq. 16]}$$

The tissue to blood partition coefficient ($K_{Tissue/Blood}$) is obtained from the ratio of concentrations of the compound in tissue to that in blood once an equilibrium has been achieved. The greater this number, the greater the *attraction* of the compound for that tissue, which generally means significant binding to tissue proteins. This may seem somewhat counter-intuitive, but having a greater capacity to accumulate a substance translates into taking a longer time to achieve equilibrium. The latter observation is exemplified by the many lipid-soluble environmental poisons (e.g., insecticides, herbicides) that take a long time to achieve equilibrium in adipose tissue, which has a large capacity to accumulate such material. The converse, loss from adipose tissue, also takes a long time. The role of the denominator is to be expected; the poorer the perfusion of the tissue by blood, the longer it takes to achieve equilibrium.

The following comparisons reflect the preceding discussion. For a given compound having the same value of $K_{Tissue/Blood}$ for all tissues, those tissues with the greatest blood perfusion per tissue volume achieve equilibrium the fastest (e.g., brain faster than skin and skin faster than bone). The approach to equilibrium, as judged by increasing $t_{1/2}$, follows the order from the greatest blood perfusion rate to the slowest. In contrast, for different compounds, the $t_{1/2}$ of distribution for a given tissue increases the greater the value of $K_{Tissue/Blood}$.

Blood perfusion may not always be the rate-limiting step to distribution. If the molecule is large or polar and must penetrate a membrane barrier, the rate-limiting step becomes permeability across that barrier. Thus, lipid-solubility and the fraction of the compound that is nonionized at blood pH determine the rate of movement across the blood–brain barrier for a series of, for example, barbiturates. Similar considerations apply to placental and mamillary transfer from the blood.

There are two other issues that substantially complicate a discussion of the distribution process: the apparent volume of distribution and plasma protein binding. The *apparent volume of distribution* (V or V_d) is a hypothetical space into which a substance distributes in the body. It is rarely a real, physiologic space, but it serves several useful functions. First, the value gives some indication of the extent of movement of the substance out of the bloodstream; although, it gives no indication where in the body the substance resides. Thus, the greater the value of V_d, more of the drug is found in tissues outside of the bloodstream. Second, V_d may serve as a useful proportionality constant between the blood concentration and the amount of the substance in the body at any given time. The latter can find use in calculation of residual amounts in the body and in designing dosing regimens. To further complicate this idea is the fact that there are several different apparent volumes of distribution, depending on the compartmental model. In a one-compartment model, there is only one apparent volume of distribution. In a two-compartment model, there is an apparent volume for each of the two compartments (V_1 or $V_{central}$ and V_2 or $V_{peripheral}$). There is also a volume referred to as the *steady state volume of distribution*, and this is noted later.

A useful definition is *the apparent volume of distribution is the imaginary volume that a substance would occupy in the body if it were present throughout the body at the same concentration as in the blood or plasma*. For example, if a substance were present in blood at a concentration of 1 mg/L and the concentration in liver tissue was 100 mg/L, the liver is behaving as if it were equal to approximately 100 L of blood for every liter volume of liver tissue. Obviously, this apparent volume is strictly a hypothetical value. Note that the reference fluid is blood or plasma: the apparent volume is relative to the concentrations of the substance in blood or plasma. This is a reasonable choice of reference fluid because it is readily accessible for sampling and it is the bloodstream that connects to all parts of the body. Another way to look at this volume is to use a different reference tissue. For example, consider the apparent volume of distribution of iodine after an IV dose. Based on the small concentrations that are produced in the blood, iodine appears to have a large apparent volume of distribution; most of that compound resides in tissues outside of the blood. Now, change the reference fluid to be the thyroid tissue, where most of the iodine is located, and one calculates, relative to the thyroid tissue, a small apparent volume of distribution; most of the iodine resides in that reference tissue.

Another way to illustrate this apparent volume is shown in Figure 15. There is a need to determine the exact volume of a tank, which is thought to hold approximately 1000 L of fluid. To do so, 1000 mg of a dye is added to the tank containing water, and the fluid is mixed well. A sample is taken. The resulting concentration of the dye, in the scenario at the top of the figure, is determined to be 1 mg/L. The volume of the tank (amount/concentration) is calculated to be 1000 L—exactly what was expected. The experiment is repeated in another tank (bottom of figure) in an identical fashion, but this time the sample is assayed to contain 0.01 mg/L with a resulting tank volume of 100,000 L. This is not possible: the tank can only hold 1000 L. What happened? As noted in the bottom figure, most of the substance has been adsorbed onto the interior surface of the tank; the molecules have been taken out of the solution. The apparent

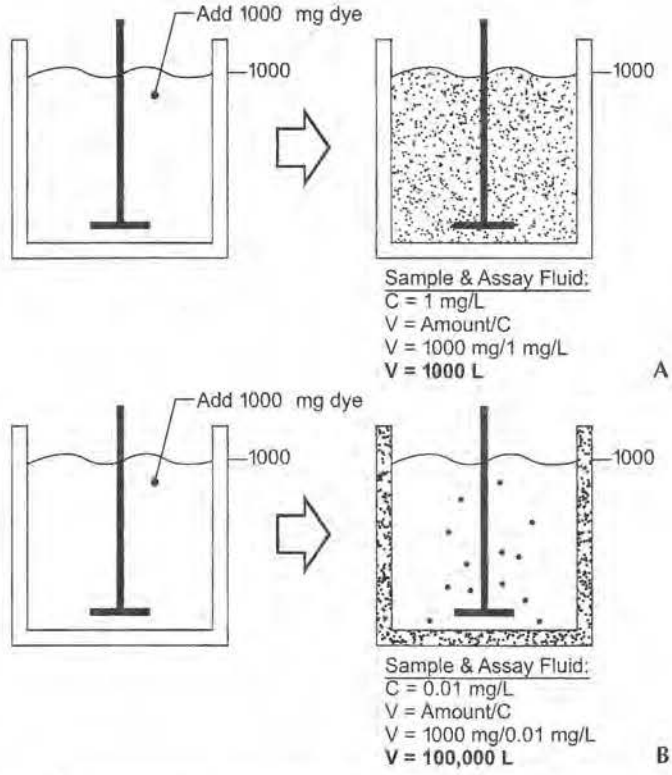


Figure 15. Illustration of the determination and meaning of the apparent volume of distribution. **A:** 1000 mg of a water-soluble dye is added to a tank that holds approximately 1000 L of water. The dye is thoroughly mixed in the fluid of the tank and a sample taken. The sample is assayed to have a concentration of 1 mg/L, and the apparent volume of the tank is determined to be 1000 L, consistent with the actual volume. **B:** The same experiment as noted previously, but this time the assay of the sample gives a concentration of dye of 0.01 mg/L. The resulting (impossible) volume of the tank is calculated to be 100,000 L. Much of the dye has been *distributed* to the surface of the tank (i.e., adsorbed), giving rise to a hypothetically large apparent volume, relative to the reference fluid. (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

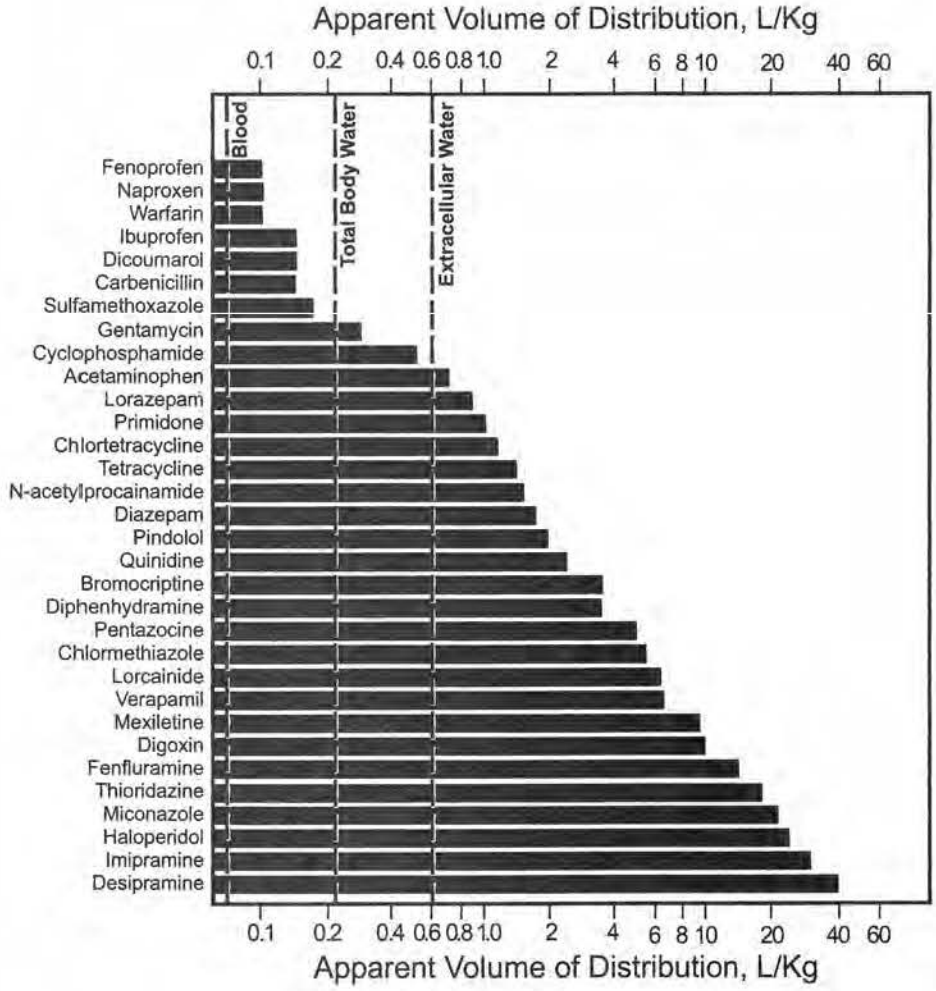


Figure 16. The apparent volumes of distribution of selected drugs (L/kg) illustrating the wide range of values (approximately 0.1 to 40 L/kg). Note that the scale is logarithmic. The three vertical lines that are being used for reference purposes illustrate real physiologic volumes. Those volumes are, from left to right, blood, extracellular water, and total body water. (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

space that the dye occupies is relative to the remaining concentration of dye in the tank fluid, a small concentration. The resulting volume is huge and not real. This is exactly what happens to compounds after they gain access to the blood; they distribute from the blood to other tissues and they bind there. The compound does not stay in the blood as it did not stay in the tank fluid, the reference fluid.

The wide range of apparent volumes of distribution among selected drugs is illustrated in Figure 16. Note that the scale is logarithmic to accommodate the wide range in values (approximately 0.1 to 40 L/kg). For comparison purposes, vertical lines illustrate three real physiologic spaces (blood, extracellular water, and total body water). The large apparent volumes are attributable to extensive binding to tissue proteins. Clearly, these are not real volumes or physiologic spaces.

Perhaps the most important role that apparent volume plays in drug disposition is as it affects terminal $t_{1/2}$. An important relationship in this regard is the following:

$$t_{1/2} = \frac{0.693 \cdot V_d}{CL_s} \qquad \text{[Eq. 17]}$$

The previous relationship is mathematically and functionally correct. Because this equation is mathematically correct, it can be used to solve for apparent volume or systemic clearance (CL_S). It is important to recognize, however, that the only way to understand the relationship among these parameters is to view them as presented in equation 17; $t_{1/2}$ is *dependent* on apparent volume of distribution and systemic clearance and not the other way around. Compounds that have a large apparent volume, in general, are expected to have a long $t_{1/2}$, unless systemic clearance is high. Again, this reemphasizes the fact that the terminal $t_{1/2}$ depends as much on distribution as it does on elimination (i.e., clearance). Dioxin present in Agent Orange, used as a defoliant during the Vietnam War, has a $t_{1/2}$ in humans of approximately 7 years (9). Compounds with a large apparent volume of distribution have a long $t_{1/2}$ because large quantities reside in areas that are not immediately accessible to the eliminating organs; they must move from the tissue to blood and then through the eliminating organ(s) to be eliminated from the body. Slow movement from such a tissue site to the bloodstream, a process referred to as *redistribution*, essentially rate-limits the elimination process and leads to a prolonged $t_{1/2}$. Recall from a previous discussion, that the rate of redistribution is the reverse of the accumulation process from blood to tissue. The $t_{1/2}$ for both processes is governed by the value, $K_{Tissue/Blood}$; the larger that value, the longer the $t_{1/2}$. Compounds with large values of $K_{Tissue/Blood}$ also have large apparent volumes of distribution.

In an attempt to provide some biologic meaning to the apparent volume of distribution and based on physiologic values in a normal healthy adult man, the following relationship has been developed (10).

$$V_d = 7 + 8 \cdot f_U + V_T\left(\frac{f_U}{f_{U,T}}\right) \qquad \text{[Eq. 18]}$$

The apparent volume of distribution (in liters) is given by a constant (7 L); the unbound or free fraction of drug in the plasma

(f_U); a *tissue* volume (V_T), which represents the space into which the drug distributes minus the extracellular space; and the unbound fraction of drug in the *tissue* ($f_{U,T}$). The unbound fractions (f_U and $f_{U,T}$) are the ratio of unbound drug concentration to total (i.e., bound plus unbound) drug concentration. A drug with a small apparent volume can be approximated by the first two terms, whereas a drug with a large volume is estimated by the last term only.

Small volume drug: $V_d \cong 7 + 8 \cdot f_U$

Large volume drug: $V_d \cong V_T\left(\frac{f_U}{f_{U,T}}\right)$ [Eq. 19]

Thus, the smallest apparent volume of a substance that is totally unbound to plasma (i.e., $f_U \cong 1$) is approximately 15 L, whereas the smallest volume for a substance that is totally bound to plasma proteins (i.e., $f_U \cong 0$) is approximately 7 L. Note that in between these two extremes, a change in plasma protein binding does not lead to a directly proportional change in volume (i.e., as f_U increases, V_d increases in a less than proportional manner).

A compound that has a large apparent volume has a large volume as a result of binding to tissue proteins. That binding is expressed by the value of $f_{U,T}$ in the third term in the general equation 18. Extensive binding to tissue protein results in a small value for $f_{U,T}$, which, in turn, makes the third term large and overwhelmingly larger than the first two terms (which are ignored in the simplification of equation 19). In this instance, any change in the unbound fraction for either plasma or tissue binding results in a directly proportional change in apparent volume. As shown in Figure 16, there are many compounds that have large apparent volumes of distribution. What are considered small and large apparent volumes? There are no definitive rules, but, as an approximation, a volume less than approximate total body water (approximately 0.6 L/kg) might be considered small, whereas a volume greater than approximately 1 L/kg might be considered large. These are arbitrary demarcations, however. Making these approximations becomes useful when attempting to predict how a change in binding might affect the $t_{1/2}$ of a drug, as discussed later under Clearance Concepts.

Plasma protein binding (especially any change in that value) and the disposition and response to a compound is one of the most confusing issues in pharmacokinetics. Many of those ideas are best developed with reference to clearance concepts, which follow this section. Protein binding is generally thought to be a simple, reversible process that may be described by principles of mass action. Binding is determined by an *in vitro* method that requires separation of unbound from total drug. The two most commonly used methods are equilibrium dialysis and ultrafiltration. It is important to keep in mind that all assays used to quantify drug concentrations in blood or plasma (e.g., those reported during therapeutic monitoring or from toxicologic screening) measure *total* concentration and not unbound concentration. This is a consequence of how the samples are handled. Plasma proteins (e.g., albumin) are not able to easily traverse the capillary membrane, and, therefore, it is generally believed that only unbound drug distributes from blood; moves across the capillary membrane; and equilibrates with unbound drug in all tissues, including the receptor at the site of action. As a consequence, it is the unbound drug concentration that drives response and toxicity. It is on this premise that there is great interest in the unbound drug concentration and any changes that may occur to it as a result of, for example, drug-drug interactions or disease states. It can be stated here, although discussed later under Multiple Dosing, that drug displacement interactions are rarely of any clinical importance. Furthermore, although seeming to be illogical and counter intuitive, *the unbound plasma concentration is not determined or affected by plasma protein binding*. This point is discussed later under Multiple Dosing.

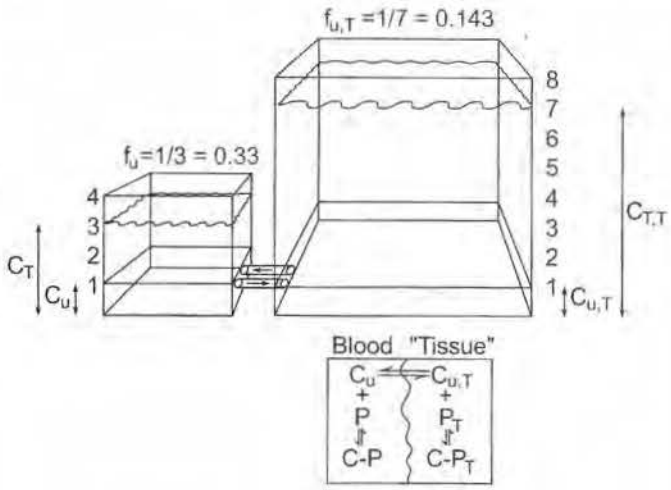


Figure 17. The bottom scheme indicates that three equilibria need to be considered when examining blood and tissue binding. These binding equilibria include: the equilibrium plasma protein binding (*left*), the equilibrium tissue protein binding (*right*), and the equilibrium of unbound drug between blood and tissue. The large graph illustrates these individual equilibrium conditions. The total concentration of drug in the blood (C_T; *left*) is three units, whereas the unbound concentration (C_U) is 1 unit. Thus, the unbound fraction of drug in blood is 0.33. The unbound drug equilibrates between blood and tissue so that the unbound concentration in the tissue ($C_{U,T}$) is the same as in the blood, 1 unit. In contrast, the total concentration of drug in tissue ($C_{T,T}$) is 7 units, giving an unbound fraction in tissue ($f_{U,T}$) of 0.143. Note $f_U \neq f_{U,T}$, but $C_U = C_{U,T}$. (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

Figure 17 illustrates the equilibrium between blood and some tissue. The bottom part of the figure illustrates the separation by a membrane of blood and some tissue and indicates that three equilibria exist. In the blood, unbound drug (C_U) binds reversibly with protein (P) to form the bound drug complex (C-P). An identical equilibrium exists in the tissue, but now unbound drug in tissue ($C_{U,T}$) binds reversibly with protein in the tissue (P_T) to form a drug-tissue protein complex (C-P_T). There is no reason to believe that those equilibria are the same (i.e., it is not likely that the extent of plasma protein binding is the same as tissue protein binding of drug; $f_U \neq f_{U,T}$). The most important equilibrium is that between blood and tissue and the figure indicates that the unbound concentrations of drug are equal ($C_U = C_{U,T}$; *not* the unbound fractions). The larger graph further illustrates this discussion. The height of the *fluid* in the blood and tissue is analogous to concentrations. The total concentration of drug in blood (left) is 3 units, whereas the unbound concentration is 1 unit (f_U = 0.33). The total concentration of drug in the tissue (on the right) is 7 units—greater than total blood concentration due to greater tissue protein binding. The unbound concentration, 1 unit, is identical to the unbound concentration in blood. Note, however, that the unbound fraction in tissue is 0.143, reflecting the greater tissue protein binding compared to plasma protein binding.

Figure 18 illustrates the wide range of plasma protein binding of drugs in humans, expressed as percent unbound, for selected drugs. Lithium is not bound (f_U = 1; 100% unbound), whereas warfarin is extensively bound to plasma proteins (f_U = 0.01; 1% unbound). For the vast majority of compounds, plasma and tissue protein binding remains constant over a fairly large concentration range, although there are instances of concentration-dependent binding. The latter is most likely to occur for com-

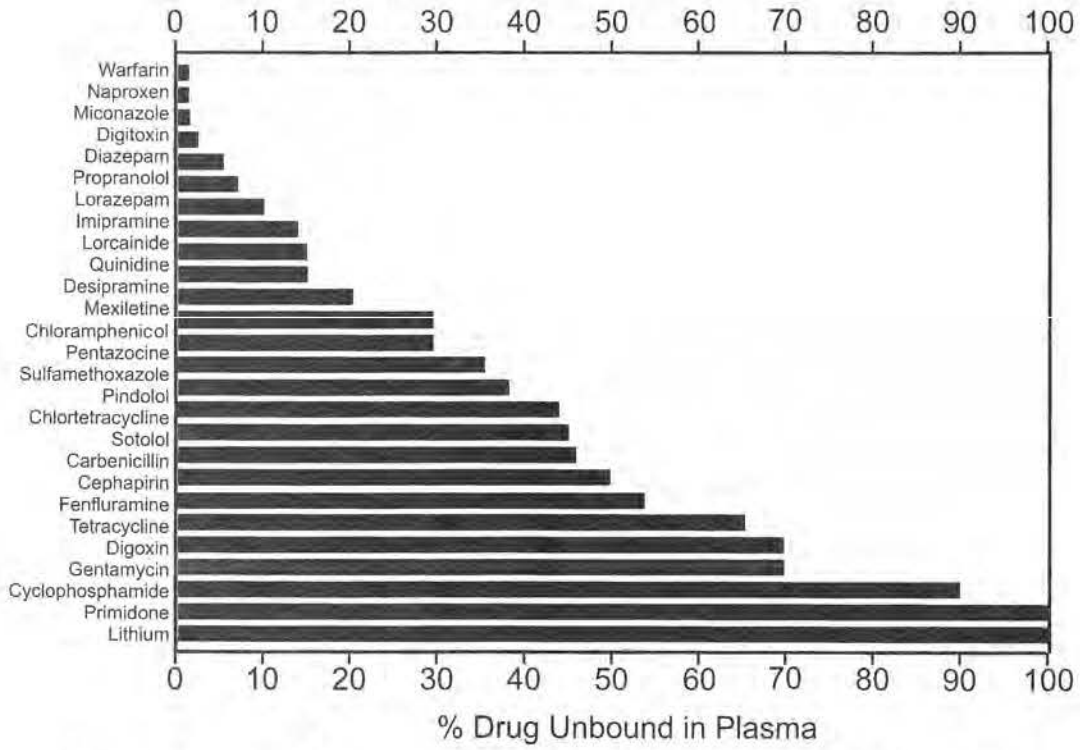


Figure 18. Illustration of the percentage drug unbound to human plasma proteins for a selection of drugs. (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

pounds present at high concentrations or those compounds that bind to proteins present at low concentrations but that have low binding capacity (e.g., α_1-acid glycoprotein). Plasma protein binding may also be influenced by disease states or age that result in a reduction in plasma protein concentration and, therefore, binding capacity. Displacement interactions can also give rise to a change in plasma protein binding of a drug, but whether these changes in f_U change the unbound plasma concentration is another matter.

Any change in plasma protein binding or tissue protein binding expressed as a change in the unbound fractions, f_U or $f_{U,T}$, results in a change in the apparent volume of distribution, which, in turn, may alter the value for terminal $t_{1/2}$. A change in the apparent volume and the direction and magnitude of change can be judged with reference to the basic volume equation 18 or, more simply, using the approximations noted in equation 19. The relationship between apparent volume and $t_{1/2}$ is illustrated in the following section.

CLEARANCE CONCEPTS

One of the most useful physiologically grounded and predictive concepts in pharmacokinetics is that of *clearance*. Clearance provides a means of understanding the basic, underlying mechanisms associated with organ elimination of a compound and how it may be altered. Clearance also serves as a unifying concept, which permits interrelating other variables and parameters (such as apparent volume, $t_{1/2}$, and plasma protein binding). Finally, clearance is what controls the ultimate plasma concentrations of a substance achieved after multiple dosing or long-term exposure (at steady state). Understanding clearance is essential if one wants to interpret, for example, drug-drug interactions or the effects that a disease state has on drug disposition.

Several measures to characterize drug elimination or loss from the body are available, including rate of elimination, the elimination rate constant, and $t_{1/2}$. The problem with each of these measures is that they cannot stand on their own; they are not *independent* estimates of the efficiency of the removal process. Rate of elimination is a function of concentration, which is usually changing with time after dosing. The rate constant of elimination and $t_{1/2}$ are a function of apparent volume and clearance, as noted in equation 17. Therefore, $t_{1/2}$, although a useful parameter and one easily understood, has little use from the perspective of understanding the physiologic basis of the elimination process or judging the mechanisms responsible for changes in its value. A good illustration of this point is the observation that the $t_{1/2}$ of certain lipid-soluble drugs (primarily eliminated by hepatic metabolism) increase with age in adult humans. This has been noted for the benzodiazepine derivative diazepam (11) and the rapidly acting IV anesthetic thiopental (12). The thiopental example is illustrated in Figure 19, which portrays the relationship between age and the terminal $t_{1/2}$, apparent volume of distribution, and clearance. The relationship between $t_{1/2}$ and age (A), taken by itself, might suggest reduced hepatic elimination efficiency with age. However, as noted in equation 17, $t_{1/2}$ depends on the apparent volume as much as it depends on elimination (given by clearance). In fact, it is the change in apparent volume with age that drives the increase in the terminal $t_{1/2}$ (B). This change in $t_{1/2}$ occurs in the absence of any change in (hepatic) clearance, as noted in the inset figure. The physiologic explanation for this relationship is that adipose tissue represents an increasing percentage of body weight as an individual ages. The consequence of this change in body composition is the expansion of the space that the compound can occupy, which is expressed as an increase in the apparent volume of distribution. This illustration stresses the importance of viewing $t_{1/2}$ in its functional form, as written in equation 17.

Whereas $t_{1/2}$ is governed by distribution and elimination processes and, therefore, reflects what is happening in the entire

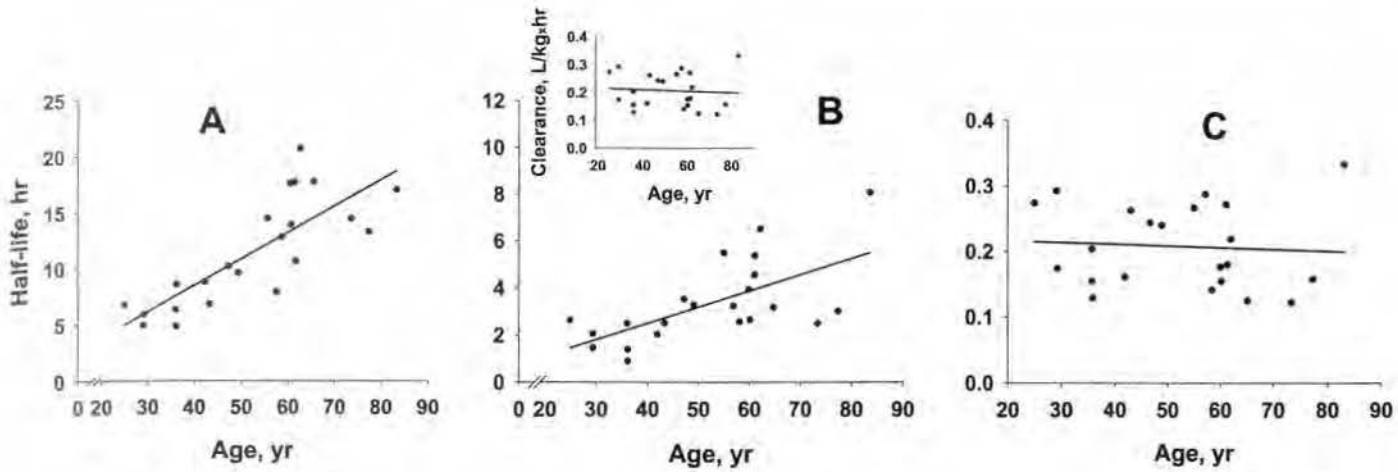


Figure 19. The influence of age (in women undergoing surgery) on the disposition parameters of the lipid-soluble, rapid-acting, intravenous anesthetic agent thiopental. Relationships are shown for terminal half-life (**A**), apparent volume of distribution (L/kg) (**B**) and systemic clearance (**B**, *inset*). Graph **C** is an enlarged version of the clearance inset in **B**. The lines represent the linear regression equation of the data. (Based on data presented in Jung D, Mayersohn M, Perrier D, et al. Thiopental disposition as a function of age in female patients undergoing surgery. *Anesthesiology* 1982;56:263–268. From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

body, clearance, on the other hand, is a measure of efficiency of elimination or removal by an organ. The basic definition of clearance is essentially a restatement of first-order kinetics.

$$\text{clearance} = \frac{\text{rate of elimination}}{\text{blood or plasma concentration}} = \frac{\text{amount/time}}{\text{amount/volume}} = \frac{\text{volume}}{\text{time}} \quad \text{[Eq. 20]}$$

Notice that the units of clearance are that of a flow, volume/time. The definition of clearance that is often cited is *clearance is the volume of blood that must be acted on and from which all substance is removed per unit of time to account for the rate at which that substance is being eliminated*. Previously, in defining first-order kinetic processes, equation 4 indicated the relationship between rate and concentration, but the proportionality constant was a first-order rate constant and not clearance, as rewritten below:

$$K = \frac{\text{rate of elimination}}{\text{blood or plasma concentration}} = \frac{\text{concentration/time}}{\text{concentration}} = \frac{1}{\text{time}} \quad \text{[Eq. 4]}$$

Clearance and K (or $t_{1/2}$), not surprisingly, are related to each other through the apparent volume of distribution (i.e., $CL = K \cdot V_d$), which is a useful expression, but this does not help in understanding clearance. As for a first-order process, clearance is *independent* of dose or concentration or time after dosing. Every eliminating organ has a corresponding value for clearance; individual organ clearances are additive (as are rate constants) and *independent* of each other. The sum of all clearances for all eliminating processes is referred to as *total body clearance* or *systemic clearance*, CL_S; the latter is the preferred term here.

For any terminal region into which drug is found, such as the urine, bile, or exhaled air, the basic relationship for clearance, equation 20, can be applied experimentally. Thus, renal clearance (CL_R) is assessed by relating the rate of urinary excretion of unchanged drug to plasma concentration at the same time. Similarly, one can experimentally determine biliary clearance (CL_{BILE}) and pulmonary exhalation clearance ($CL_{PULMONARY}$) of unchanged drug. Each of these clearances has one thing in common: a terminal fluid can be collected and assayed for unchanged drug, from which an estimate of rate of drug appearance can be made. How does one go about experimentally determining hepatic clearance (CL_{HEP}) or systemic clearance? The former cannot be done noninvasively, and the latter would require experimentally measuring all possible clearing mechanisms. Some other method must be applied to calculate values for those clearance terms.

The direct answer to this question comes from a common and practical mathematical procedure: convert the rate to an amount through integration. If the rate expression presented in equation 20 is integrated, the following is obtained:

$$\text{systemic clearance} = CL_s = \frac{\text{rate}}{\text{concentration}} = \frac{\int_0^\infty \text{rate} \cdot dt}{\int_0^\infty C \cdot dt} = \frac{\text{IV dose}}{(AUC)_0^\infty} \quad \text{[Eq. 21]}$$

Systemic clearance can be calculated by dividing the IV dose by the corresponding total area under the plasma concentration-time curve (from time zero to infinity) for the unchanged drug. The IV dose is used here because, by definition, the entire IV dose is completely available to the systemic circulation. This is not necessarily true for any other route of administration. Recall that the area may be considered to be an index of exposure to the compound. Systemic clearance can be viewed as affecting the exposure resulting from administration of a given dose. Thus, the greater the clearance, the smaller the exposure from a unit dose of compound. The inverse is also true: a small value of CL_S results in a large exposure to a unit dose of compound. Because clearance is a constant, any increase in dose results in a proportional increase in area under the curve.

Determination of hepatic (or metabolic) clearance requires that the numerator in equation 21 be the rate of metabolite formation, the integral of which is the amount of metabolite formed (not dose). The latter is generally determined after measurement of the fraction of the dose that is converted into metabolite. Another feasible calculation is to subtract all known values for clearance from systemic clearance and assume that the remainder is hepatic or metabolic clearance (e.g., $CL_{HEP} = CL_S - CL_R - CL_{OTHER}$). Also, the ratio of any given organ clearance to systemic clearance gives the fraction of the dose that undergoes

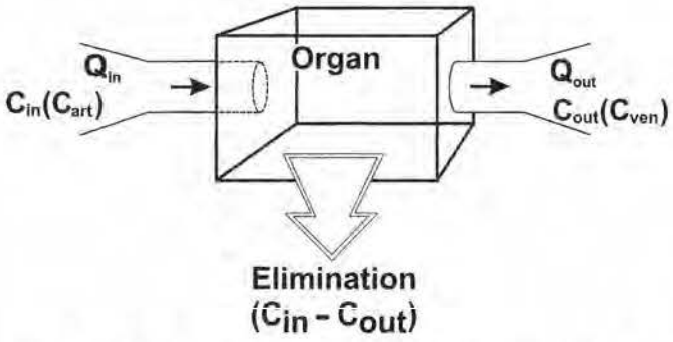


Figure 20. A hypothetical eliminating organ that receives in-flowing (arterial) blood (Q_{in} or C_{art}) and out-flowing (venous) blood (Q_{out} or Q_{ven}). The arterial blood has a concentration of C_{in}, and the venous blood has a concentration of C_{out}. Any difference between C_{out} and C_{in} ($C_{out} < C_{in}$) represents elimination or organ extraction of drug. Extraction ratio, ER, is defined as $C_{in} - C_{out}/C_{in}$. (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

that pathway. Thus, the ratio of CL_R to CL_S represents the fraction of the dose that is excreted unchanged via the kidney. This is the same fraction that is represented by the ratio of the individual rate constant for urinary excretion (k_U) and the overall elimination rate constant (K).

There are several useful graphical ways to illustrate different aspects of clearance. Figure 20 illustrates a basic term, *extraction ratio* (ER), which provides a measure of efficiency of drug removal by the hypothetical organ illustrated. The organ receives arterial blood flow (Q_{in} or Q_{art}) that contains drug entering the organ at a concentration of C_{in} (or C_{art}). The exiting venous blood flow (Q_{out} or Q_{ven}) contains drug at a concentration of C_{out} (or C_{ven}). If this were a noneliminating organ or tissue, then the concentration exiting the organ would exactly equal the concentration entering ($C_{out} = C_{in}$). In contrast, if some of the drug is eliminated, then the outflowing concentration must be less than the inflowing concentration ($C_{out} < C_{in}$) and the difference, shown by the arrow, is what has been eliminated or extracted by that organ. The efficiency of this process can be expressed by the ER, which is the difference in concentrations normalized by the inflowing concentration.

$$\text{extraction ratio} = ER = \frac{C_{in} - C_{out}}{C_{in}} \qquad \text{[Eq. 22]}$$

The three possible situations are

I.	$C_{out} = C_{in}$	$= 0$	noneliminating organ
II.	$C_{out} = 0$	$ER = 1$	extremely efficient eliminating organ
III.	$C_{out} < C_{in}$	$0 < ER < 1$	varying elimination efficiency

For an eliminating organ, most compounds fall into category III, and every organ has a unique value of ER for a given substance. The ER represents the fractional removal of substance by the organ. Thus, an ER value of 0.2 indicates that 20% of the substance in the blood is removed by the extracting organ as the blood perfuses that organ. The ER value is a measure of efficiency of removal and has no bearing on the extent or completeness of removal by that organ. Thus, two compounds may undergo total hepatic metabolism (i.e., 100% metabolized) yet have different ER values. The former value indicates the primary route of elimination and that ultimately all of the drug is metabolized. The ER value suggests how efficiently the removal process occurs. It seems reasonable that the compound with the greatest ER value is likely to have the shortest $t_{1/2}$, keeping in mind the modulating effect of apparent volume of distribution. It would not be surprising to find that organ clearance is related to ER. This can be easily shown by considering the basic relationship for clearance and with reference to Figure 20. The rate of drug entry into the organ is the product of blood flow in and concentration in, and the rate of drug exit is the product of blood flow out and concentration out:

$$\text{Rate in} = Q_{in} \cdot C_{in} \quad \text{Rate out} = Q_{out} \cdot C_{out} \qquad \text{[Eq. 23]}$$

The rate of elimination or extraction is the difference between the rate in and the rate out:

$$\text{Rate of elimination} = Q_{in} \cdot C_{in} - Q_{out} \cdot C_{out} = Q_{in} \cdot (C_{in} - C_{out}) \qquad \text{[Eq. 24]}$$

Because flow in is equal to flow out, Q_{in} has been factored out and used in the equation. The basic relationship used to define clearance has rate of elimination in the numerator divided by the blood concentration. Substituting equation 24 for the numerator gives

$$\text{clearance} = \frac{\text{rate of elimination}}{\text{blood concentration}} = \frac{Q_{in}(C_{in} - C_{out})}{C_{in}} = Q_{in} \cdot ER \qquad \text{[Eq. 25]}$$

Clearance by a given organ is the product of the blood flow to that organ multiplied by the organ ER for that compound. Thus, if ER is 0.2, the clearance of that compound is equal to 20% of blood flow; 20% of that compound is removed from the blood as it perfuses the organ. Going back to the three scenarios discussed previously,

I.	$C_{out} = C_{in}$	$ER = 0$	$CL = 0$	noneliminating organ
II.	$C_{out} = 0$	$ER = 1$	$CL = Q$	extremely efficient eliminating organ
III.	$C_{out} < C_{in}$	$0 < ER < 1$	$CL = ER \cdot Q$	varying elimination efficiency

The most interesting aspect of the previous chart is situation II: when ER is the largest possible value, clearance is equal to organ blood flow. This is the statement of a rate-limiting step; *a compound cannot be cleared by an organ any faster than it is delivered (by blood) to that organ*. In fact, there is a clinical application of this principle. Consider diagnostic agents that are used to measure organ blood flow, such as indocyanine green (hepatic blood flow) and para-aminohippurate (PAH) (renal blood flow). These compounds have one pharmacokinetic characteristic in common: they all have a specific organ ER of approximately one. Thus, organ clearance measured *in vivo* after an IV dose cannot exceed organ blood flow. The largest possible value for systemic clearance is total blood flow or cardiac output. Any value of CL_S greater than cardiac output suggests a mechanism of elimination that is independent of blood flow. For example, a compound that is chemically or metabolically altered in the blood *per se* would not be influenced by blood flow, and the resulting clearance could take on any value in excess of cardiac output. The latter appears to be the situation for organic nitrates, such as nitroglycerin, that are metabolized along the surface of blood vessels (13). There are several older but thorough reviews of clearance and blood flow (14,15).

Another way to examine extraction and clearance is illustrated in Figure 21 for three different compounds. The hypothetical organ receives 10 ml of blood per minute and, at time zero, each of the three drugs is present at a concentration of 10 ng/ml. One-

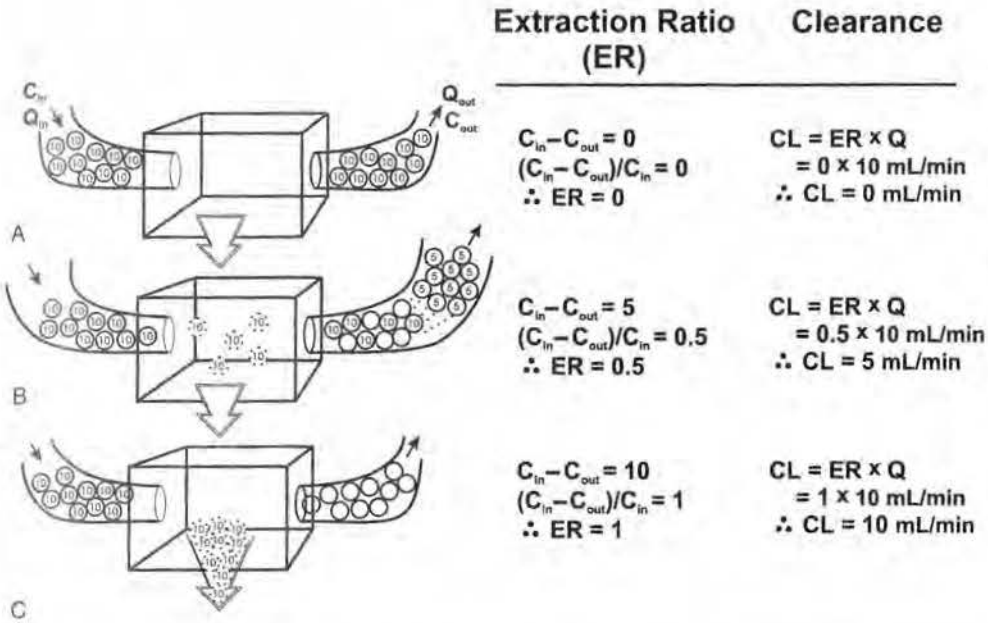


Figure 21. Schematic diagram of the extraction and clearance of three different drugs. The hypothetical organ system receives 10 ml of blood per minute. The compounds have ER, from top to bottom, of 0, 0.5, and 1.0. What is shown is one-minute snapshots of the drug entering and then leaving the organ. At time zero, the concentration in the delivering blood is 10 ng/ml for each compound. **A:** One minute after perfusing the organ, the exiting and incoming concentrations are equal. Thus, this is a noneliminating organ for that drug having an ER and CL of zero. **B:** The exiting concentration of 5 ng/ml is one-half of the entering concentration. The ER value is 0.5, resulting in an organ clearance of 5 ml/minute. Note that what is retained (i.e., eliminated) in the organ is the mass comparable to what was contained in 5 ml of blood. **C:** The exiting concentration of zero gives an ER of 1.0 and a clearance equal to organ blood flow, 10 ml/minute. Again, note that what is eliminated by the organ is the mass comparable to what was contained in the volume cleared. (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

minute snapshots for each of the three compounds is shown. For the compound at the top of the figure, the exiting concentration equals the incoming concentration, and, therefore, no drug has been extracted or eliminated. The value for ER and CL for this drug is zero; this is a noneliminating organ. The compound in the center has an exiting concentration of 5 ng/ml 1 minute after blood perfuses the organ. The value for ER is the difference between the in and out concentrations divided by the incoming concentration: $10 - 5/10 = 0.5$. The resulting value for clearance is ER multiplied by organ blood flow, or 5 ml/minute. The figure illustrates that the organ has retained (or eliminated) the total drug content in 5 ml of blood, or 50 ng. Clearance is the flow equivalent to the mass of compound removed by the organ (what volume of blood contains 50 ng?). The bottom figure indicates that the exiting concentration is zero, which must indicate total clearance of the compound by the organ (ER = 1 and CL = 10 ml/minute). Extraction can never be more efficient than this; clearance equals organ blood flow.

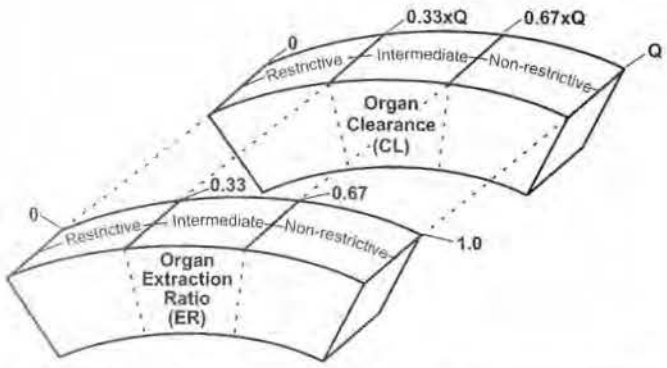


Figure 22. *Rainbows* illustrating the range of organ ERs and CLs. The clearance *rainbow* is connected to the extraction ratio by organ blood flow (CL = ER · Q). Each *rainbow* is divided into thirds. A low ER is less than approximately 0.33, whereas a large ER is greater than approximately 0.67. Intermediate values fall within that range. Drugs with low CL values are less than approximately one-third of organ blood flow, whereas drugs with large CL have a value greater than approximately two-thirds of organ blood flow. Intermediate CL values fall within that range. Note that low clearance drugs are also referred to as being *restrictively* cleared, whereas drugs with high clearance are referred to as being *nonrestrictively* cleared. See text for explanation. (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

Figure 22 illustrates *rainbows* for organ ERs and corresponding organ clearances. The ER *rainbow* is in front of the clearance *rainbow* and connected to it by organ blood flow (CL = ER · Q). Values for ER and CL are divided into three parts: low, intermediate, and high. Although the demarcations are arbitrary, a small ER is less than approximately 0.33, whereas a large ER is greater than approximately 0.67. Intermediate vales are in between those ranges. The identical separation is shown for CL, except that the values are multiplied by organ blood flow. Thus, low clearance is any value less than approximately one-third of blood flow, whereas a large clearance is any value greater than approximately two-thirds of blood flow. Intermediate clearances are in between those extremes. Also notice that the term *restrictive* clearance is used to describe those compounds with low clearance and *nonrestrictive* is used to describe those compounds with high clearance. As noted later, the former indicates that clearance is restricted by plasma protein binding, whereas for high clearance compounds, clearance is not restricted by plasma protein binding. Figure 23 illustrates the clearance rainbow with flow values and with drug examples for each division and using the average values for liver blood flow (1500 ml/minute) and renal blood flow (1200 ml/minute) in a normal healthy adult man.

Another way to view clearance is with reference to its basic definition, as illustrated in Figure 24. The panel of three graphs project into the page. The first graph is a linear plot of plasma concentration as a function of time after an IV bolus dose and assuming a one-compartment model. The resulting exponential curve is described by the equation noted to the right. The graph just behind the first is a plot of the rate of elimination versus time, and it is connected by dotted lines to the graph in the front at corresponding times. Because rate of elimination is a function of concentration and a rate constant, K (or clearance, CL), the middle curve declines in parallel with the concentration-time curve, as noted in the equations to the right. Clearance is defined as the relationship between rate of elimination and the driving force concentration. Dividing the middle curve, which describes

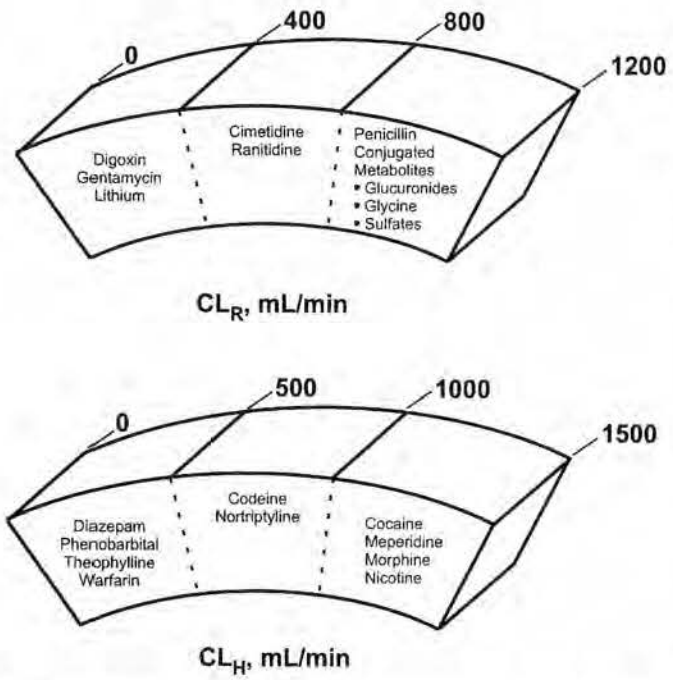
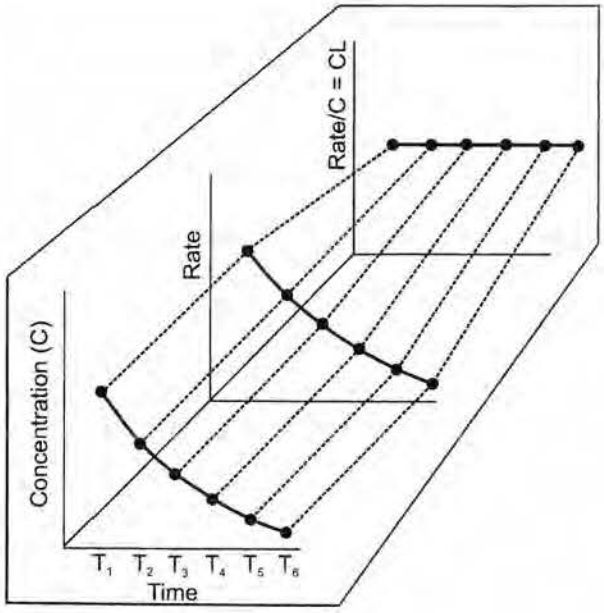


Figure 23. *Rainbows* of extraction ratio and clearance (CL) for drugs that undergo renal CL (CL_R) and hepatic CL (CL_H). The average values for renal (1200 ml/minute) and hepatic (1500 ml /minute) blood flows in a normal 70-kg man have been used and divided into three parts, as noted in Figure 22. Drug examples are provided for each division. (From Mayersohn M. Toxicokinetics: Measurement of disposition half-life, clearance and residence times. In Maines M, ed. *Current protocols in toxicology*. New York: John Wiley and Sons, 2000:5.3.5, with permission of Saguaro Technical Press, Inc, 2002, Tucson, AZ.)

rate of elimination, by the corresponding concentration-time values in the front curve, results in clearance, which is projected onto the back-most graph. Clearance is constant with time, but its magnitude (height) varies from compound to compound. This difference among compounds can be seen in Figure 25. There is a series of three panels, each representing a different drug and each panel is made up of three graphs projecting into the page as described. The compound on the left has the smallest rate of elimination, resulting in a relatively shallow rate versus time curve. The consequence is that clearance, which is a ratio of rate/concentration, is a relatively low value, which can be noted by inspecting the graph in the back of the panel. In contrast, the compound on the right has a rapidly declining concentration-time curve, indicating a large value for the elimination rate constant. The graph just behind indicates a rapid decline in the rate versus time curve. As a consequence, the ratio of rate to concentration or clearance for this compound must be relatively high, as noted in the rear graph. The compound in the center panel is intermediate between the other two compounds. What is it about the compound on the right that results in high clearance? If it is assumed that these three compounds all underwent metabolic clearance by the same enzyme, then there is something about this compound that makes it a better substrate for that enzyme. This difference among compounds can be better understood by expressing a term called *intrinsic clearance* (CL_{int}), which, as noted later, is the ratio of V_{max} to K_m; however, ultimately the explanation lies with how that molecule resides at the active site of the enzyme.

Before discussing the idea of CL_{int}, it is useful to view clearance in yet another way that provides a basis for a comparison between clearance, an expression of organ efficiency, and $t_{1/2}$, which reflects loss of drug from the body. Figure 26 illustrates sequential 1-minute *snapshots* of the extraction of a compound and its movement through the body. The hypothetical compound is given as an IV bolus at a dose of 150,000 ng. The resulting initial plasma concentration is 10 ng/ml. The organ of elimination receives blood flow at the rate of 50 ml/minute and the ER of this compound is 0.3. In the first minute, 50 ml of blood each containing 10 ng of drug perfuses the clearing organ. As the blood traverses the organ, 30% of the compound is removed from the blood during the first minute. This is illustrated by the organ retaining 15 ml of the total of 50 ml of blood, which has perfused the organ. Of course, blood flow is conserved; what is retained by the organ is the total mass of compound contained in 15 ml of blood. Organ clearance is 15 ml/minute (0.3 × 50 ml/minute), and the amount eliminated by the organ is the total content in 15 ml of blood, 150 ng (10 ng/ml × 15 ml). On exit, there are 15 *empty* ml of blood, which reequilibrates with the



$$CL = \frac{Rate}{C} \quad (vol/t)$$

$$Rate = -K \cdot X$$
$$= -K \cdot (V \cdot C)$$
$$= CL \cdot C \quad (amt/t)$$

$$C = C^{\circ} \cdot e^{-kt} \quad (amt/vol)$$

Figure 24. There are three graphs in this panel, which project into the page. The first graph is a linear plot of plasma concentration versus time after an intravenous bolus dose (and assuming a one-compartment model) whose equation is noted to the right. The graph immediately behind is that of rate of elimination versus time. The two graphs are shown connected by dotted lines at the same times. The equations that describe this rate versus time plot are shown to the right. Because the ratio of rate to concentration is defined as clearance (CL), dividing the middle graph by the first graph gives CL, which is noted as the graph in the back. (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc. Tucson, AZ, 2002.)

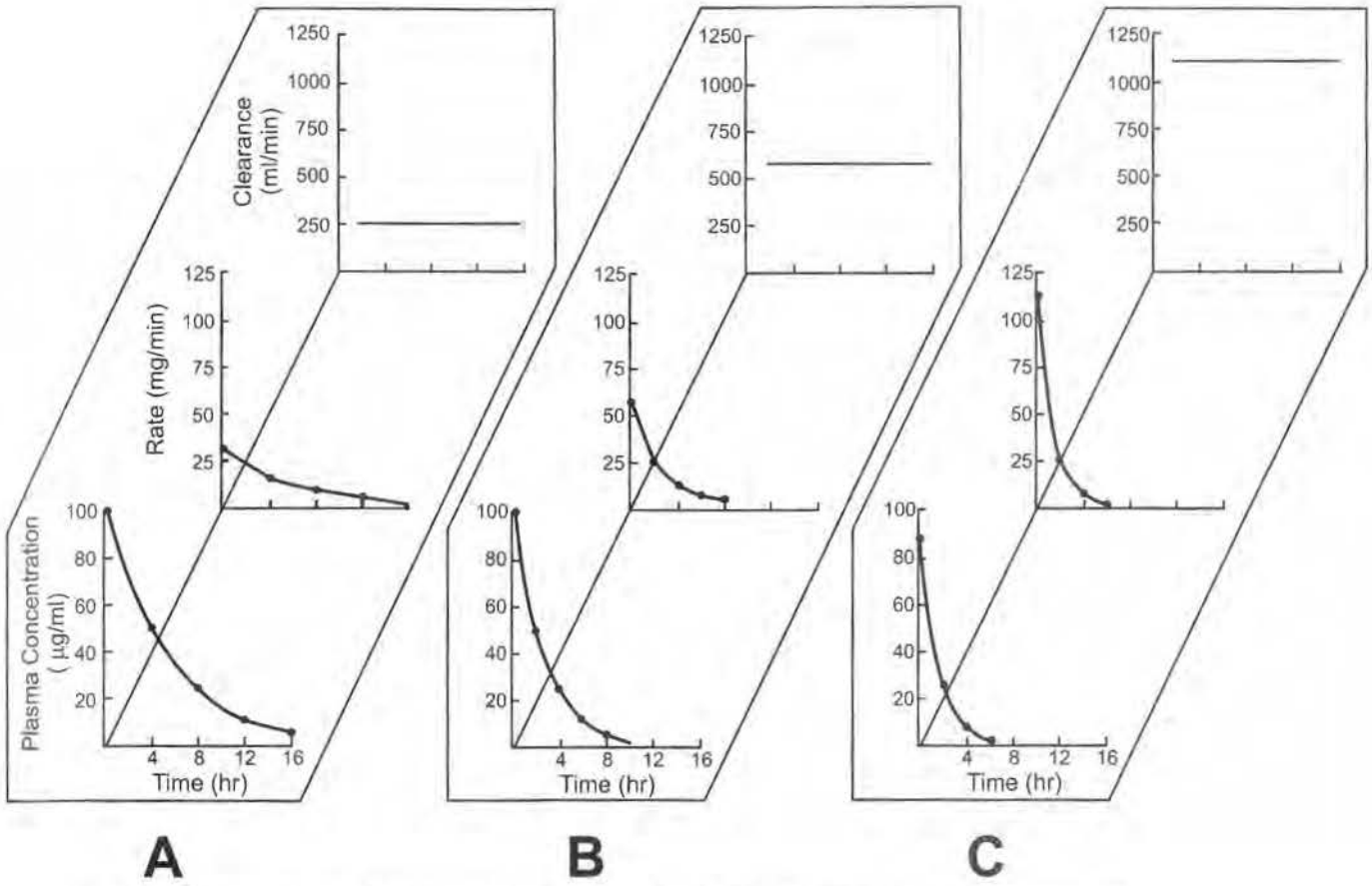


Figure 25. This figure is identical to that described in Figure 24, except three different compounds are being compared. In each of the three panels that project into the page are graphs of, from front to back, plasma concentration versus time, rate of elimination versus time, and rate of elimination/concentration versus time (i.e., clearance vs. time). Each panel represents a different drug with its own rate-concentration (or clearance) relationship. All drugs have the same initial plasma concentration. The terminal rate constant increases (or half-life decreases) when going from **A** to **C**. This is easily seen by comparing the concentration-time curves from **A–C**. Because rate of elimination is lowest for **A**, the ratio of that rate to the corresponding plasma concentration (which is clearance) is low, giving rise to a relatively low clearance. In contrast, **C** has the greatest rate of elimination relative to concentration and, therefore, the ratio of rate to concentration results in a large clearance. **B:** The compound is intermediate between **A** and **C**. (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

other 35 ml of blood to give a final exiting concentration of 7 ng/ml. Whereas this is a relatively efficient removal of compound from the blood by the organ, does this represent a substantial removal from the *body*? In 1 minute, only 150 ng out of a total dose of 150,000 have been lost from the body. This illustrates the difference between clearance and $t_{1/2}$. In fact, if it were assumed that the ER value was 1.0, the most efficient clearance possible, only 500 ng out of a total of 150,000 ng would be removed in 1 minute. Removal of the compound from the blood results in a trivial change in blood concentration. The $t_{1/2}$ of this compound is approximately 11 hours.

Before the blood perfuses the organ during the second minute, it must mix with the rest of the blood in the body. Because all of the rest of the blood has a concentration of 10 ng/ml, the blood exiting the clearing organ at a concentration of 7 ng/ml results in a trivial dilution of the concentration and the new concentration is 9.99 ng/ml. The process repeats during the second and all subsequent minutes. The ER value and clearance are the same at all times, but the amount extracted by the organ decreases with time as the amount in the body declines. In the second minute, a little less than 150 ng is removed from the blood. The exiting blood concentration has a value of approximately 6.99 ng/ml. When the exiting blood mixes with all of the rest of the blood (at a concentration of 9.99 ng/ml), the resulting concentration is 9.98 ng/ml, which is the new concentration that perfuses the organ during the third minute. This process continues until all of the compound has been eliminated from the body. Of course, this process does not happen in short 1-minute bursts; it is happening all of the time, resulting in a smooth exponential decline in concentration with time.

What is it that drives organ clearance for a specific compound? The ER determines the value for organ clearance. What drives ER? In the model that has been used, which is referred to by several terms (venous equilibrium, blood flow- or perfusion-limited or well-stirred model), the ER is a function of CL_{int}, as noted in the following relationship:

$$\text{extraction ratio} = \frac{CL_{int}}{CL_{int} + Q} \qquad \text{[Eq. 26]}$$

Notice that for ER to approach its maximum value of 1.0, CL_{int} must be a large value and larger than organ blood flow (i.e., when $CL_{int} >> Q$; ER ≅ 1.0 and CL ≅ Q). Such compounds have large values for organ clearance (approximately equal to organ blood flow) and fall into the right side of the organ clearance

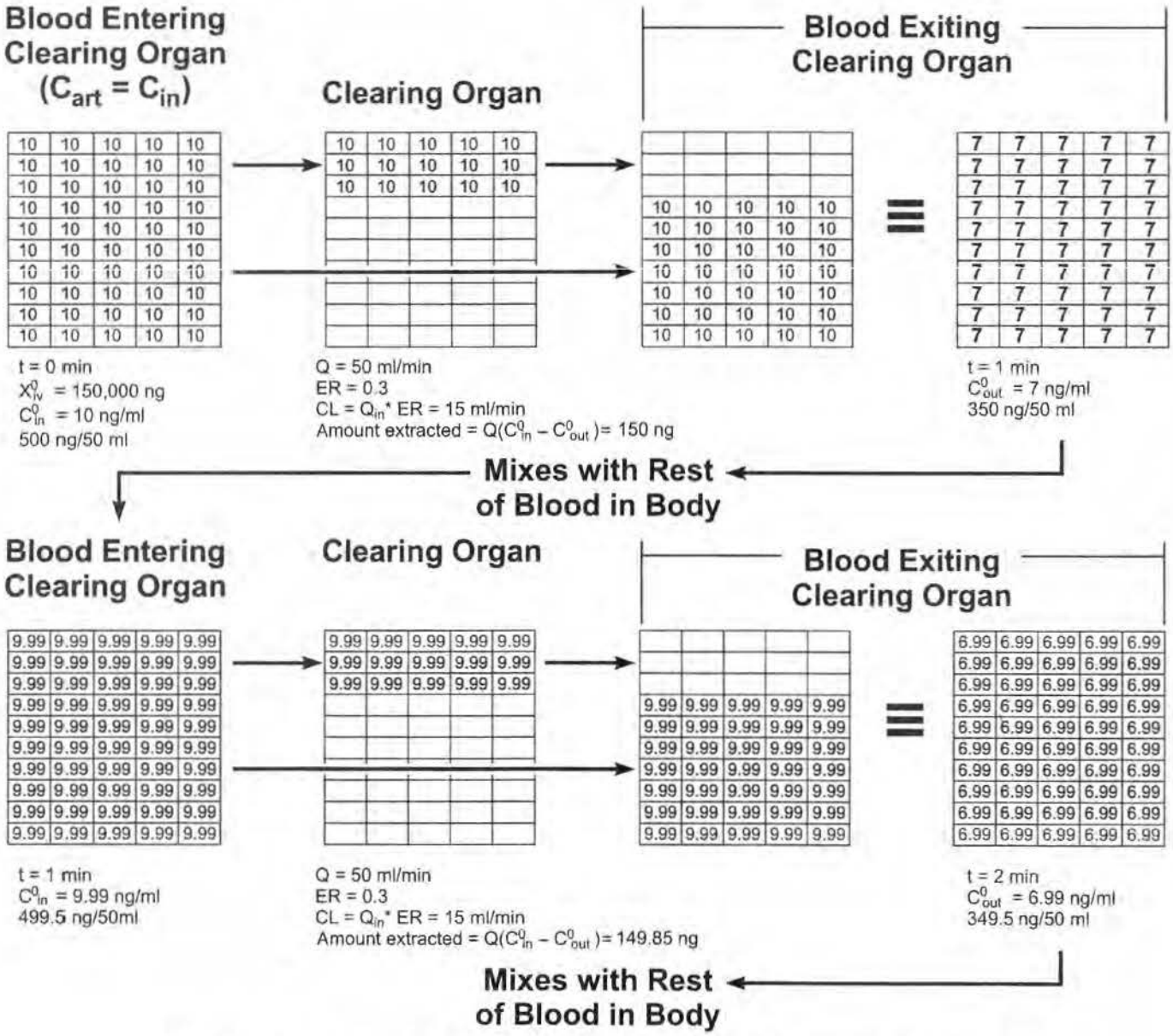


Figure 26. Sequential 1-minute *snapshots* illustrating the extraction of a drug as it traverses the eliminating organ and moves through the body. An intravenous dose is given (150,000 ng), which produces an initial blood concentration of 10 ng/ml. The only organ that eliminates the compound has an extraction ratio (ER) of 0.30, and it receives blood at a rate of 50 ml/minute (Q = 50 ml/minute). At time zero, 50 ml of blood (shown as 50 boxes) at a concentration of 10 ng/ml enters the eliminating organ for the first time. Because the ER is 0.3, 30% of the compound in the blood is removed as blood traverses the organ. This is comparable to saying that the content in 30% of the organ blood volume is removed. This is illustrated with there being 15 boxes or 15 ml of blood (0.3 × 50 ml = 15 ml) devoid of compound. Thus, the clearance (CL) of the compound is 15 ml/minute. As the blood exits the organ, the *empty* boxes now reequilibrate with the rest of the exiting blood to give a homogenous concentration of 7 ng/ml. The organ has removed 30% of the compound that was presented to it in the first minute (i.e., 0.3 × 10 ng/ml × 50 ml/minute = 150 ng removed in the first minute). A physiologic model of this system is shown to indicate that as compound exits the organ, the exiting venous blood concentration is affected by mixing with venous blood perfusing the rest of the body. This mixing results in an increase in the blood concentration before its next entry into the eliminating organ. The exiting venous blood (7 ng/ml) meets up with, mixes, and reequilibrates with the concentration in the rest of the blood (10 ng/ml) to give a concentration of 9.99 ng/ml. This is the new blood concentration that enters the eliminating organ in the second minute. Another 1-minute *snapshot* is shown for the second minute. Fifty milliliters of blood at a concentration of 9.99 ng/ml enters the eliminating organ. Because the ER is the same, 30% of compound once again is removed from the blood (i.e., 0.3 × 9.99 ng/ml × 50 ml/minute = 149.8 ng removed in the second minute). The CL is the same (i.e., 0.3 × 50 ml/minute = 15 ml/minute). On exiting the organ, the concentration of compound reequilibrates to give an exiting concentration of 6.99 ng/ml, which mixes with the rest of the blood (9.99 ng/ml) to give a final venous concentration of 9.98 ng/ml. The latter is now the new concentration entering the organ beginning in minute 3. (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

rainbow (Fig. 22). In contrast, compounds that have small values for CL_{int}, and that fall into the left side of the organ clearance *rainbow*, have an organ clearance approximately equal to CL_{int} (i.e., when $CL_{int} << Q$; $ER \equiv CL_{int}/Q$ and $CL \equiv CL_{int}$). The definition of CL_{int} is a *clearance that is not dependent on organ blood flow.* Thus, the rate-limiting step for CL_{int} is not delivery of the compound to the site of clearance (e.g., the hepatic enzymes). In the whole body or for an isolated organ, this cannot apply; blood flow necessarily rate-limits clearance, with the exception of low clearance compounds. Thus, if there were no limit to the ability to pump blood to an organ, at sufficiently large blood flow, CL_{int} would be measurable.

CL_{int} is what is measured in a test tube when a compound is added to some form of enzyme (e.g., pure isozyme, homogenized liver, hepatocytes), and the rate of metabolite formation is determined (or disappearance of parent compound). Adding the compound to the enzyme preparation is instantaneous; there is no measurable delivery rate, as there is in the body via blood flow. The resulting *in vitro* measure of clearance is CL_{int}, because that value is independent of any flow. Numerically, CL_{int} is greater than or approximately equal to organ clearance determined in the body, depending on the magnitude of CL_{int}. The best way to visualize this process is to consider the *in vitro* situation illustrated in Figure 27. Ten molecules of a drug are added to a test tube containing 10 ml of an enzyme solution and rapidly mixed. At time zero, the concentration of drug is 1 mol/ml. One minute later, the enzyme reaction is stopped and the amount of metabolite produced is determined. Four molecules of metabolite have been produced. The rate of metabolite production is 4 mol/minute. The corresponding clearance, which is rate of metabolite formation (4 mol/minute) divided by the starting drug concentration (1 mol/minute), is 4 ml/minute. In 1 minute, 4 ml of starting solution have been completely cleared of drug. This value, 4 ml/minute, is the intrinsic metabolic clearance of that drug. Changing enzyme activity by induction of inhibition alters intrinsic metabolic clearance accordingly.

The equation noted for ER in equation 26 can be substituted for ER in equation 25 to give a more descriptive relationship:

$$CL = \frac{CL_{int} \cdot Q}{CL_{int} + Q} \qquad \text{[Eq. 27]}$$

Low clearance compounds have small values for CL_{int} and because $CL_{int} << Q$, $CL \equiv CL_{int}$. An IV bolus dose of such a compound allows determination of the CL_{int} of that compound. In this instance, blood flow does not rate-limit the organ clearance of the compound. Any factor affecting CL_{int} affects clearance. An example is altered enzyme activity by the presence of another compound.

In contrast, high clearance compounds have large values for CL_{int}, and because $CL_{int} >> Q$, $CL \equiv Q$. An IV dose of such a compound gives a value of clearance that is actually an estimate of organ blood flow. The clearance of such a compound can only be affected by changes in organ blood flow (e.g., altered cardiac output) and not by changes in CL_{int}.

This analysis has ignored those compounds that fall into an intermediate clearance category. The clearance of such compounds is affected to different degrees by changes in CL_{int} and organ blood flow. Thus, unlike the previous situations, the equation noted in 27 cannot be simplified for intermediate clearance compounds.

There is, finally, one more variable to consider and that is plasma protein binding. Plasma protein binding may affect the clearance of those drugs that have low clearances; these have been referred to as being *restrictively cleared*. The clearance of such compounds is restricted by binding to plasma proteins. This leads to the need to define and illustrate another term, *unbound intrinsic clearance*, $CL_{U,int}$. $CL_{U,int}$ is CL_{int} in the absence of plasma protein binding or adjusted for that binding. This definition is illustrated in Figure 28, which is similar to the scenario noted in Figure 27 and which is for the same compound. In this instance, however, there is binding protein present in the enzyme solution. At time zero, the total concentration of drug is 1 mol/ml. Of that total, 50% is bound to protein, giving an unbound concentration of 0.5 mol/ml. One minute later, two molecules of metabolite are formed giving a rate of formation of 2 mol/minute. The clearance of this compound is 2 mol/minute divided by 1 mol/ml or 2 ml/minute. This value represents the intrinsic metabolic clearance of the drug under the conditions specified. Note that this clearance is one-half the value of CL_{int} when no binding protein was present; the binding has reduced the CL_{int} of the compound (CL_{int}, 4 ml/minute; Fig. 27). If this value of CL_{int} is corrected for only those molecules that are not bound to protein by dividing CL_{int} by the unbound fraction of compound (i.e., 0.5), 4 ml/minute is obtained. The latter value is $CL_{U,int}$ and is identical to the value determined experimentally in the absence of binding protein (Fig. 27). $CL_{U,int}$ is the most fundamental measure of clearance, as it is independent of blood flow and plasma protein bind-

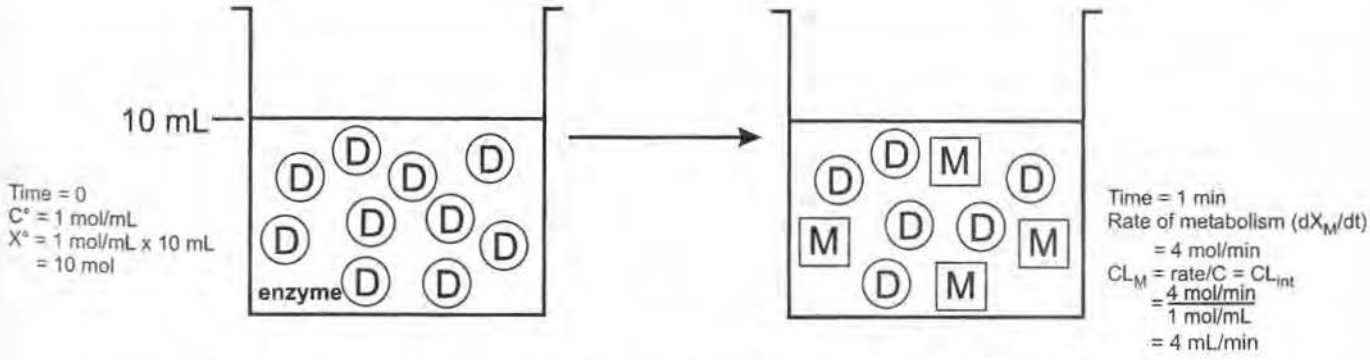


Figure 27. An *in vitro* experiment designed to measure intrinsic metabolic clearance (CL_{int}). At time zero, 10 molecules of drug (D) are added to 10 ml of solution containing enzyme. The initial time zero concentration is 1 mol/ml. One minute later, the reaction is stopped, and the amount of metabolite formed is measured. Four molecules of metabolite (M) are formed in 1 minute; thus, the rate of metabolite formation is 4 mol/min. Because CL is rate (4 mol/minute) divided by concentration (C; 1 mol/ml), the clearance value for this drug is 4 ml/minute. In other words, 4 ml of starting solution have been completely cleared of the drug by having been converted to metabolite. This value of 4 ml/minute is the intrinsic clearance of the drug. (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

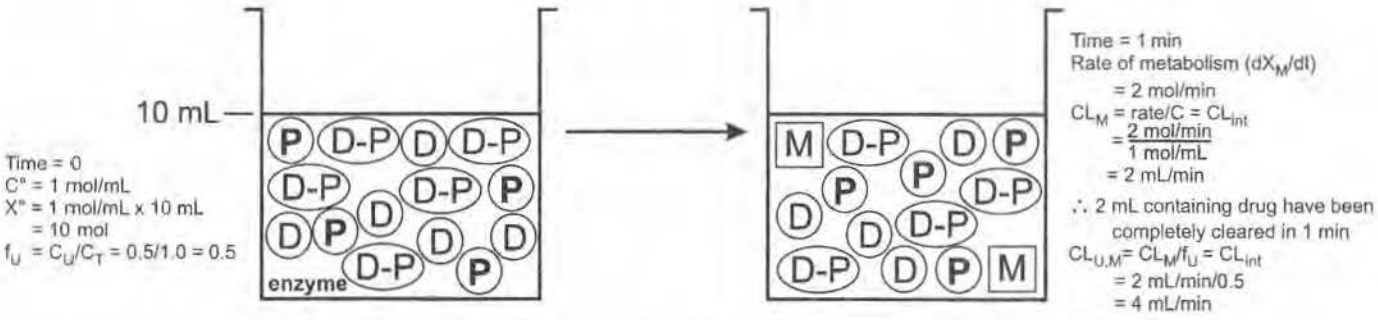


Figure 28. The same scenario as in Figure 27 for the measurement of intrinsic metabolic clearance (CL_{int}). In this instance, however, the enzyme reaction solution contains binding protein. At time zero, ten molecules of drug (D) are added to 10 ml of enzyme solution. One-half of the drug molecules are bound to the protein so that the unbound fraction (f_U) is 0.5. At time zero, the initial total drug concentration is 1 mol/ml, and the unbound concentration is 0.5 mol/ml. One minute later, the reaction is stopped, and the amount of metabolite formed is determined. Two molecules of metabolite (M) are formed in 1 minute; thus, the rate of metabolite formation is 2 mol/minute. Because clearance is rate (2 mol/minute) divided by (total) concentration (1 mol/ml), the clearance value for this drug is 2 ml/minute. In other words, 2 ml of starting solution have been completely cleared of the drug by having been converted to metabolite. This value of 2 ml/minute is the intrinsic clearance of the drug. Note that this is one-half of the value for CL_{int} in the absence of binding protein (4 ml/minute; Fig. 27). The binding protein has protected the drug and reduced its clearance. This leads to the need to estimate unbound intrinsic metabolic clearance, $CL_{U,int}$. The latter is the value of intrinsic clearance corrected for the fraction of drug that is unbound. In this instance, $CL_{U,int}$ is 2 mol/ml divided by 0.5 or 4 ml/minute. The latter value is identical to the one determined in the absence of binding protein in Figure 27. (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

ing, CL_{int}, is the product of the unbound fraction and $CL_{U,int}$ (i.e., $CL_{int} = f_U \cdot CL_{U,int}$).

Based on the previous development, the final and most useful relationship for defining clearance can be written as follows:

$$CL = \frac{f_U \cdot CL_{U,int} \cdot Q}{f_U \cdot CL_{U,int} + Q} \qquad \text{[Eq. 28]}$$

This expression incorporates all factors that can possibly affect the clearance of a compound by an organ, and it is useful in interpreting data and in making predictions. Thus, for a low clearance compound (restrictively cleared), $f_U \cdot CL_{U,int} << Q$ and, therefore, $CL \equiv f_U \cdot CL_{U,int}$. The only factors that can affect the clearance of such a compound are those that affect plasma protein binding and/or $CL_{U,int}$. Changes in blood flow should have no effect.

In contrast, for a compound with a large clearance (nonrestrictively cleared), $f_U \cdot CL_{U,int} >> Q$ and, therefore, $CL \equiv Q$. Only factors that can affect organ blood flow affect the clearance of this type of drug. Changes in plasma protein binding or in $CL_{U,int}$ are not expected to have an effect. As noted previously, intermediate clearance compounds depend on blood flow, plasma protein binding, and $CL_{U,int}$.

The influence of blood flow and plasma protein binding on clearance is illustrated in Figure 29. The effect of $CL_{U,int}$ is discussed under Multiple Dosing. Figure 29A illustrates the relationship between clearance of three different compounds in the isolated perfused rat liver and perfusate flow through the liver (16). Perfusate flow is a surrogate measure of *blood* flow in the body. The clearance or low clearance (or low CL_{int}) compounds, such as antipyrine, is not expected to be influenced by blood flow. As noted previously, the clearance of such a compound depends only on plasma protein binding and $CL_{U,int}$. This is what is seen in the figure; antipyrine clearance is independent of perfusate flow. In contrast, the clearance of a high clearance (or high CL_{int}) compound, such as lidocaine, is expected to be directly related to blood flow, as is the case shown in the figure. As noted previously, the clearance of such a compound depends only on organ blood flow. The intermediate clearance compound, ethanol, depends on blood flow at low flow rates but then becomes independent of flow at higher flow rates. Knowing the clearance category for a compound allows one to predict the relationship between clearance and organ blood flow.

Figure 29B illustrates the influence of plasma protein binding on the clearance of warfarin in rats (17). The greater the percentage of warfarin unbound in serum, the greater the clearance of the drug. One would conclude that warfarin is a low clearance drug because only for such drugs would one expect plasma binding to affect clearance (i.e., $CL \equiv f_U \cdot CL_{U,int}$). Of course, a direct estimation of the clearance category of the drug is to calculate ER by comparing measured clearance with the value of blood flow to the organ responsible for clearance, in this case liver blood flow in the rat. If one knew that warfarin fell into the low clearance category, one would predict the relationship illustrated in Figure 29B.

ER drives clearance and CL_{int} drives ER; what determines CL_{int}? This has been alluded to in a previous discussion of Michaelis-Menten enzyme kinetics. The rate of an enzyme reaction at low concentrations was given by equation 12.

Dividing both sides of the equation by the driving force concentration, C gives the corresponding relationship for enzyme or metabolic clearance:

$$\frac{\text{rate (or, v)}}{C} = \text{Clearance} = \left(\frac{V_{max}}{k_{mm}}\right) \qquad \text{[Eq. 29]}$$

Clearance at low *in vitro* concentrations is actually the ratio of the maximal rate of enzymatic metabolism, V_{max}, to the Michaelis constant, k_{mm}. The clearance term noted in the equation is equal to CL_{int}. The magnitude of the CL_{int} of a compound is determined by those factors that affect V_{max} and k_{mm}. $CL_{U,int}$ would be the ratio of V_{max} to k_{mm}, corrected for binding.

What happens to clearance if the system is dose-dependent and becomes nonlinear? Writing the Michaelis-Menten equation expressed as clearance

$$\frac{\text{rate (or, v)}}{C} = \text{Clearance} = \frac{V_{max}}{k_{mm} + C} \qquad \text{[Eq. 30]}$$

At low concentrations, as noted previously, $C << k_{mm}$ and clearance is a constant given by V_{max} divided by k_{mm}. At higher concentrations, the denominator becomes larger and larger (i.e., C

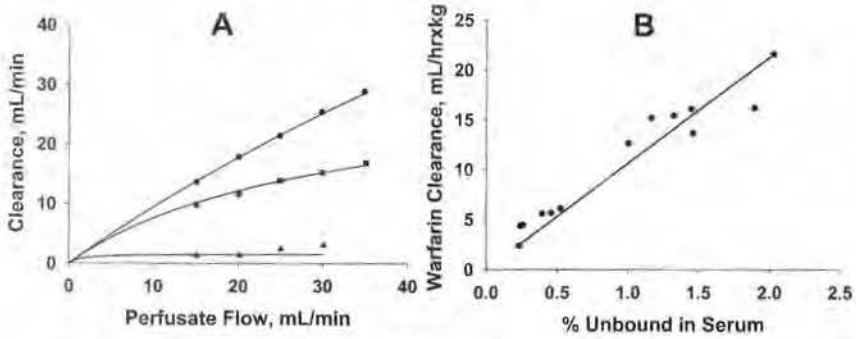


Figure 29. **A:** Clearance as a function of perfusate (*blood*) flow in the isolated perfused rat liver for three compounds having low, intermediate, and high clearances. The high (lidocaine, ●) and intermediate (ethanol, ■) clearance compounds illustrate a dependence on *blood* flow. The low clearance compound (antipyrine, ▲) has a clearance that does not depend on *blood* flow. (From Sinha V, Brendel K, Mayersohn M. A simplified isolated perfused rat liver apparatus: characterization and measurement of extraction ratios of selected compounds. *Life Sci* 2000;66:1795–1804, used with permission of Saguaro Technical Press.) **B:** Warfarin clearance in rats as a function of the percentage unbound in serum. (Based on data in Levy G. Clinical implications of interindividual differences in plasma protein binding of drugs and endogenous substances. In: Benet LZ, ed. *The effect of disease states on drug pharmacokinetics*. Washington, DC: American Pharmaceutical Association, 1976:137–151.) This relationship indicates that warfarin must fall into a low clearance category because for such compounds, $CL \equiv f_U \cdot CL_{U,int}$.

$>> k_{max}$), and clearance becomes smaller and smaller and, in theory, approaches zero. Thus, for a saturable or nonlinear system, clearance decreases with concentration, and, as a result, $t_{1/2}$ increases with dose or concentration.

Based on the previous discussions, plasma protein binding or changes in binding affect the apparent volume of distribution (equation 18) and may or may not affect clearance, depending on the category of clearance. It is not at all obvious how such a change in binding affects the $t_{1/2}$ of a drug, because $t_{1/2}$ depends on volume and clearance. In fact, the only rational approach to predicting how a change in plasma protein binding affects $t_{1/2}$ is to consider the fundamental relationship for $t_{1/2}$ as noted in equation 17, and this is illustrated under Nonvascular Input: Absorption and Bioavailability.

ELIMINATION PROCESSES

There are numerous routes of drug elimination, but the most significant are renal excretion and hepatic metabolism. The kidney and liver are anatomically and biochemically well suited for their role in processing drugs and other foreign compounds for their ultimate elimination from the body. Other routes of elimination could become relatively more important, depending on the compound, and these routes include nonhepatic metabolism (e.g., blood, kidney, muscle); biliary excretion; exhalation; perspiration; and so forth. Elimination processes are almost always synonymous with events that occur after a drug has gained access to the body, (i.e., the bloodstream). There are, however, elimination processes that may occur before drug gaining access to the body, and these are best referred to as *presystemic elimination*. The latter events occur at or near the site of drug administration or exposure. An example is chemical breakdown or enzymatic alteration of a compound in muscle tissue after intramuscular dosing. Perhaps the best examined and most significant are the presystemic elimination processes that occur during oral administration and that may substantially affect the dose reaching the systemic circulation. These are discussed in the Absorption and Bioavailability section and include processes such as decomposition or metabolism in gastrointestinal (GI) fluid, metabolism in the GI wall and liver before systemic distribution, and bacterial metabolism in the lower end of the gut.

The elimination process of parent drug from the body is schematically illustrated in Figure 30, which assumes a one-compartment body model that contains the major eliminating organs, the liver and kidney. Each organ is associated with a first-order rate constant for a specific compound, which is represented by k_m for hepatic metabolism and k_u for urinary excretion. The sum of these constants forms the apparent overall elimination rate constant, K. The scheme to the right of the model illustrates the elimination with parallel (or competing) eliminating processes for the kidney and liver. The parent compound in the body, X_B, is excreted via the kidney to form unchanged drug in the urine, X_U, and it is also metabolized by the liver to form metabolite, X_M. The subsequent appearance of metabolite in the urine via the kidney (X_{MU}) is downstream of

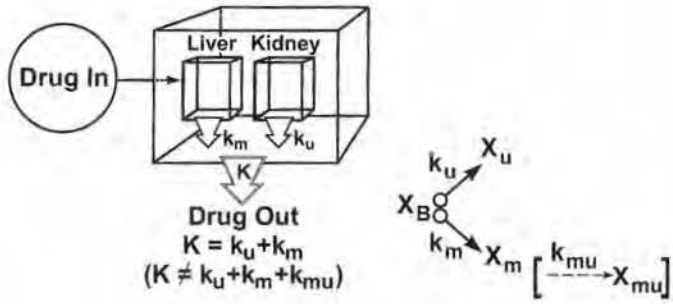


Figure 30. Schematic representation of elimination *via* hepatic metabolism and renal excretion in a one-compartment body model. The apparent overall first-order elimination rate constant, K, is the sum of the individual rate constants associated with loss of parent drug from the body. Thus, K is the sum of the urinary excretion rate constant, k_u, and the hepatic metabolic rate constant, k_m; $K = k_u + k_m$. The scheme used to describe elimination is shown to the right of the model. It is important to note that only those steps responsible for processing the parent drug (indicated as arrows connected to X_B, the amount of parent drug in the body) form part of K. Thus, the down-stream loss of metabolite via urinary excretion by the kidney, k_{mu}, is not part of parent drug elimination. (From Mayersohn M. Toxicokinetics: Measurement of disposition half-life, clearance and residence times. In: Maines M, ed. *Current protocols in toxicology*. New York: John Wiley and Sons, 2000:5.3.5, with permission of Saguaro Technical Press, Inc, 2002, Tucson, AZ.)

parent drug elimination and has no bearing on the value of K. This point is sometimes confused in the literature. Assume that 100% of the compound is metabolized by the liver and that all of that metabolite ultimately appears in the urine. The statement that the *compound is excreted into the urine* is not correct; it is the metabolite that is excreted into the urine and that process is not related to elimination of the parent compound, which is strictly metabolism. In that instance, systemic clearance is equal to hepatic metabolic clearance (renal clearance is zero).

Renal Excretion

The kidney is ideally suited as an organ of elimination on the basis of its specialized anatomy and biochemistry and high blood flow. The functioning unit of the kidney is the nephron, of which there are approximately 1.3 million in each human kidney. The nephron is schematically illustrated in Figure 31. Although not thoroughly illustrated, the nephron consists of the glomerulus, proximal and distal tubules, loop of Henle, and the collecting duct. Approximately 20% of cardiac output (in a normal, lean 70-kg adult man), approximately 1200 ml of blood, perfuses the kidneys each minute. Assuming a hematocrit of approximately 0.5, renal plasma flow is approximately equal to 600 ml/minute. Because only approximately 20% of plasma is filtered by the glomerulus, glomerular filtration rate (GFR) (actually, *filtration clearance*) is approximately 120 ml/minute.* This *filtration fraction* of 0.2 is calculated by the ratio of glomerular filtration clearance (for a compound that only undergoes that process; e.g., inulin, approximately 120 ml/minute) to an estimate of renal plasma flow (as measured by tubular secretion clearance of a compound that exclusively undergoes active tubular secretion; e.g., PAH). Urine production is approximately 1 ml/minute, which represents the difference between what is filtered, approximately 120 ml/minute, and what is reabsorbed, or approximately 119 ml/minute, indicating efficient reabsorption of water.

Arterial blood flows through the glomerulus, which is responsible for the passive filtration of compounds from the blood. The filtered material includes waste products as well as drugs and other foreign chemicals. This passive process is governed by a variety of factors, including glomerular integrity, molecular size of the compound, and binding to plasma proteins. Large molecules, such as proteins, are generally too large to be filtered. Compounds that are highly plasma protein bound are protected from filtration; only the unbound form is filtered. Creatinine and inulin are used as indices of GFR. Although the latter may more accurately reflect glomerular filtration, it requires exogenous dosing. In contrast, creatinine is an endogenous biochemical, which provides a sufficiently accurate estimate of glomerular filtration without the need for exogenous dosing. Because creatinine clearance is seldom determined experimentally in a patient, there are useful approximating relationships for its estimation based on patient gender, age, weight, and serum creatinine concentration.

Because glomerular filtration permits passage of only the unbound form of the material from plasma into the urine, the rate of filtration of the substance is a function of the GFR and the unbound plasma concentration (C_U) of the substance. The latter represents the driving force for filtration,

$$\text{Filtration rate} = GFR \cdot C_U = GFR \cdot f_U \cdot C_{TOTAL} \qquad \text{[Eq. 31]}$$

in which C_{TOTAL} is the total concentration (i.e., bound plus unbound) of the substance in plasma. Therefore, filtration clearance of a substance is simply the filtration rate divided by the total drug concentration,

$$CL_{FILTR} = \frac{\text{filtration rate}}{C_{TOTAL}} = \frac{GFR \cdot C_{TOTAL} \cdot f_U}{C_{TOTAL}} = GFR \cdot f_U \quad \text{[Eq. 32]}$$

As a consequence, renal clearance, CL_R, of a substance by glomerular filtration only, should be equal to the GFR of that subject multiplied by the unbound fraction of the substance in plasma. If renal clearance of the compound exceeds the value for CL_{FILTR}, the drug undergoes some tubular secretion. In contrast, if CL_R is less than the value for CL_{FILTR}, the compound undergoes reabsorption. Of course, it is always possible that all of these processes are taking place at the same time. Notice, from equation 32, that CL_{FILTR} is not dependent on plasma concentration of the substance, as long as GFR and plasma protein binding do not change.

In contrast to glomerular filtration, which is a passive process, *tubular secretion* and *tubular reabsorption* are active and saturable, nonlinear processes, much like Michaelis-Menten enzyme kinetics. In fact, the identical relationship can be used to describe those processes, although T_{max}, for transport maximum, sometimes replaces V_{max}. Tubular secretion and tubular reabsorption may be described by the same equation, the only difference is the sign placed in front of the equation, to indicate movement out of or into the body, respectively.

$$\text{Rate of secretion} = \frac{V_{max}^{secr} \cdot C}{k_{mm}^{secr} + C} \qquad \text{Rate of reabsorption} = \frac{V_{max}^{reabs} \cdot C}{k_{mm}^{reabs} + C} \quad \text{[Eq. 33]}$$

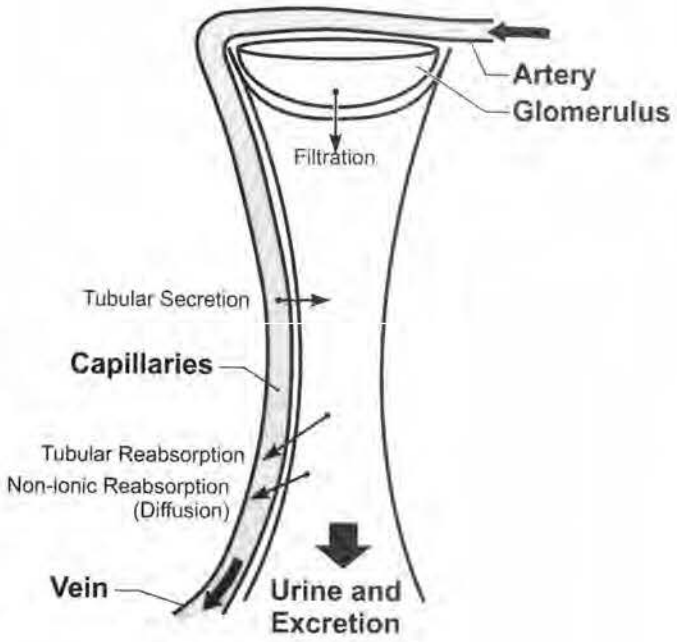


Figure 31. Schematic diagram illustrating the nephron, the functioning unit of the kidney. Arterial blood flow to the glomerulus results in the passive filtration of compound. Tubular secretion is an active, energy-dependent process resulting in movement of a compound against a concentration gradient into the urine. In the distal tubules, compounds present in the urine can undergo active, energy-dependent reabsorption back into the blood. A passive, nonionic diffusion process can also result in reabsorption of certain compounds from the urine back into the blood, depending on their pK_a, oil/water partition coefficient, and urine pH. Filtered and secreted compound is excreted into the formed urine. (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

*It is of historical note that the concept of clearance was developed by renal physiologists.

The corresponding relationships for clearance by secretion and reabsorption are

$$CL_{SECR} = \frac{\text{rate of secretion}}{C} = \frac{V_{max}^{secr}}{k_{mm}^{secr} + C} \qquad [Eq. 34]$$

$$CL_{REABS} = \frac{\text{rate of reabsorption}}{C} = \frac{V_{max}^{reabs}}{k_{mm}^{reabs} + C}$$

As plasma concentrations increase as a result of larger doses, secretion clearance and reabsorption clearance decrease; they become less efficient processes, just as one sees with saturable enzyme kinetics. Compounds such as PAH and penicillin undergo active tubular secretion, whereas many endogenous biochemicals (e.g., glucose, amino acids, vitamins, and so forth) undergo tubular reabsorption.

Net urinary excretion rate and renal clearance are a function of all renal mechanisms. Thus, the net urinary excretion rate equals: filtration rate + secretion rate – reabsorption rate – non-ionic reabsorption rate. Dividing each of those rates by plasma concentration gives the corresponding values for clearance.

$$CL_R = CL_{FILTR} + CL_{SECR} - CL_{REABS} - CL_{N.I.REABS} \qquad [Eq. 35]$$

Renal clearance of a compound is determined experimentally by obtaining plasma and urine excretion data and plotting, according to the basic relationship for clearance, rate of urinary excretion versus plasma concentration at the same time or amount excreted versus AUC for corresponding times.

Figure 32A illustrates the rate processes that PAH undergoes as a function of unbound plasma concentration (18). Filtration rate increases directly with concentration, as expected of a passive process. Secretion, in contrast, becomes saturated, and the rate of secretion becomes constant (approaches a V_{max} or a transport maximum, T_{max}). This is exactly what was noted previously for the rate of enzyme metabolism described by Michaelis-Menten kinetics. Because net urinary excretion is the sum of secretion and filtration, that value increases as concentration increases, filtration becoming numerically more important as concentration increases.

The corresponding clearance-concentration relationships are illustrated in Figure 32B. These graphs are obtained by dividing the rates (shown in Figure 32A) by plasma concentrations of PAH. Filtration clearance remains constant, independent of plasma concentration, as expected of a passive, first-order process. Clearance due to secretion decreases as concentrations rise; the process becomes less efficient. Renal clearance, which is the sum of filtration and secretion clearances, decreases as concentrations increase and, ultimately, approaches the value for filtration clearance. The expression for PAH renal clearance is

$$CL_R = CL_{FILTR} + CL_{SECR} = CL_{FILTR} + \frac{V_{max}^{secr}}{k_{mm} + C} \qquad [Eq. 36]$$

As PAH plasma concentrations, C, increase, the term on the right approaches zero and CL_R is approximately equal to CL_{FILTR}.

The comparable graphical relationships for a compound, such as glucose, that undergo tubular reabsorption are illustrated in Figure 33 (19). Rates of the different renal mechanisms as a function of glucose plasma concentration are illustrated in Figure 33A. Filtration increases directly with glucose concentration. Up to a glucose plasma concentration of approximately 2 mg/ml, all of the glucose that has been filtered is reabsorbed back into the body; no glucose appears in the urine. The reabsorption mechanism becomes saturated, as noted for PAH secretion, and rate of secretion becomes constant (a V_{max} or T_{max} is achieved). As a consequence, the net excretion rate is zero until a glucose plasma concentration of approximately 2 mg/ml, beyond which filtration takes over and glucose excretion increases with concentration.

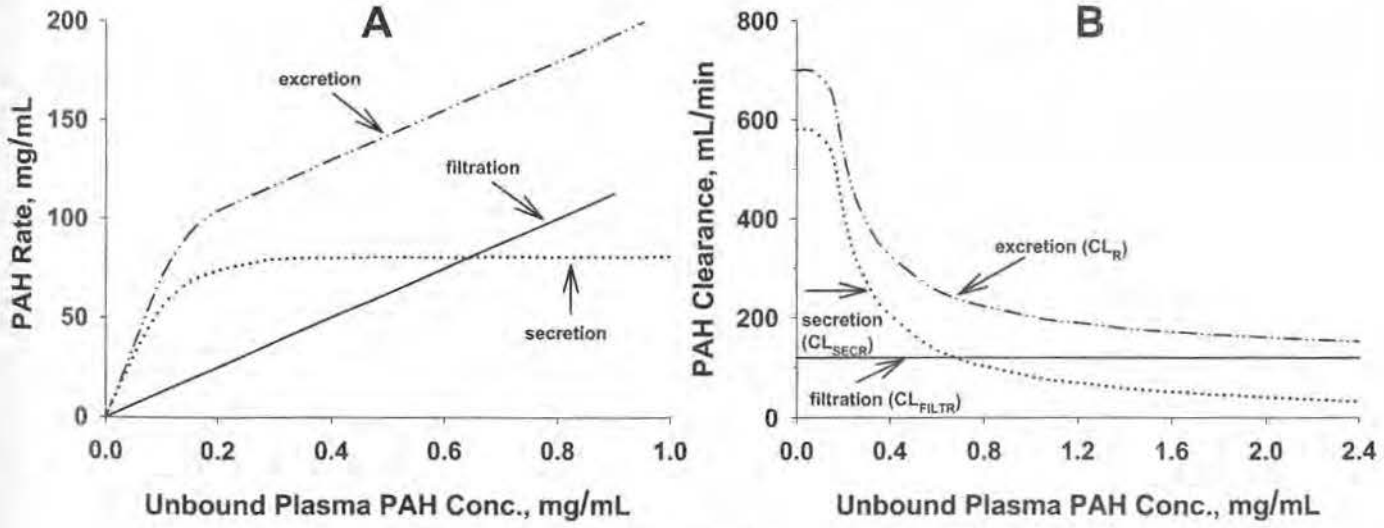


Figure 32. A: Rate of para-aminohippurate (PAH) processing by different renal mechanisms as a function of unbound plasma PAH concentrations. Excretion rate is the sum of filtration rate, which remains constant, and secretion rate, which becomes saturated (approximately 80 mg per minute) above a plasma concentration of approximately 0.1 mg/ml. At low plasma concentrations, excretion rate is equal to secretion rate, whereas above saturation concentrations, filtration rate becomes more important. **B:** The rate processes in **A** have been divided by unbound plasma PAH concentrations to give corresponding clearance values plotted as a function of unbound PAH plasma concentrations. Filtration clearance (CL_{FILTR}) remains constant, whereas secretion clearance (CL_{SECR}) decreases with PAH concentration. As a result, net renal clearance (CL_R) of PAH decreases, approaching the value of CL_{FILTR}. (Based on data recovered from Pitts RF. *Physiology of the kidney and body fluids*, 3rd ed. Chicago: Year Book 1974:141–142. From M. Mayersohn, unpublished, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

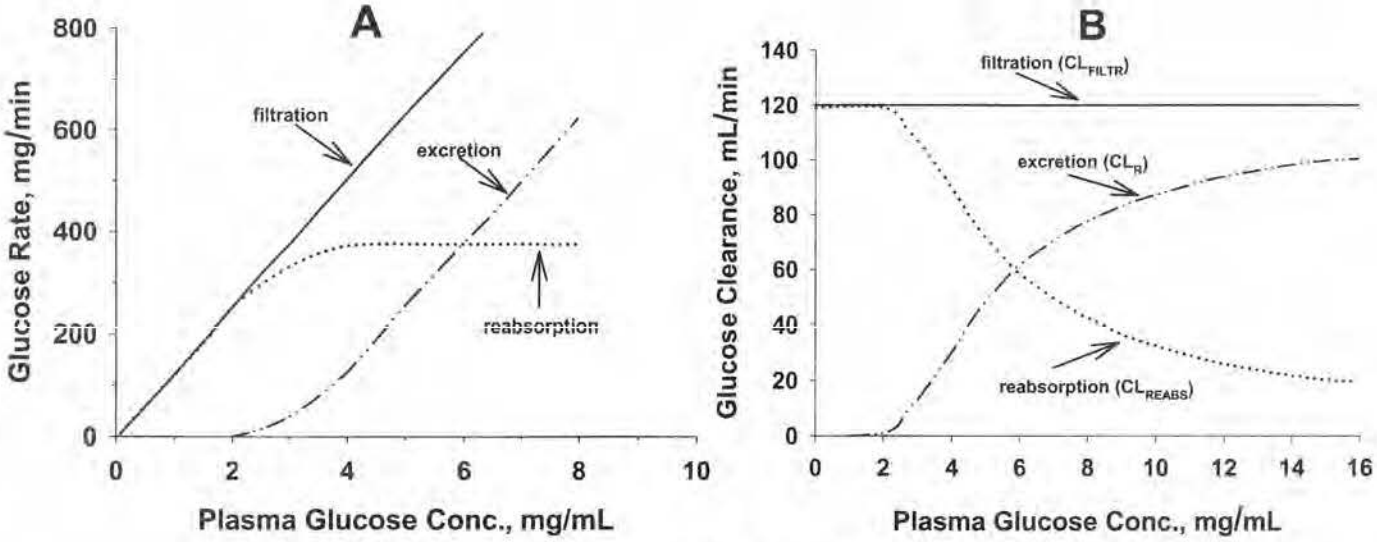


Figure 33. **A:** Rate of glucose processing by different renal mechanisms as a function of glucose plasma concentrations. Excretion rate is the sum of filtration rate, which remains constant, and reabsorption rate, which becomes saturated (approximately 400 mg/minute) above a plasma concentration of approximately 2 mg/ml. At low plasma concentrations, excretion rate is approximately zero, because what is filtered is reabsorbed. At higher plasma concentrations, filtration exceeds reabsorption, and glucose is excreted into the urine. **B:** The rate processes in **A** have been divided by glucose plasma concentrations to give corresponding clearance values plotted as a function of glucose plasma concentrations. Filtration clearance (CL_{FILTR}) remains constant, whereas reabsorption clearance (CL_{REABS}) decreases with glucose concentration. As a result, net renal clearance (CL_R) of glucose increases, approaching the value of CL_{FILTR}. (Based on data recovered from Pitts RF. *Physiology of the kidney and body fluids*, 3rd ed. Chicago: Year Book 1974:73–74. From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

The corresponding clearance relationships for glucose are illustrated in Figure 33B. Filtration clearance does not change with glucose plasma concentrations. Reabsorption clearance, however, becomes less efficient and decreases with glucose concentration, approaching a value of zero. The net renal clearance increases from zero until it approaches filtration clearance as described by

$$CL_R = CL_{FILTR} - CL_{REABS} = CL_{FILTR} - \frac{V^{reabs}_{max}}{k_{mm} + C} \quad \text{[Eq. 37]}$$

As glucose plasma concentrations, C, increase, the term on the right approaches zero and CL_R is approximately equal to CL_{FILTR}.

The other reabsorption process, which has been referred to as *nonionic reabsorption* or *nonionic diffusion*, is passive, non–energy-requiring transport. To undergo this process, a compound must have sufficient lipophilicity (as measured by oil/water partition coefficient) and an ionization constant (pK_a) such that a reasonable fraction of the compound is unionized at urine pH. The latter are two important factors that affect the movement of any compound across an epithelial membrane. For some compounds, urine flow may also be important. Because the unionized form of a compound has the greatest lipophilicity, and it is that form that most readily penetrates biologic membranes, the urine pH that minimizes ionization is expected to promote reabsorption. Of course, just the opposite is true with regard to renal excretion; the urine pH that increases ionization is expected to decrease reabsorption and promote excretion. The latter observation is the basis for treatment of overdose of certain acidic or basic compounds whose clearance is partially renal. The efficiency of such urine pH manipulation, however, must be viewed cautiously and with consideration of the basic pharmacokinetic properties of the compound. An illustration of the effect of urine pH on the urinary excretion of a basic compound, methamphetamine, is presented in Figure 34 (20). Acidification of urine is expected to ionize the compound in urine and thereby minimize reabsorption and increase renal clearance. In contrast, alkalinization of urine is expected to create the opposite condition: decreased ionization, increased reabsorption, and reduced renal clearance. That is exactly what is seen in Figure 34 for rate of urinary excretion versus time and for the total amount recovered in 16 hours after oral dosing in humans (bar graphs to the right). The rate of urinary excretion is given by excretion rate = $CL_R \cdot C$. Excretion rate increases as a consequence of an increase in renal clearance in the presence of acidified urine. Just the opposite occurs during alkalinization of urine. Under the proper circumstances, alteration of urine pH might prove effective for treatment of overdose for certain weakly acidic or basic compounds.

A good example to illustrate the previous point is urine acidification in an attempt to enhance excretion of the basic drug, phencyclidine (PCP; $pK_a = 8.5$). Table 2 summarizes the analysis (21). Under uncontrolled urine pH conditions, renal clearance accounts for less than approximately 10% of the elimination of the compound (i.e., $CL_R/CL_S \cong 0.1$), whereas the nonrenal component (CL_{NR}), hepatic metabolism, which represents the major route of elimination, accounts for the remainder, approximately 92%. When the urine is made acidic, the value of nonrenal clearance is not expected to change; it remains approximately 350 ml/minute. It is important to keep in mind that organ clearances are independent of each other, except as a result of some indirect mechanism. In contrast, the renal clearance of PCP increases dramatically from 30 ml/minute to a value approximately four to five times greater, 135 ml/minute. The latter value now represents approximately 28% of systemic clearance (i.e., $CL_R/CL_S = 135/485 = 28\%$). What is the return for this large increase in renal clearance? Systemic clearance, which determines $t_{1/2}$, only increases by 28%, resulting in a decrease in $t_{1/2}$ of a similar magnitude. Thus, a dramatic increase in organ clearance, as noted here for PCP renal clearance,

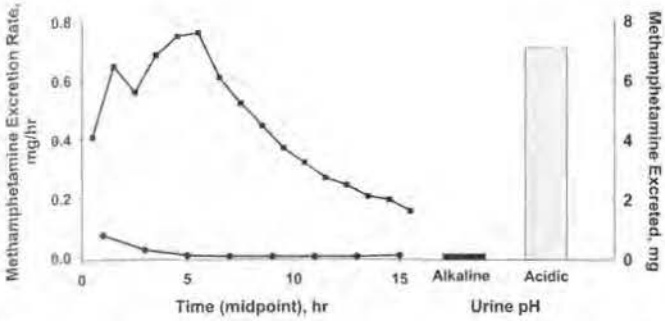


Figure 34. Urinary excretion rate of methamphetamine versus time after the oral administration of 11 mg of the drug to human subjects. The two lines represent different urine pH conditions: acidic pH (■), alkaline pH (●). The total area under the rate curves, which represents the cumulative amount of unchanged methamphetamine excreted into the urine up to 16 hours after dosing, is presented to the right in the form of bar graphs. (Based on data presented in Beckett AH, Rowland M. Urinary excretion kinetics of methylamphetamine in man. *Nature* 1965;206:1260–1261. From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

TABLE 2. Influence of urine acidification on phencyclidine elimination in humans[a]

Parameter	Urine pH	
	Uncontrolled	Acidic (<5)
Clearance (ml/min)		
Systemic (CL_S)	380	485
Nonrenal (CL_{NR})	350	350
Renal (CL_R)	30	135
CL_R as % CL_S	8	28
Percent increase in CL_S	—	350
Percent increase in CL_S	—	28
Elimination $t_{1/2}$(h)	13	10
Percent decrease in $t_{1/2}$	—	23

CL_S, systemic clearance; CL_{NR}, nonrenal clearance; CL_R, renal clearance; $t_{1/2}$, half-life.
[a]Based on data in Mayersohn M. Rational approaches to treatment of drug toxicity: recent considerations and application of pharmacokinetic principles. In: Barnett G, Chiang CN, eds. *Pharmacokinetics and pharmacodynamics of psychoactive drugs.* Foster City, CA: Biomedical Publications, 1985:120–142.

does not necessarily translate into a similar, dramatic change in systemic clearance or $t_{1/2}$. In fact, renal clearance would need to increase by approximately tenfold, for $t_{1/2}$ to decrease by 50%. The success of overdose treatment by manipulating urine pH, in terms of enhancing elimination of a poison and clinical outcome, depends on the contribution of the renal pathway to overall clearance; the greater that fraction, the greater the impact of altered urine pH.

Urine flow is another variable that may affect renal clearance of compounds that undergo reabsorption (22). As noted in Figure 35A, there is a direct relationship between renal clearance of three barbiturates in humans and urine flow. The magnitude of this effect varies among the specific compounds. Figure 35B is a nice illustration of how urine pH alone or with urine flow can affect the renal clearance of a compound, in this case phenobarbital. The renal clearance of the weak acid phenobarbital is increased by urine alkalinization, which promotes ionization, reduces reabsorption, and increases excretion. Increasing urine flow, in conjunction with urine alkalinization, further promotes renal clearance. This observation has led to the idea of *forced alkaline diuresis* for overdose treatment of susceptible organic acids. Compounds that display a pH dependence in renal clearance are also urine flow dependent to an extent that depends on the degree of tubular reabsorption.

Hepatic (Metabolic) Elimination and Metabolite Kinetics

As noted for the kidney, the liver is ideally suited for its role as an eliminating organ by being able to metabolically alter, via

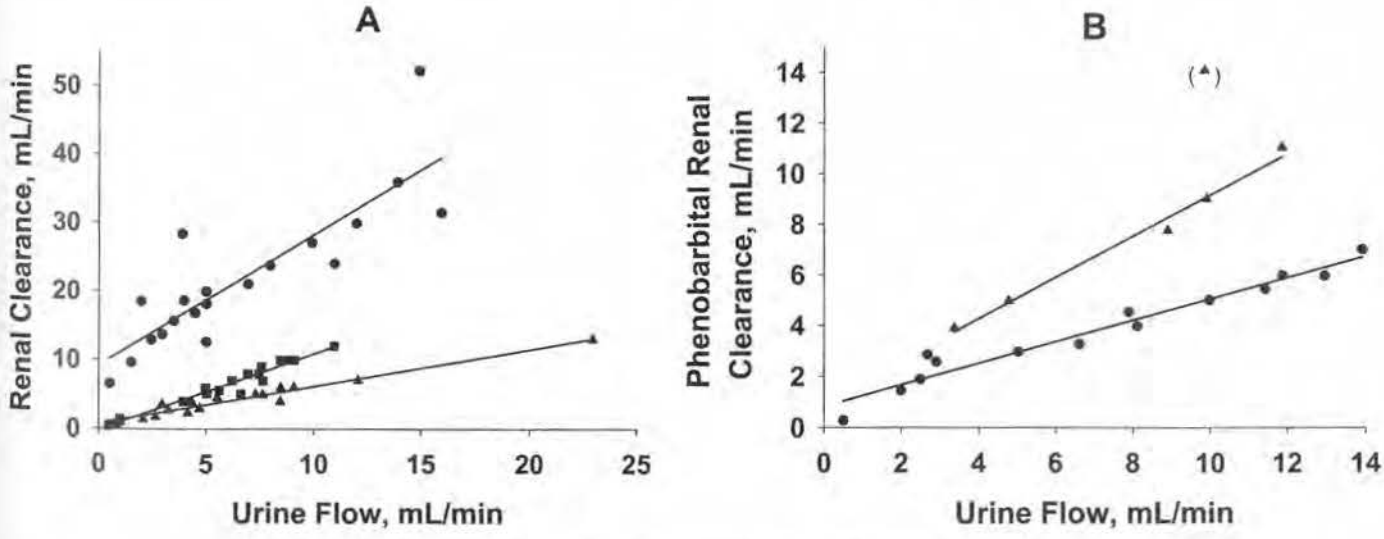


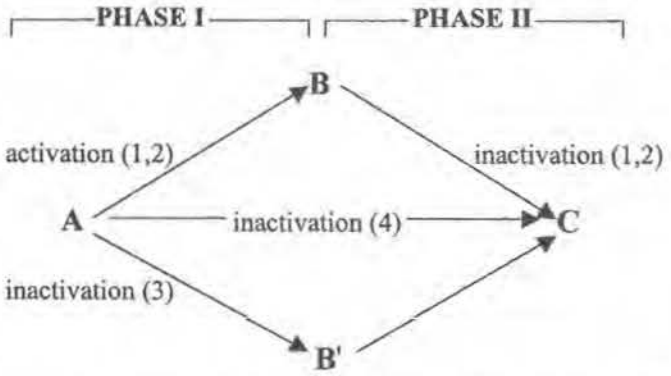
Figure 35. A: Renal clearance of several barbituric acid derivatives in humans as a function of urine flow. Each line represents the linear regression analysis of the data. Amobarbital, ▲; butabarbital, ■; cyclobarbital, ●. **B:** Renal clearance of phenobarbital in humans as a function of urine flow and urine pH. Each line represents the linear regression analysis of the data. One point (in parentheses) has not been used in the regression analysis. Alkalinized urine, pH > 7.6, ▲; uncontrolled urine pH, ●. (Based on the data in Linton AL, Luke RG, Briggs JD. Methods of forced diuresis and its application in barbiturate poisoning. *Lancet* 1967;2:377–380. From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

enzyme action, and endogenous and exogenous compounds. Whereas other tissues (e.g., lung, kidney, muscle) have metabolic enzyme capability, the liver is a virtual storehouse of enzyme activity. The liver, as noted for the kidney, receives a substantial blood flow (approximately 1500 ml per minute). In addition, the liver occupies a unique anatomical position by receiving all absorbed material from the GI tract (for processing) via the portal circulation before systemic distribution. The latter results in the *hepatic first-pass effect*, which is discussed in the Absorption and Bioavailability section. The liver is also capable of extracting compounds from blood and excreting them into bile. The bile then flows to the GI tract where the compound might undergo absorption (*entero-hepatic circulation*), further metabolism (with or without subsequent absorption), or loss via the feces. A discussion of the complex anatomical and biochemical features of the liver is beyond the scope of this chapter.

The process of urinary excretion of a compound (or metabolite) is relatively similar among normal, healthy people, because there are relatively few variables that affect the efficiency of urinary excretion (e.g., urine pH, urine flow). The efficiency of renal function can be gauged rather well with reference to creatinine clearance. The latter measure gives a good *handle* on the functional activity of the kidney, and it serves to relate to and predict the kinetics of drug excretion from the body. There is no comparable measure of liver function that one can use to relate to enzymatic metabolic efficiency; there is not a *handle* on hepatic efficacy as there is with renal function. Furthermore, there are a host of variables that may affect metabolic function, including age, gender, genetics, environmental exposure, nutrition, other drugs, disease states, and so forth. As a consequence, it is not at all surprising to find that the metabolic activity for a given compound varies enormously among even a young, healthy population. This is especially true of $t_{1/2}$ values, which result from the individual variations in both apparent volume of distribution and metabolic clearance.

The metabolite(s) produced by biotransformation reactions are often, but not always, more water-soluble than the parent drug, allowing the metabolite to be excreted into the urine. In general, the metabolite is formed irreversibly, but there are some exceptions in which the metabolite may undergo reversible metabolism to the parent compound. The pharmacologic and toxicologic activity of the parent/metabolite pair allows several possibilities: The metabolite may have less, about the same, or greater activity/toxicity than the parent compound. Understanding which situation applies is obviously of great importance in toxicology and in treatment of overdose. For example, an overdose of methanol or ethylene glycol leads to toxic metabolites. The only appropriate strategy to take in that instance, in addition to maintaining life signs, is to try and reduce the intake, if possible (e.g., reduce absorption), and remove the parent compound from the body while slowing conversion to metabolites. In fact, effective treatment of toxicity created by ingestion of those compounds includes the application of extracorporeal devices (e.g., hemodialysis) to remove the parent compound and administration of ethanol or 4-methylpyrazole to inhibit the metabolism to the toxic metabolites. This specific example is discussed in the next section.

An older but still useful depiction of metabolism of exogenous compounds divides all such events into phase I and phase II processes. This is noted in the following Scheme 1. Phase I processes are those associated with chemical modifications that involve oxidation, hydrolysis, or reduction. The predominant enzymes here are those in the cytochrome P-450 superfamily. Phase II reactions, in contrast, involve addition of chemical groups and are referred to as conjugation reactions. Examples include glucuronidation, glycination, sulfation, acetylation, or methylation. These derivatives are



Scheme 1. General scheme depicting drug metabolism reactions falling into phase I and phase II processes.

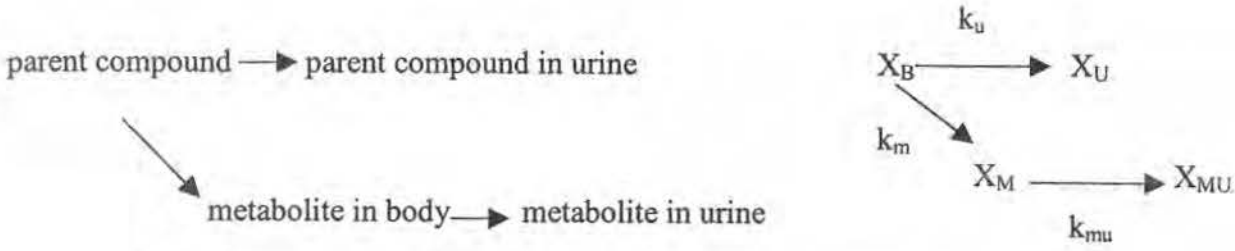
virtually always more water-soluble than the parent compound and are found excreted into urine or bile. Although conjugates are most often inactive, they can possess pharmacologic activity (e.g., morphine-6-glucuronide) or exert toxicity (e.g., some acyl glucuronides). In the previous scheme, *activation* and *inactivation* may refer to pharmacologic or toxicologic properties. In possibility 1, compound A is inactive and is converted into active compound B, which is then inactivated by conjugation to compound C. Possibility 2 assumes that compound A is active and is converted into compound B, which has similar or different activity from A. In possibility 3, compound A is active and is converted into inactive compound B', which is further metabolized by conjugation into compound C. Finally, compound A is active or inactive and is directly converted into compound C of lesser, equal, or greater activity. The metabolic schemes for a large number of compounds are readily available in the extensive metabolism literature.

As noted in First-Order (Linear) Kinetic Processes, the vast majority of compounds undergoes first-order elimination kinetics. The notable exceptions are those compounds ingested in large doses (perhaps during an overdose) and those relatively rare compounds that have Michaelis constants below the plasma concentrations resulting from ingestion or exposure. The consequences of non–first-order or nonlinear elimination have been discussed in Non–First-Order (Nonlinear) Kinetic Processes. Therefore, the assumption that metabolite formation and subsequent elimination occur by first-order processes can be made here. The relatively simple Scheme 2 considers parallel or competitive elimination of the parent compound and sequential formation and subsequent elimination of the metabolite.

The portion of the scheme that is of interest for this discussion is parent compound to metabolite in body to metabolite in urine (or to another metabolite). This sequential kinetic scheme is sometimes referred to as an *A to B to C* system, and it occurs with some frequency in pharmacokinetics (e.g., it is often used in describing parent drug in the blood after absorption). The plasma concentration of metabolite (C_m) formed as a function of time after IV bolus administration of parent compound is given by the following relationship:

$$C_m = \frac{k_m \cdot X^0}{V_m(k_{mu} - K)} \cdot (e^{-K \cdot t} - e^{-k_{mu} \cdot t}) \equiv A \cdot (e^{-K \cdot t} - e^{-k_{mu} \cdot t}) \quad \text{[Eq. 38]}$$

in which V_m is the apparent volume of distribution of metabolite, X^0 is the IV bolus dose, K is the apparent overall first-order elimination rate constant ($K = k_m + k_u$), and A is a constant equal to the value of the terms shown in the coefficient. An equation containing the difference between two exponential terms rises and declines with time. At time zero, C_m is zero (because e^{-0} is 1 and 1 minus 1 is zero) and at time infinity C_m



Scheme 2. Simple scheme illustrating parallel (or competitive) elimination of parent compound and consecutive metabolite formation and elimination. The amount of each form (parent or metabolite) is represented by X, and the subscript indicates the form and location.

is zero (because $e^{-\infty}$ is 0). Because one of the two rate constants in the exponential terms must be larger than the other one (i.e., $K > k_{mu}$ or $k_{mu} > K$), the product of that rate constant and time must be greater than the other rate constant and time. The larger product raised as a negative to any base value approaches zero before the other, numerically smaller, exponential term. Thus, at some time, only one exponential term predominates, leading to a log-linear relationship whose slope reflects the smaller of the two rate constants. This is similar to the discussion of multi-compartment models; the terminal slope (e.g., given by β or λ) is always the numerically smallest of all of the rate constants that appear in exponential form (i.e., $\beta < \alpha$ or $\lambda_n < \lambda_{n-1}$). The rule that applies here is that in any sequence of kinetic steps, the slowest step (i.e., smallest rate constant) rate-controls or rate-limits the entire process, and that step (or rate constant) determines the terminal slope of, in this case, plasma metabolite concentration versus time. This idea of a *rate-limiting step* is useful and frequently encountered in pharmacokinetics whenever sequential processes are seen (e.g., as with absorption into the body).

Plasma metabolite concentrations rise after administration of the parent compound as the metabolite is formed, reach a peak, and then decline. When those data are plotted on semilog axes, ultimately there is a log-linear terminal line, indicating that one exponential dominates, and the slope of that line is a function of either K or k_{mu}. If parent compound plasma concentrations are also determined with time, that slope by definition is given by K; then, by comparison, one can ascribe meaning to the slope of the metabolite profile. The slope is the same as the parent compound (i.e., K), in which case, $k_{mu} > K$, or the slope is smaller than that for K, in which case, the slope must be k_{mu} (i.e., $K > k_{mu}$). Consider the two possible cases.

CASE I

If the metabolite is formed slowly but eliminated rapidly, then $k_{mu} > K$. This is referred to as *metabolite formation rate-limited elimination*. Because the rate-limiting step is K, the terminal slope is a function of K. At some time, once the fast exponential term approaches zero, the remaining slower exponential term is given by

$$C_m \equiv A \cdot (e^{-K \cdot t}) \qquad \text{[Eq. 39]}$$

This case is quite common. An example is shown in Figure 36 for morphine given as an IV bolus to humans and two formed morphine glucuronide metabolites (23). One of the latter metabolites (morphine-6-glucuronide) has been of considerable interest because of its known analgesic activity; however, a recent study suggests that it contributes relatively little to the overall analgesic activity derived from morphine dosing (24). Notice that the terminal lines for morphine and each metabolite are parallel, indicating the same value for the terminal slope, which, by definition, must correspond to the terminal $t_{1/2}$ for the parent drug, morphine. This parallelism in lines indicates that the metabolites are formed slowly and then rapidly eliminated.

CASE II

In contrast to the previous situation, the metabolite is formed rapidly but then undergoes slow elimination, slower than the parent compound: $k_{mu} < K$. This is referred to as *excretion rate-limited elimination*. Because the slower and rate-limiting step is k_{mu}, the terminal slope of the metabolite concentration-time data must be governed by that rate constant. In contrast, the terminal slope for the parent compound, by definition, must be given by K. At some time, the exponent containing K approaches zero leaving the other, single (terminal) exponent,

$$C_m \equiv A \cdot (e^{-k_{mu} \cdot t}) \qquad \text{[Eq. 40]}$$

A number of parent-metabolite pairs fall into this category. One such example is procainamide and its metabolite, *N*-acetyl-

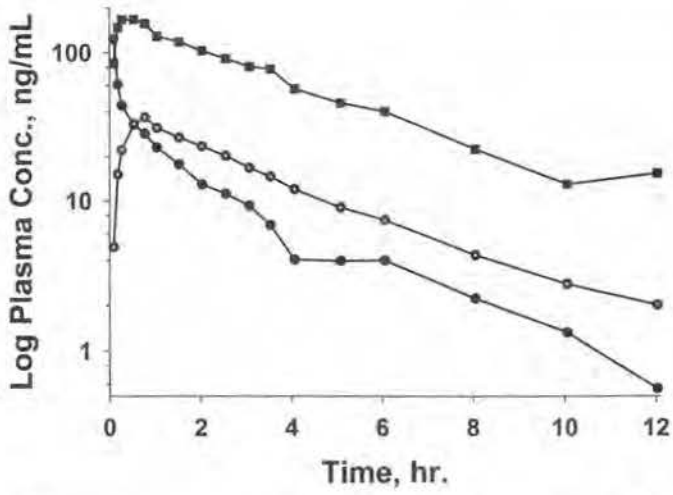


Figure 36. Plasma concentrations of morphine (●) and its formed metabolites, morphine-3-glucuronide (■) and morphine-6-glucuronide (○), after a 5-mg intravenous bolus dose of morphine to ten human subjects. Note that the terminal lines for all compounds are parallel. (Based on the data in Osborne R, Joel S, Trew D, et al. Morphine and metabolite behavior after different routes of morphine administration: demonstration of the importance of the active metabolite morphine-6-glucuronide. *Clin Pharmacol Ther* 1990;47:12–19.)

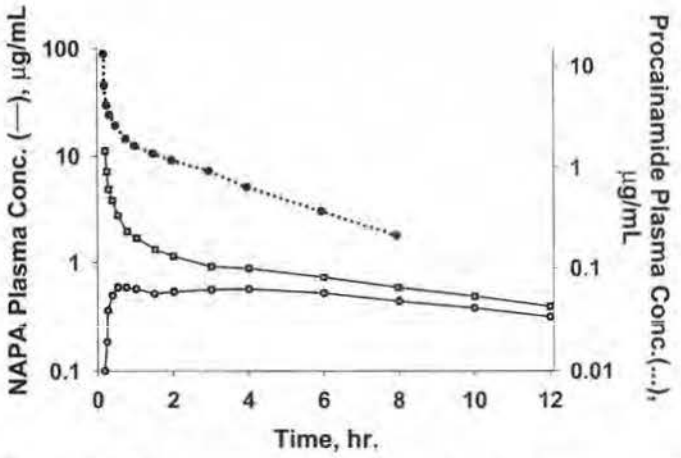


Figure 37. Plasma concentrations of procainamide (●; y-axis on right) and the concentrations of its formed metabolite, *N*-acetylprocainamide, NAPA (○; y-axis on left), after a 436-mg intravenous dose of procainamide in one human subject. Also shown are the concentrations of *N*-acetylprocainamide after a 268-mg intravenous dose of *N*-acetylprocainamide in the same subject (□; y-axis on left). The procainamide plasma concentrations have been plotted on the right-side y-axis using an elevated scale for the two intravenous curves not to coincide. Note that the terminal lines for *N*-acetylprocainamide are parallel to each, but they are not the same as that of procainamide. This is an example of metabolite excretion being slower than its formation. (Based on the data in Dutcher JS, Strong JM, Lucas SV, et al. Procainamide and *N*-acetylprocainamide kinetics investigated simultaneously with stable isotope methodology. *Clin Pharmacol Ther* 1977;22:447–457. From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

procainamide. Figure 37 illustrates the plasma concentrations of procainamide and the formed *N*-acetylprocainamide metabolite after IV dosing of procainamide in a human subject (25). The terminal slopes of those two compounds are not the same; the metabolite concentration-time data results in a shallower slope compared to the parent compound, suggesting rapid metabolite formation and slow subsequent elimination. That conclusion is further supported by the value of the terminal slope of the metabolite data after its IV administration, the slope of which must be given by k_{mu}. The latter line is parallel to the formed *N*-acetylprocainamide line, and neither is equal to the procainamide slope.

Alterations in metabolism may result from increased (induction) or decreased (inhibition) enzymatic activity. The latter are often the result of drug-drug and nutrient-drug interactions. Most of those interactions involve the cytochrome P-450 enzyme family, which is the predominant system responsible for drug metabolism. Among the numerous hepatic isozymes present in the body, only a handful is responsible for the majority of the interactions. One isozyme, CYP 3A4 alone, accounts for approximately 50% of the known interactions (leading to its being referred to as a *promiscuous* enzyme). Approximately 90% of the reported interactions can be accounted for with CYP 3A4 and the following CYP isozymes: 1A2, 2C9/10, 2C19, 2D6, and 2E1. A recent text has provided a thorough review of this area (26).

A simple method to predict the possibility of an interaction resulting from inhibition by a compound can be obtained if certain assumptions are made. Assuming that the inhibition is competitive and that the linear rate versus substrate concentration curve exists, percentage inhibition is approximated by the following relationship:

$$\% \text{ inhibition} = \frac{100 \cdot (I)}{k_i + (I)} \qquad \text{[Eq. 41]}$$

Where (I) is the concentration of inhibitor and k_i is an inhibitor constant. The inhibitor constant is the concentration of inhibitor necessary to produce a 50% inhibition in the enzymatic reaction (similar in concept to the Michaelis-Menten constant, k_{MM}). When the inhibitor concentration is low, $(I) < k_i$, inhibition is a function of both (I) and k_i.

$$\% \text{ inhibition} \cong \frac{100 \cdot (I)}{k_i} \qquad \text{[Eq. 42]}$$

If, for example, (I) is 10 nM and k_i is 100 nM, an inhibition of approximately 10% is expected. The more serious situation occurs when the inhibitor concentration exceeds the inhibition constant $[(I) > k_i]$. In that case, the relationship approximates 100% inhibition.

There are many recent examples of clinically significant interactions resulting in serious toxicity as a result of inhibition interactions. These include interactions initiated by grapefruit juice and the antifungal agent ketoconazole, both of which inhibit CYP 3A4 metabolism of a variety of drugs. One example involves the first nonsedating antihistamine, terfenadine, which was withdrawn from the marketplace as a result of the inhibition of its metabolism leading to life-threatening cardiotoxicity referred to as torsade de pointes (prolongation of the QT interval). In this instance, it was the parent compound that was responsible for toxicity. The relative importance of these metabolic interactions after oral dosing depends on the value of the hepatic ER of the compound whose metabolism is being inhibited. The greater the hepatic ER, the more dramatic the effect of inhibition on the plasma concentrations and AUCs of the parent compound. Boxenbaum (27) has shown that the ketoconazole-terfenadine interaction results in a greater than 35-fold increase in terfenadine concentration or AUC. Terfenadine has a hepatic ER of approximately 0.95. In contrast, ketoconazole results in an approximate fourfold increase in the AUC of alprazolam whose hepatic ER is 0.065. It is the *first-pass effect*, discussed in the Absorption and Bioavailability section, that accounts for this dramatic dependence on hepatic ER.

In contrast to the previous examples, and one that illustrates the useful side of an interaction, is enzyme inhibition that results in reduced toxicity by minimizing the formation of a toxic metabolite(s). The classic examples are methanol (methyl alcohol; wood alcohol) and ethylene glycol (*antifreeze*). Methanol metabolism via alcohol dehydrogenase leads to the formation of the toxic metabolites formaldehyde and formic acid. Ethylene glycol metabolism via alcohol dehydrogenase results in a series of toxic compounds (glycoaldehyde, glycolic acid, glyoxylic acid, and oxalic acid). In addition to the use of hemodialysis to remove the parent compounds from the body (discussed below), an effective means to reduce the formation of the toxic metabolites is to administer ethanol. Ethanol competitively inhibits the metabolism of methanol and ethylene glycol because it has a greater affinity for the enzyme. Slowing the metabolism of the parent compound prolongs the formation of the toxic metabolites and prevents the metabolites from reaching toxic concentrations. Another compound, 4-methylpyrazole (fomepizole), is also an effective inhibitor or alcohol dehydrogenase, and it offers an alternative to the use of ethanol (28,29).

Extracorporeal Elimination

Increasing the rate of elimination of a compound from the body by enhancing metabolism may present a problem if active/toxic metabolites are produced, as noted for methanol and ethylene glycol. In contrast, efforts at enhancing removal of the parent compound from the body via urinary excretion or other routes/modes of elimination do not offer such a problem. As discussed previously, however, increasing urinary excretion proves efficient only if a substantial portion of the dose can be

cleared by renal mechanisms. The latter is not an option for a compound that undergoes primarily hepatic metabolism. One mode that offers an additional route of elimination falls under the category of *extracorporeal* elimination. Such processes offer a new route of elimination from the body that the compound can use. Examples include peritoneal dialysis, hemodialysis, and hemoperfusion.

All dialysis (from the Greek, *to separate*) techniques are based on the same principles. A common laboratory technique referred to as *equilibrium dialysis* uses a semipermeable membrane to separate a protein-bound compound (present on one side of the membrane, for example, in a plasma sample) from unbound material capable of diffusing across the membrane into a solution on the other side of the membrane (generally a buffer). This technique is used to measure plasma protein binding. The unbound form of the compound equilibrates on both sides of the membrane in this, generally, static closed system procedure. By knowing the unbound concentration on one side of the membrane and the total concentration at the beginning of the experiment, the unbound fraction can be calculated. The same idea is applied to the removal of waste materials from the blood of patients with renal failure and, of interest here, for the removal of toxic compounds from the body. In *peritoneal dialysis*, the peritoneal membrane serves as the dialyzing membrane after the peritoneum is filled with dialyzing solution. The exact procedure applied varies and the modes used include intermittent, continuous, continuous ambulatory, and continuous cyclic peritoneal dialysis. Peritoneal dialysis finds its greatest use in the treatment of severe renal impairment. This is generally not an efficient procedure for the rapid removal of a toxic compound from the body after an overdose.

The dialysis method of choice for maintaining renally diseased patients and for treatment of overdose is *hemodialysis*, which has been referred to as the *artificial kidney*. This method is many times more efficient than peritoneal dialysis in removing substances from the blood; however, it is more complex and requires an expensive device. Figure 38 is a diagrammatic sketch of the important aspect of this process: the movement of molecules of the compound present in blood across a semipermeable membrane and into dialyzing fluid. The arterial blood is removed from the body via a pump and placed into a dialyzing machine, which has an extensive network of coils of semipermeable membrane, which are, in turn, filled with dialyzing fluid. The *unbound* form of the compound present in the blood moves down a concentration gradient and diffuses across the membrane into the dialysis fluid. As long as there is a concentration gradient, the compound continues to diffuse across the membrane and is removed from the blood. This is a dynamic process, preventing equilibrium from being achieved, unless the same fluid continues to be recycled through the machine. It is important to note that it is only the *unbound* form that diffuses across the membrane; the protein-bound form does not diffuse. Therefore, it should seem reasonable that highly plasma protein bound compounds are not good candidates for efficient removal by hemodialysis.

As for any other organ of elimination, the efficiency of dialysis removal of a compound from the blood can be judged by a dialysis ER and *dialysis clearance*, CL_D (often referred to in the renal literature as *dialysance*). All of the principles previously developed and discussed for organ clearance apply to hemodialysis clearance. Thus, clearance is from the blood, the fluid containing the compound, and from which extraction occurs. The maximum value for CL_D equals blood flow to the dialysis machine, which is generally approximately 200 ml/minute. Only the unbound form of the compound is dialyzed from the blood. Regardless of the efficiency of dialysis clearance, even

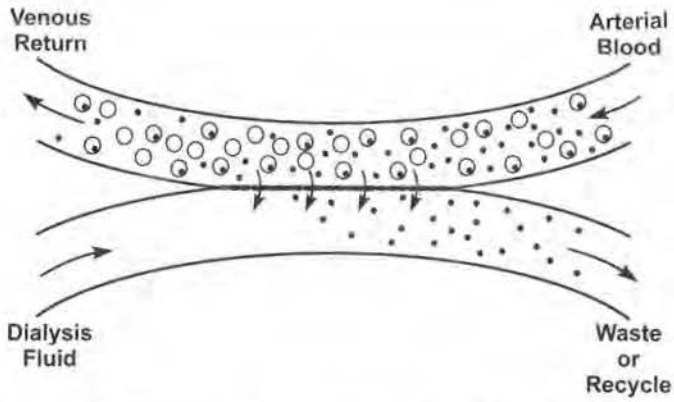


Figure 38. A diagrammatic sketch to illustrate the diffusion of a compound from blood during hemodialysis. Arterial blood is pumped into a hemodialyzer where it is separated from dialyzing fluid by a semipermeable membrane. The unbound form of the compound in the blood (*small solid circles*) moves down a concentration gradient as it diffuses across the membrane into the dialysis fluid, where it is carried away to waste (or is recycled). Note that the protein bound form (*small solid circle within the larger open circle*) is not removed from the blood. This dynamic process continues until the end of the dialysis period. (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

complete removal of the compound from the bloodstream during a single dialysis period (approximately 4 to 6 hours) does not mean efficient removal from the body (i.e., little change in $t_{1/2}$). This is the identical issue that was discussed previously: efficient removal from the bloodstream versus effective removal from the entire body. Recall that $t_{1/2}$ is a function of clearance and apparent volume of distribution. The larger the apparent volume of distribution, less of the compound is removed from the body during dialysis (i.e., little effect on $t_{1/2}$).

Whether hemodialysis is an effective means for treating an overdose depends on two primary factors: plasma protein binding and the apparent volume of distribution. This has been nicely established by examination of the amount of drug removed from the body during dialysis as a function of those two pharmacokinetic parameters (30). That analysis provides a guideline for predicting the use of hemodialysis in treatment of drug overdose. A somewhat more unified approach is to incorporate both of those parameters into a single parameter, the *unbound apparent volume of distribution*, V_U. The unbound apparent volume of distribution is the apparent volume that the drug would occupy in the body if it were completely unbound to plasma proteins, and it is calculated as the apparent volume divided by the unbound fraction in the plasma (31):

$$V_U = \frac{V}{f_U} \qquad \text{[Eq. 43]}$$

The greater the value of V_U, the less efficient is dialysis clearance in removing the compound from the body. This is illustrated in the relationship presented in Figure 39. The y-axis on the left is the reciprocal of the fraction removed from the body; the greater the unbound volume of distribution, the greater that inverse fraction and the smaller the amount removed from the body. The relationship may be seen more directly by referring to the y-axis on the right, which plots the percentage of compound removed from the body and whose values decrease moving up the scale. Thus, the greater the unbound volume of distribution, the smaller the percentage of the compound removed from the body. Efficient hemodialysis removal only occurs for compounds on the left side of the graph, which have small, unbound volumes. Thus, compounds such as digoxin ($V_U \cong 33$ L/kg), methaqualone ($V_U \cong 30$

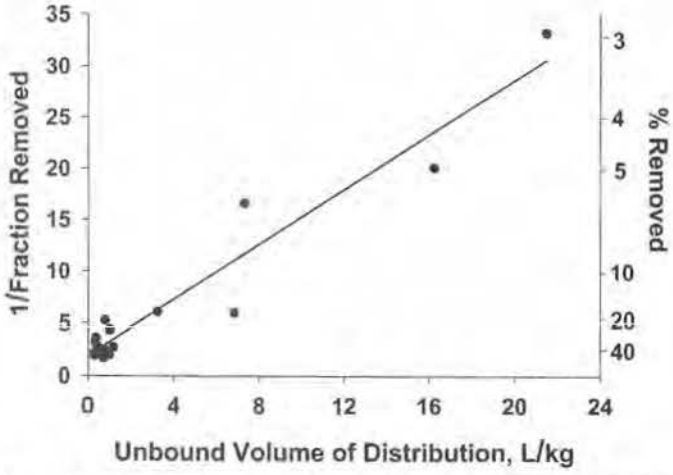


Figure 39. The reciprocal of the fraction of drug removed from the body during a 6-hour hemodialysis period as a function of the unbound apparent volume of distribution (i.e., the apparent volume of distribution divided by the unbound fraction of drug in plasma, V/f_U). The y-axis on the right is the corresponding percentage of the drug removed (note the inverse scale). The equation of the regression line is $Y = 1.33 \cdot X + 2.01$ ($r^2 = 0.930$). (Based on the data reported in Gwilt PR, Perrier D. Plasma protein binding and distribution characteristics of drugs as indices of their hemodialyzability. *Clin Pharmacol Therapeutics* 1978;24:154–161; and from Mayersohn M. Rational approaches to treatment of drug toxicity: recent considerations and application of pharmacokinetic principles. In: Barnett G, Chiang CN, eds. *Pharmacokinetics and pharmacodynamics of psychoactive drugs*. Foster City, CA: Biomedical Publications, 1985:131, with permission.)

L/kg), and flurazepam ($V_U \equiv 133$) are poor candidates for hemodialysis removal after an overdose. The basic principle noted here is often overlooked in attempts to apply hemodialysis for the treatment of overdose.

Another issue that is often misinterpreted involves the use of *in vitro* dialysis clearance values as an estimation of the efficiency of hemodialysis for removing a compound from the body. *In vitro* dialysis clearance gives a reasonable estimate of the dialyzer's ability to extract the compound under the experimental conditions, which rarely if ever involves binding of the compound to the *blood* fluid being tested. The latter is most often a simple aqueous solution. The resulting *in vitro* clearance may bear no reasonable relationship to what is observed in the body and, therefore, must be considered an inadequate predictor of *in vivo* dialysis clearance and a poor predictor of the efficiency of removal from the body. This, in fact, has been shown to be the case (30). A group of compounds that might be the exception to this rule are small, polar compounds that do not bind to blood proteins such as methanol, ethanol, ethylene glycol, and so forth. The latter compounds tend to distribute into total body water (approximately 0.6 L/kg), and, therefore, they have a small, unbound volume of distribution: numerically, approximately equal to the apparent volume (because $f_U \equiv 1$). In fact, for the compounds just noted, hemodialysis is often used in treatment of overdose, because it is an efficient means of removing those agents from the body. As noted previously, methanol and ethylene glycol overdose treatment often involves both ethanol dosing to reduce the rate of toxic metabolite formation and hemodialysis to remove the parent compound as well as the toxic metabolites that are produced. Figure 40A illustrates the direct dependence of methanol dialysis clearance on blood flow to the dialyzer (32). This relationship suggests a high dialysis ER and that blood flow appears to rate-limit methanol dialysis clearance. The translation of that information into the effect of hemodialysis on methanol (Fig. 40B) and ethylene glycol (Fig. 40C) elimination from the body is also illustrated (33,34). During each dialysis period, methanol and ethylene glycol concentrations decline far more rapidly (decreased $t_{1/2}$) compared to the interdialysis period (longer $t_{1/2}$). Furthermore, several of the toxic metabolites, being small polar molecules, are also effectively removed from the body by dialysis.

It is also important to note that there is no *rebound* effect at the end of a dialysis period. The latter is often seen when blood concentrations drop to low values (i.e., most of the compound is dialyzed from the blood) but then rise again when dialysis stops. This phenomenon (i.e., postdialysis *rebound*) occurs as a result of the tissues reequilibrating with blood, because there is now a concentration gradient from tissue to blood. Compounds that have a large apparent volume of distribution or that reequilibrate slowly with blood

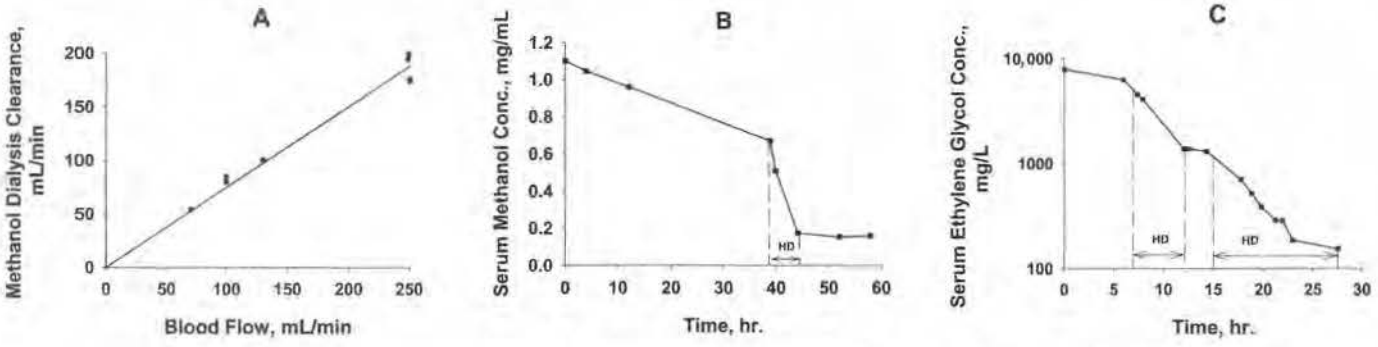


Figure 40. A: Hemodialysis clearance of methanol as a function of blood flow to the dialyzer. This relationship indicates the efficient extraction of methanol from blood by hemodialysis. (Based on the data in Gonda A, Gault H, Churchill D, et al. Hemodialysis for methanol intoxication. *Am J Med* 1978;64:749–758.) **B:** Serum methanol concentrations as a function of time in a 23-year-old male subject who ingested windshield washer fluid. Multiple intravenous doses of ethanol were administered during the time period illustrated. Methanol concentrations dropped dramatically during hemodialysis (HD). (Based on the data in Palatnick W, Redman LW, Sitar DS, et al. Methanol half-life during ethanol administration: implications for management of methanol poisoning. *Ann Emerg Med* 1995;26:202–207.) **C:** Serum ethylene glycol concentrations as a function of time in a 58-year-old male subject who ingested antifreeze. The subject received intravenous ethanol during the time period illustrated. Note the dramatic decline in serum concentrations during each of the two hemodialysis (HD) periods in comparison with the interdialysis periods. (Based on the data in Eder AF, McGrath CM, Dowdy YG, et al. Ethylene glycol poisoning: toxicokinetic and analytical factors affecting laboratory diagnosis. *Clin Chem* 1998;44:168–177. From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

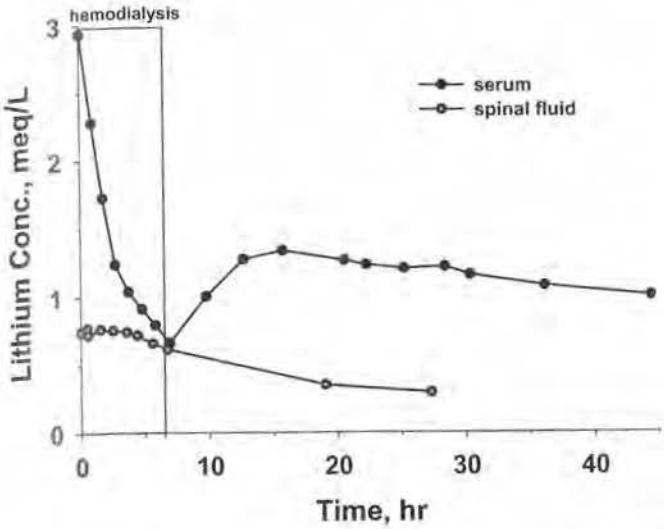


Figure 41. Serum and spinal fluid concentrations of lithium as a function of time during and after a 6.5-hour hemodialysis period. The 48-year-old man subject continued lithium therapy after developing renal failure resulting in toxic lithium concentrations. Note the rapid decline in serum concentrations during hemodialysis, which *rebounds* when dialysis was discontinued as a consequence of tissue redistribution to blood. (Based on the data in Amdisen A, Skjoldborg H. Haemodialysis for lithium poisoning. *Lancet* 1969;2:213.)

display such a profile (e.g., digoxin). An excellent example of this phenomenon is presented in Figure 41 (35). A patient continued lithium therapy after developing renal failure. Because renal excretion is the major route of lithium elimination, lithium accumulated and resulted in toxic concentrations. Serum lithium concentrations declined dramatically during hemodialysis but then rose again when dialysis was discontinued. Spinal fluid concentrations begin to decline only toward the end of and after completion of dialysis as a consequence of the redistribution from tissues to blood.

Another extracorporeal mechanism that holds great promise for treatment of overdose is *hemoperfusion*. Unlike dialysis methods, there is no membrane separating the blood from a dialyzing solution. In hemoperfusion, the blood is pumped out of the body and passed through a solid bed of adsorbing or binding material such as charcoal or ion-exchange resin. Thus, all formed elements of the blood and compounds dissolved in blood mix intimately with the solid phase. This method has the potential to be the most efficient means for removing drug and metabolites from the body. The extraction could be made even more efficient if the solid support contained in a cartridge used material with great affinity for specific drugs or category of drugs. For example, antibodies with a high specificity for the agent to be removed could produce an ER as high as one. Under that circumstance, blood flow through the hemoperfusion material would rate-limit clearance.

In general, the efficiency of dialysis clearance and the amount of compound extracted per unit of time, follows the order hemoperfusion greater than hemodialysis, and hemodialysis greater than peritoneal dialysis. Several publications have reviewed use of extracorporeal methods for treatment of drug overdose (36–38).

NONVASCULAR INPUT: ABSORPTION AND BIOAVAILABILITY

The development of pharmacokinetic principles generally begins with the simplifying assumption of intravenous bolus dosing, as done in the preceding sections. Although the simplicity is useful, it does not reflect the practical, real-world situation. IV bolus drug dosing is relatively uncommon (with the exception of illicit drug use), and when used it is done in a hospital or clinic setting. Drug dosing or exposure in general typically relies on other routes to gain access to the systemic circulation. The primary routes of entry into the body for drugs as well as environmental compounds include oral, buccal (sublingual), dermal, inhalation, subcutaneous, intramuscular, rectal, and vaginal. There are two basic differences between these nonvascular routes and vascular dosing. First, all nonvascular routes require that the substance placed at the site of administration penetrate one or more biologic membrane barriers to gain access to the systemic blood circulation. Second, all nonvascular doses must be formulated into a *dosage form* to permit administration. The dosage form is defined by its physical form (e.g., tablet, liquid, and so forth); by the characteristics of the drug in that form (e.g., crystal form, particle size, salt form, and so forth); and by other formulation factors (e.g., compression forces applied, coatings used, and so forth). The *in vivo* performance of a drug administered as a dosage form may be, and often is, quite different from what is seen from the pure drug or from IV administration. The principles of and some of the factors affecting the concentration-time profile after oral administration are discussed here, but for a more thorough exposition, the readers are referred elsewhere (39).

Gastrointestinal Absorption

The GI tract, which is a major barrier between the body and the environment, has as its primary functions the secretion of specialized fluids, the storage and digestion of ingested food and other materials, and absorption of those processed materials into the bloodstream. The GI tract is lined with epithelial cells specialized for those functions. As with all other membranes of the body, these epithelial cells are best described by the *fluid mosaic* model. The membrane is composed of a lipid bilayer or sandwich that has polar groups reaching into and out of the membrane, separated by two layers of long lipid chains. The latter provide the lipid-like nature of the membrane. Throughout the membrane are transmembrane proteins, and attached to the surface of the membrane are peripheral proteins and carbohydrates. It is this structure that determines the membrane permeability of any drug or chemical. Generally, small polar molecules (e.g., methanol, ethanol, and so forth) are able to traverse such membranes rapidly, whereas larger molecules need to have sufficient ability to partition between an aqueous and a lipid phase. The latter is often measured by the oil to water partition coefficient ($K_{O/W}$).

The vast majority of substances undergo an absorption process that is governed by physical chemical principles, and, therefore, absorption may be described by passive, first-order, or linear kinetics. The most important physical chemical properties of the molecule are its $K_{O/W}$, pK_a, water solubility, and molecular size. The rate of movement across a membrane is given by Fick's first law of diffusion, which may be expressed as

$$\text{Rate of membrane diffusion} = D_M \cdot A_M \cdot P_{M/AQ} \cdot \frac{[C_{gut} - C_{blood}]}{\Delta X_M} \qquad \text{[Eq. 44]}$$

In which D_M, A_M, $P_{M/AQ}$, and ΔX_M are the diffusion coefficient through the membrane, the area of the absorbing membrane, the partition coefficient between the membrane, and the aqueous gut solution and the thickness of the membrane, respectively. The driving force for diffusion is the concentration gradient between the substance in the gut fluid (C_{gut}) and that in the

compound at absorption site ⟶ compound in body ⟶ compound eliminated

$$X_{ABS} \xrightarrow{k_a} X_B \xrightarrow{K} X_E$$

Scheme 3. Schematic representation of a simple, sequential absorption process. Where X_{ABS}, X_B, and X_E represent the amount of substance at the absorption site, in the body, and eliminated from the body, respectively. The first-order rate constants describe absorption, k_a, and elimination, K.

blood (C_{blood}). This relationship can be simplified by incorporating all of the constant terms into a permeability coefficient, P:

$$\text{Rate of membrane diffusion} = P \cdot [C_{gut} - C_{blood}] \cong P \cdot C_{gut} \quad \text{[Eq. 45]}$$

Because the concentration on the blood side of the membrane is generally small compared to the concentration in the gut fluids (because blood flow carries the absorbed material rapidly away from the site of absorption), the relationship simplifies to a rate equation, which expresses a first-order process. As a consequence, in general, absorption processes for most substances follow first-order kinetic principles (e.g., absorption rate depends on GI fluid concentration or dose; the amount absorbed increases linearly with dose; the fraction of the dose absorbed is constant, independent of dose; and so forth).

As noted in the discussion of metabolite kinetics, the kinetics of absorption may be described by a sequence of steps often referred to as an *A to B to C* system. In which A is the substance in the gut (or any site of absorption), B is that compound in the body (or bloodstream), and C is the substance eliminated from the body (in urine, as metabolite, and so forth). Scheme 3 describes this sequence.

The amount of substance at the absorption site declines exponentially according to the first-order rate constant for absorption, k_a. The amount of drug in the body or plasma concentration is described by a biexponential equation, of a form identical to that used to describe metabolite concentration as a function of time after IV bolus dosing of parent compound (see equation 38). The relationship that describes the plasma concentration of parent compound is given by

$$C = \frac{k_a \cdot F \cdot dose}{V(k_a - K)} \cdot (e^{-K \cdot t} - e^{-k_a \cdot t}) = A \cdot (e^{-K \cdot t} - e^{-k_a \cdot t}) \quad \text{[Eq. 46]}$$

The only new term here that has not been defined is F, the fraction of the dose absorbed intact sometimes referred to as *systemic bioavailability*. The value for F can range from zero to one and it is used, as noted later, to characterize the absorption efficiency of commercial products, and it forms the basis for estimation of *bioequivalence* (i.e., comparability among the same drug products made by different manufacturers). Because all of the terms in the coefficient may be considered to be a constant after a given dose, they may be replaced by a composite constant, A (having units of concentration). A plot of plasma concentration versus time results in a curve that rises and then declines (again, in analogy to the metabolite plasma concentration-time curve after an IV bolus dose of parent compound). As for the metabolite situation or for any sequential process, one of the steps in the sequence must be the slowest and rate-limit the overall process. The terminal slope represents the slowest step. In the absorption scenario, either absorption or elimination is the rate-limiting step. Thus, if absorption is fast, $k_a >> K$, at some time the exponential containing k_a approaches zero before the other exponent, resulting in the terminal slope being given by the overall elimination rate constant, K. This terminal line parallels that seen after IV bolus dosing.

$$C \cong \frac{k_a \cdot F \cdot dose}{V(k_a - K)} \cdot (e^{-K \cdot t}) = A \cdot (e^{-K \cdot t}) \quad \text{[Eq. 47]}$$

In contrast, if absorption is slow, $k_a << K$, the terminal slope is given by the slowest step, the absorption rate constant:

$$C \cong \frac{k_a \cdot F \cdot dose}{V(K - k_a)} \cdot (e^{-k_a \cdot t}) = A \cdot (e^{-k_a \cdot t}) \quad \text{[Eq. 48]}$$

The terminal line in this situation does not parallel the line describing plasma concentrations after IV bolus dosing, but rather it has a smaller slope. The latter situation occurs for drug products designed to release drug slowly (controlled or sustained release dosage forms) to sustain plasma concentrations, for poorly water-soluble compounds in which rate of dissolution rate-limits absorption, or for compounds that have poor membrane permeability.

A comparison of several of these factors is shown in Figure 42. Graph A illustrates the effect of the absorption rate constant on the shape of the curve for the same compound (and same value of K). The smaller the absorption rate constant, the smaller the value of the maximum plasma concentration, C_{max}, and the longer it takes to achieve that concentration, T_{max}. Because the slowest rate constant in all cases is the elimination rate constant, the terminal slope is given by, $-K/2.3$. Because the same fraction of the dose is absorbed in each case, the total area under the curve must be the same. Graph B illustrates the effect of the fraction of the dose absorbed on the shape of the plasma concentration-time curve. The smaller the value of F, the smaller the value for C_{max}, but there is no change in T_{max}. The most dramatic difference, however, is the total area under the curve: the smaller the value for F, the smaller the AUC. Because the slowest rate constant is the elimination rate constant, the terminal slope is given by, $-K/2.3$. Graph C illustrates the effect of a change in the rate-limiting step on the plasma concentration-time curve. In one case, the slowest rate constant is the elimination rate constant and the terminal slope is given by $-K/2.3$. In contrast, for the other case, the slowest rate constant is the absorption rate constant, which now becomes the rate-limiting step. As a consequence, the terminal slope is given by, $-k_a/2.3$. This is sometimes referred to as a *flip-flop model*. For this reason, the $t_{1/2}$ obtained from the log-linear line after nonvascular dosing is always correctly referred to as the terminal $t_{1/2}$. The terminal slope may not reflect the disposition $t_{1/2}$. The value for C_{max} decreases and T_{max} increases when the absorption rate constant gets small (as noted in Fig. 42A); however, the total areas under the curves are the same.

The elimination $t_{1/2}$, although variable among people, remains relatively constant for one individual. Therefore, the major variable affecting the plasma concentration-time curve is the input process: factors relating to the performance of the dosage form and GI absorption. There are four possible factors that may rate-limit the absorption process. The two most significant are dissolution rate and membrane permeability. The other two possible, but generally less important, factors are gastric emptying rate and GI tract blood flow. Two important observations, which have become principles with regard to GI tract absorp-

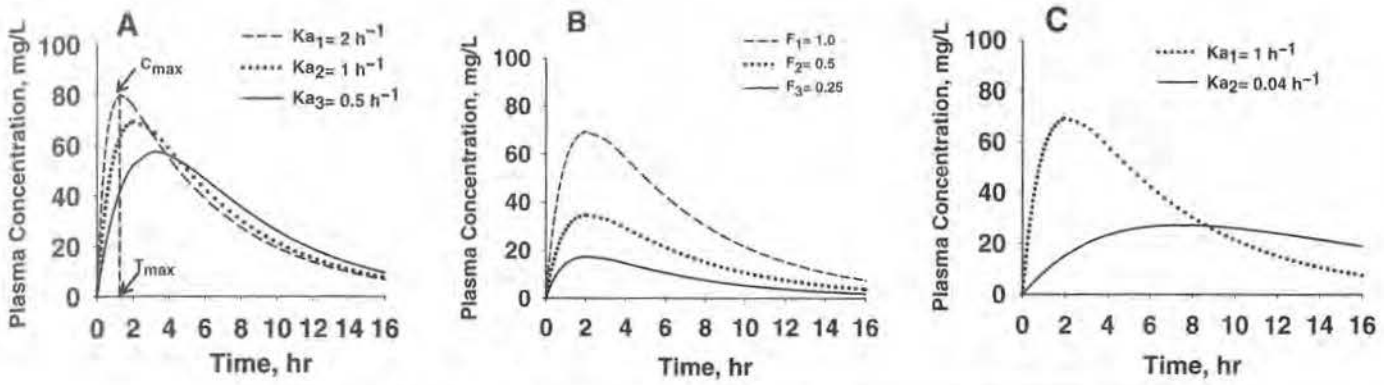


Figure 42. **A:** Hypothetical plasma concentration-time profiles of the same compound administered orally in three different dosage forms. The elimination rate constant is the same for each situation (0.173 hour^{-1}; $t_{1/2}$ = 4 hours); only the absorption rate constants vary. The absorption rate constants are 2.0 hour^{-1}, 1.0 hour^{-1}, and 0.5 hour^{-1}. Note that the smaller the absorption rate constant, the smaller the maximum concentration (C_{max}) and the greater the time of its occurrence (T_{max}). **B:** Hypothetical oral plasma concentration-time profiles for the same compound as shown in **A**, with an elimination rate constant of 0.173 hour^{-1} ($t_{1/2}$ = 4 hour) and absorption rate constant of 1.0 hour^{-1}. The only difference among these curves is the fraction of the dose absorbed (F; bioavailability). The values for F are 1.0, 0.5, and 0.25. **C:** Hypothetical oral plasma concentration-time curves for the same compound as in **A**, with an elimination rate constant of 0.173 hour^{-1} ($t_{1/2}$ = 4 hour). The absorption rate constant is larger than K (k_a = 1.0 hour^{-1}; ···) in one case but smaller than K in the other case (k_a = 0.04 hour^{-1}; —). The terminal slope is given by the smallest rate constant. The situation illustrated for $k_a << K$ is sometimes referred to as a *flip-flop* model. (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

tion, are the following. For a compound to be absorbed, it must first be in solution in the fluids of the GI tract. The idea of particulate absorption (so-called *persorption*), although it appears to exist, contributes insignificantly to the overall absorption process. This is the reason *dissolution rate* is so important for poorly water-soluble compounds; the faster and the more completely the compound dissolves, the greater the rate and completeness of absorption. Thus, the absorption of poorly water-soluble compounds is frequently dissolution rate-limited. Second, all compounds, whether weak acids or bases, are best absorbed from the small intestine. The idea referred to as the *pH-partition hypothesis*, which suggests that compounds are better absorbed in the environment that favors nonionization, has been misinterpreted. If all other factors along the GI tract were the same, an acidic compound would be best absorbed from the more acidic environment of the stomach, because the nonionized form has a greater oil/water partition coefficient, which would increase the permeability coefficient (see Equation 44) and, thereby, promote absorption. Similarly, basic compounds would be better absorbed from the relatively more alkaline pH of the small intestine. However, the small intestine is uniquely capable of providing the most efficient site for absorption compared to all other regions of the GI tract by virtue of its enormous absorbing surface area (one estimate suggests that the area is similar to that of a tennis court). Thus, all compounds, whether acids or bases, are best absorbed in the small intestine. Another argument against the stomach as being a good site for absorption applies to weak acids that are poorly water-soluble, though such compounds are cited (incorrectly) as undergoing gastric absorption. The rate-limiting step for the absorption of any poorly water-soluble compound, including weak acids, is dissolution rate. In fact, such weak acids dissolve most readily in the relatively more alkaline pH of the small intestine, because ionization favors dissolution.

Restating these two governing principles, a compound must be in solution to be absorbed and all compounds are best absorbed in the small intestine. Therefore, another possible rate-limiting step in absorption is gastric emptying rate. Any delay in the compound moving from the stomach to the small intestine, the primary site of absorption, delays the absorption process. Generally, however, assuming that the compound is stable in the GI tract and is absorbed by passive diffusion, gastric emptying rate is not expected to affect the completeness of absorption. Another possible, but rarely seen, rate-limiting step to absorption is blood flow to the GI tract. Usually that flow is quite high, consistent with one of the primary functions of the GI tract, efficient absorption. If blood flow is slowed sufficiently, then the concentration gradient of the compound between the gut and the blood, the driving force for diffusion, becomes small (see equation 45). This diminution in concentration gradient occurs as a consequence of the compound no longer being carried away rapidly from the site of absorption and the compound accumulating on the blood side of the GI tract membrane. In situations of reduced or relatively static GI tract blood flow, such as might be seen during episodes of fainting or reduced blood volume (e.g., due to blood loss), one may see diminished absorption.

Although the vast majority of compounds move across the absorbing GI tract membrane by passive diffusion, there are many water-soluble nutrients (e.g., monosaccharides, amino acids, vitamins, and so forth) and some drugs (e.g., L-dopa, some aminopenicillins, some aminocephalosporins) whose absorption involves active participation of cell membrane transporters. Such processes are described by specialized (sometimes, active) transport. The absorption kinetics of such compounds are analogous to what has been noted in discussions of renal transport mechanisms (e.g., tubular secretion and reabsorption). Thus, the amount absorbed increases to a maximum value as dose increases and thereafter remains constant (the fraction absorbed decreases with dose). Such specialized processes may be inhibited by other compounds with similar structure.

There is also a family of *efflux transporters*, referred to as *P-glycoproteins*, which are found in epithelial cells of the GI tract (as well as in the liver, kidney, and blood–brain barrier), that are responsible for the movement of substrate out of the absorbing cell back into the gut lumen. These transporters obviously perform a protective role in preventing the systemic absorption of materials that might cause the body harm. These transporters may undergo inhibition or induction in response to certain

drugs, which is the basis for a class of drug-drug interactions. Examples of drug substrates that use this transporter include digoxin, quinine, verapamil, and cyclosporin A.

The movement of ingested materials down the GI tract involves esophageal, gastric, intestinal, and colonic transit. Generally, the movement of ingested materials down the esophagus is rapid, especially if a liquid is swallowed alone or with a solid substance. There are instances, however, of solid oral drug dosage forms *attaching* to the esophageal surface and causing erosion of the local tissue. Gastric emptying is a complex process that is influenced by a variety of physiologic factors including the presence and volume of food ingested, the type of food present, and certain drugs. As noted previously, any delay in emptying into the small intestine delays the onset of absorption. Fatty meals are the strongest inhibitor of emptying, and drugs that exert anticholinergic activity, such as narcotic analgesics, slow emptying. Slower gastric emptying rate generally reduces the rate of absorption and results in a lower C_{max} and longer T_{max}. The extent of absorption may be reduced if the compound is unstable in the GI tract fluids or increased if a greater residence time in the GI tract permits more complete dissolution and absorption. Compounds absorbed by a specialized process high in the small intestine (e.g., vitamin C) may evidence more complete absorption in the presence of slow gastric emptying as a result of avoiding saturation of transporters.

Under fasting conditions, the activity of the GI tract is governed by the so-called *migrating motility complex*, or the interdigestive myoelectric complex. This complex cycles approximately every 2 hours. This only occurs, however, during fasting and begins in the proximal stomach and terminates at the ileocecal valve. There are four phases involved in the entire cycle. Phase 1 (45 to 60 minutes) and phase 2 (30 to 45 minutes) are of relatively low activity. It is phase 3, called the *housekeeper wave*, that has intense activity lasting for approximately 5 to 15 minutes, which is responsible for clearing any remaining material from the stomach. This is the only time that relatively large single units (e.g., intact tablets) can be swept into the small intestine. Oral dosing on an empty stomach, relative to the start of the housekeeper wave, determines about how long ingested products remain in the stomach.

Intestinal transit tends to be somewhat more uniform than gastric emptying patterns, and, in general, the average amount of time that it takes a dosage form to transit from the pylorus to the end of the small intestine is approximately 4 hours. This tends to be true regardless of the nature of the substance (solid or liquid) and in the absence or presence of food. Because the small intestine is the major site of absorption, this time *window* for absorption of approximately 4 hours would appear to limit the absorption process. Drug absorption can continue beyond 4 hours after dosing as evidenced by controlled release products and the slow absorption of poorly water-soluble compounds. Compounds can remain in the colon for 24 hours and longer and, therefore, although this is not a particularly efficient site for absorption (due to the small surface area and low fluid volume), the long residence time there may compensate for the lower efficiency.

Efficient oral drug therapy necessitates adequate and, ideally, complete and consistent GI absorption. In contrast, of course, effective treatment of an oral overdose attempts to minimize systemic absorption. This is often the first approach used in treatment along with maintaining life signs but before attempts to removing materials already systemically absorbed (e.g., extracorporeal devices for enhancing elimination). Evacuating and somehow *immobilizing* the orally ingested overdose are the two approaches that may be used. Evacuation may be achieved by inducing vomiting or pumping the stomach or by slow, constant flushing of the gut contents for excretion with fecal material. *Immobilization* is used here to indicate that the overdosed compound is made into a form not available for systemic absorption. The latter may involve the use of specific agents that chemically bind to the toxic compound to prevent further absorption (e.g., chelating agents that form water-insoluble heavy metal chelates to reduce heavy metal poisoning; ion-exchange resins that bind to charged compounds). Alternatively, nonselective materials may be used that are effective for a wide range of toxic compounds, such as activated charcoal and perhaps single or binary phase fluids for lipid-soluble compounds (e.g., nonabsorbable lipids or oil-in-water emulsions). The cardinal rule for the effectiveness of these approaches is the sooner they are applied, the better (for both approaches), and the more used, the better (for *immobilization*). A good example of this idea of *soon and large amount* can be illustrated with charcoal administration. The relative percentage of an acetaminophen dose absorbed after oral administration of a solution of the drug with 5 or 10 g of activated charcoal (given immediately after the acetaminophen solution) was 53% and 39%, respectively. The same 10-g dose of charcoal given 30 minutes after the oral acetaminophen solution resulted in 69% of the dose being absorbed, considerably less efficient compared to immediate administration of charcoal (39%). When administering charcoal in the same ratio to the acetaminophen dose (10:1), less of the drug is absorbed the greater the absolute amount of charcoal (percentage absorbed, g charcoal/g acetaminophen): 42.5%, 5 g/0.5 g; 34.9%, 10 g/1 g; 22.6%, 20 g/2 g; 14.8%, 30 g/3 g (40). An identical observation has been made for the effect of activated charcoal on aspirin absorption (41). In general, the antidotal efficacy of activated charcoal increases with the amount of charcoal administered (42).

Charcoal administration has also been shown to have a dramatic effect on the elimination kinetics of some compounds that are excreted into the bile and that undergo enterohepatic recirculation. An excellent example is phenobarbital whose terminal $t_{1/2}$ was reduced from an average of 110 hours to 45 hours as a result of an increase in CL_s from 4.4 to 12.0 ml/kg per hour (43). Charcoal adsorbs the phenobarbital excreted into the small intestine, interrupting the cycle and, therefore, reduces the $t_{1/2}$ of the compound. In such a circumstance, it is useful to administer charcoal in a multiple dosing fashion to continue to disrupt the cycle (44). Doing so reduced the terminal $t_{1/2}$ of phenobarbital from 110 hours to approximately 20 hours. Other compounds that undergo a similar process include theophylline and carbamazepine. This mode of treatment has been reviewed (45).

A particularly important consideration, especially for GI absorption, is those processes that affect the chemical form of the compound before the parent compound reaching the systemic circulation. In general, these processes are referred to as *presystemic elimination*. The ingested parent compound may be altered, chemically or metabolically, at numerous sites along the GI tract, as illustrated in Figure 43. Perhaps the most significant of the individual sites and processes noted are those that occur in the intestinal wall and liver. The gut wall and liver are virtual storehouses for enzymes. Because the entire absorbed dose must first go through these organs before being systemically distributed, metabolism may represent a significant portion of the dose being altered before systemic absorption. This process has been referred to as the *first-pass effect*, the most important being intestinal wall and hepatic first-pass effects. The importance of any of these first-pass effects depends on the ER or clearance of those individual processes. In addition, it should be appreciated that these effects are sequential, meaning that the net numerical result is multiplicative. Thus, for a compound that undergoes hepatic metabolism, the value of hepatic clearance determines the ER and that, in turn, determines what fraction of the dose survives the first movement through the liver and reaches the systemic circulation. If it is assumed that the orally administered compound is completely absorbed intact

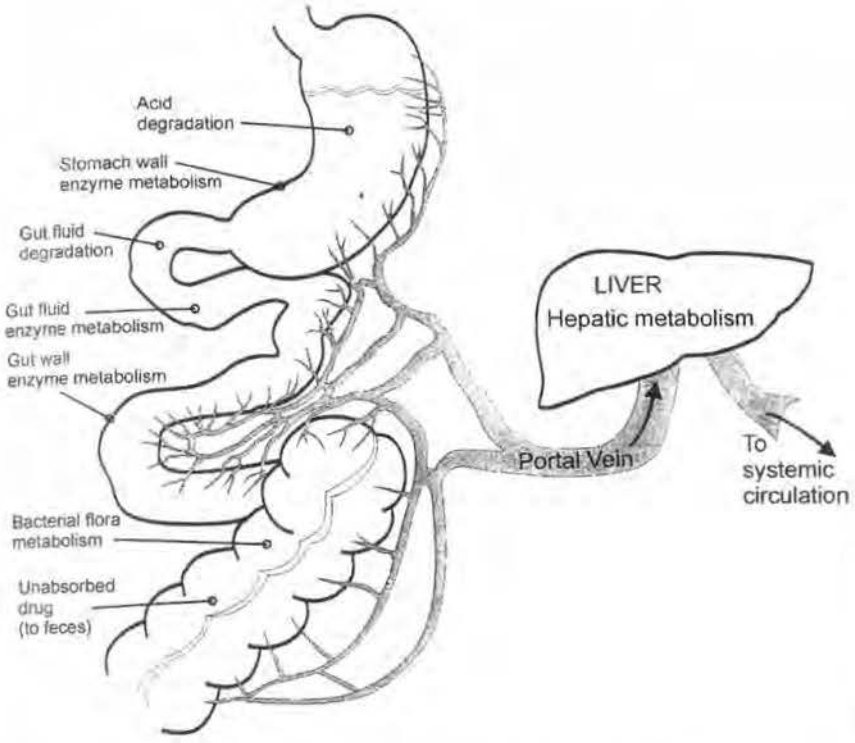


Figure 43. Schematic representation of the numerous sites along the gastrointestinal tract where the orally ingested parent compound may be chemically or metabolically altered. Taken together, these are referred to as *presystemic elimination processes*, and they include intestinal wall and hepatic first-pass effects. (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

through the intestinal wall and gets into the portal circulation, the fraction of that dose that survives the liver and gets into the systemic circulation intact is given by

$$F = 1 - ER_{HEPATIC} = 1 - \frac{CL_{HEPATIC}}{Q_{HEPATIC}} \quad \text{[Eq. 49]}$$

If all of the possible steps noted in Figure 43 are considered, F is equal to the product of the fractions (f) that survive each sequential step. For example, consider the following sequence of steps: stomach fluid degradation, intestinal wall metabolism, and liver metabolism:

$$F = f_{RELEASED} \cdot f_{GASTRIC\ FLUID} \cdot f_{INTESTINAL\ WALL} \cdot f_{LIVER} \quad \text{[Eq. 50]}$$

The first term represents the fraction of the dose that is released from the form ingested (maximum value is one). All of the other terms represent the fractions that survive each of the individual metabolic steps (i.e., 1-ER). Therefore, if 10% of the dose is chemically altered in gastric fluid (90% survives), and 40% of the dose is extracted by the intestinal wall (60% survives) and 50% of what survives that process is extracted by the liver, the fraction that reaches the systemic circulation is less than approximately 30% of the dose ($0.9 \times 0.6 \times 0.5$). Clearly, this can be an important consideration for those compounds that have high ERs for several of the presystemic elimination steps.

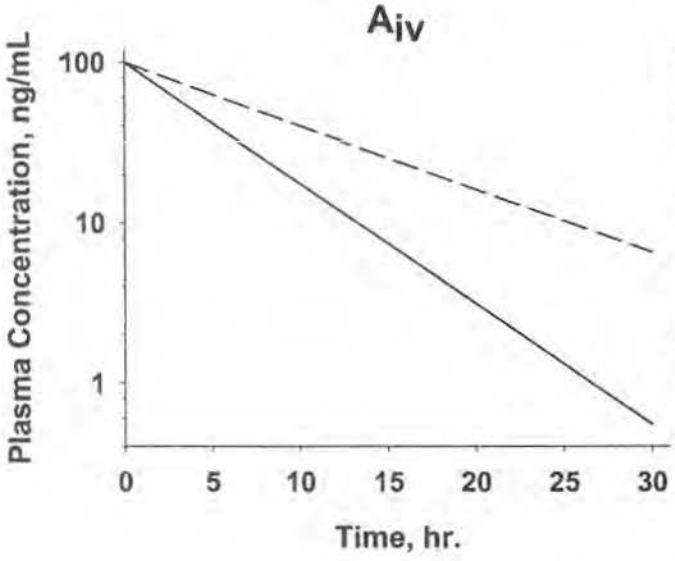
The significance of presystemic elimination needs to be considered with respect to the form of the compound that is pharmacologically and toxicologically active. Assuming, as often happens, that the parent compound is active and toxic, then any of the first-pass effects reduce the magnitude of those responses. Inhibiting such metabolic (or chemical) processes results in enhanced activity. This is especially true for compounds that have a high first-pass effect (i.e., ER >0.9). An interesting example of the latter (discussed previously for terfenadine) is the effect of grapefruit juice and certain drugs (e.g., ketoconazole) on the inhibition of cytochrome P-450 3A4 in the gut wall and liver. Induction of that pathway would have reduced the plasma concentrations of the parent drug, increased the concentration of metabolite (which is active, but not toxic), and minimized the chance of toxicity.

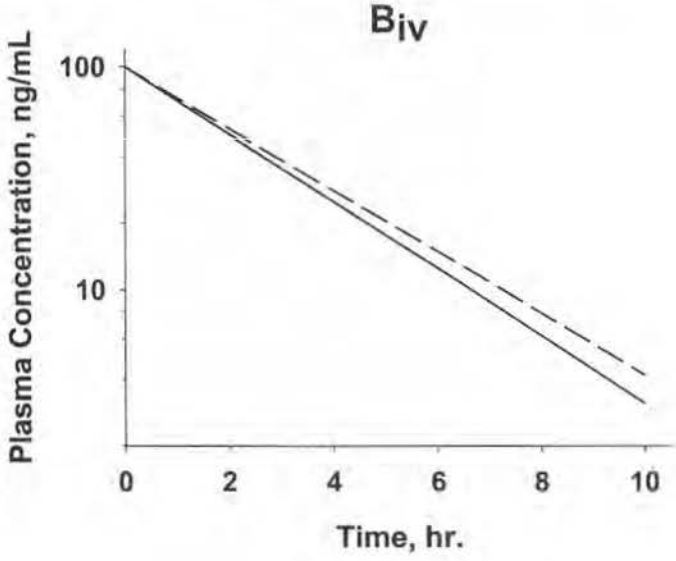
Just the opposite considerations apply for a compound whose metabolite is active or toxic. A classic example is that of the insecticide parathion (46). Parathion is inactive until it is metabolized to paraoxon, which exhibits cholinesterase activity. The infusion of parathion into the portal vein results in greater activity compared to dosing into the vena cava, as a consequence of metabolic activation via the hepatic first-pass effect. In contrast, the active form, paraoxon, is far more active on vena cava administration compared to dosing via the portal vein. In the latter instance, the hepatic route reduces the activity of paraoxon by further metabolism.

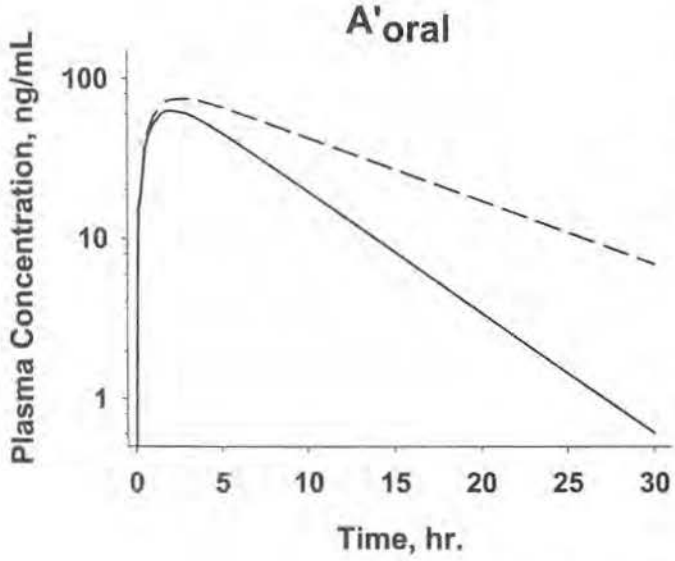
It is especially instructive to examine the interactions that are expected to occur for high and low hepatic ER drugs after IV bolus and oral dosing. This comparison is illustrated in Figure 44 assuming inhibition in metabolism. Two compounds that undergo complete hepatic metabolism but with different values for intrinsic hepatic clearance and ER are considered after IV and oral dosing before and after enzyme inhibition. Compound A has a low CL_{int} and ER (150 ml/minute and 0.091) compared to compound B, which has a high CL_{int} and ER (15,000 ml/minute and 0.909). The solid lines in the top panel illustrate the concentration-time profiles after IV dosing (A_{iv}, B_{iv}). In each instance, the values for CL_{int} are cut in half to reflect the inhibition of hepatic clearance. Thus, for A_{iv}, CL_{int} goes from 150 to 75 ml/minute and ER decreases by approximately one-half (0.091 to 0.048) with a similar change in systemic clearance, CL_S (137 to 72 ml/minute). The dotted line indicates the new concentration-time profile after inhibition (top left). $t_{1/2}$ increases by almost twofold (4.0 to 7.6 hours), as does the area under the curve (577 to 1100 ng · hour/ml). All of these changes are not surprising, because, for a low clearance compound, $\downarrow CL_S \equiv \downarrow CL_{int} = f_U \cdot \downarrow CL_{U,int}$. Inhibition decreases the value of $CL_{U,int}$ and, in the absence of any change in plasma protein binding, is directly equivalent to the change in CL_{int}. $t_{1/2}$ increases, because in the absence of any change in apparent volume of distribution, $t_{1/2}$ is inversely related to systemic clearance, whose value has decreased: $\uparrow t_{1/2} = (0.693 \cdot V_d)/\downarrow CL_S$

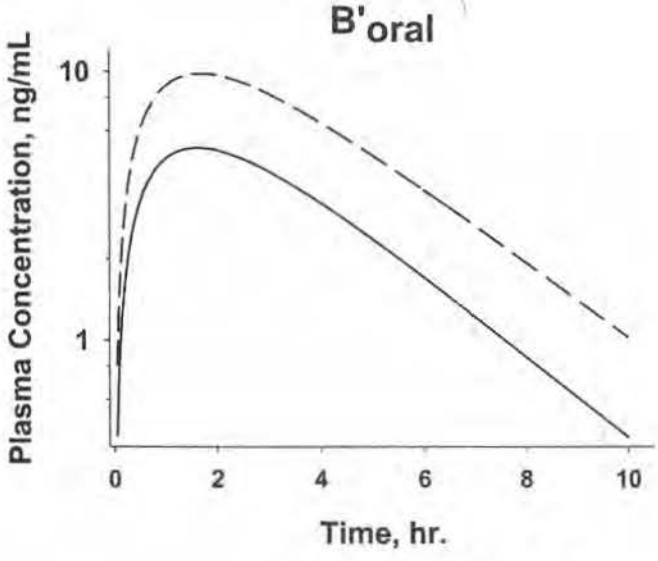
	mL/min			$T_{1/2}$,	AUC,
	CL_{int}	CL_S	ER	hr	ng x hr/mL
Control (—):	150	137	0.091	4.0	577
Inhibition (····):	75	72	0.048	7.6	1100

	mL/min			$T_{1/2}$,	AUC,
	CL_{int}	CL_S	ER	hr	ng x hr/mL
Control (—):	15000	1364	0.909	2.0	289
Inhibition (····):	7500	1250	0.833	2.2	315









	CL_0, mL/min	AUC, ng x hr/mL
Control (—):	151	525
Inhibition (····):	76	1047

A

	CL_0, mL/min	AUC, ng x hr/mL
Control (—):	14989	26
Inhibition (····):	7485	53

B

Figure 44. Hypothetical plasma concentration-time relationships for two drugs (**A** and **B**) given by intravenous bolus (A'_{iv}, B'_{iv}) or as oral doses (A'_{oral}, B'_{oral}) under control conditions (*solid line*) or after metabolic inhibition (*dashed line*). The control and metabolic inhibition conditions are specified above the graphs. Both compounds are totally metabolized by the liver, whose blood flow is assumed to be 1500 ml/minute. Compound A has a low intrinsic hepatic clearance (150 ml/minute) and extraction ratio (0.091). Compound B has a high intrinsic hepatic clearance (15,000 ml/minute) and extraction ratio (0.909). For both compounds, the intrinsic hepatic clearance is halved under conditions of inhibition. See text for discussion. (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

The story is different for a high clearance compound given intravenously, as can be seen in B_{iv} (top right). Although the value for CL_{int} is halved, there is a less than a 10% decrease in ER and CL_S. As a consequence, there is little change in $t_{1/2}$ and AUC, as noted by the solid and dotted lines. Given normal experimental variability, the data forming these two lines essentially overlap. Again, this is not surprising because, for a high clearance compound, clearance is approximately equal to organ blood flow ($Q_{hepatic}$ = 1500 ml/minute): $CL_S \equiv Q_{hepatic}$. Because there is no change in hepatic blood flow, there is little change in systemic clearance, which leads to little change in area under the curve (289 to 315 ng · hour/ml) and $t_{1/2}$ (2.0 to 2.2 hours). If one were attempting to examine a drug-drug interaction using this protocol, the conclusion of there being no interaction is incorrect. There is, in fact, a substantial change in intrinsic hepatic clearance, but one is unable to view the change experimentally because the IV data do not reflect that change for this compound but, rather, organ blood flow. This would be a failed experiment (actually, the experimenter failed).

The bottom panels of Figure 44 illustrate the identical experiment for the same two compounds but after oral dosing and assuming complete absorption (i.e., 100% of the dose reaches the liver). For the low clearance compound (A'_{oral}), the changes are essentially the same as those seen after IV dosing (A_{iv}) with regard to areas and $t_{1/2}$, because it is intrinsic hepatic clearance that is being measured after oral and IV dosing. Perhaps the most interesting comparison is shown for B'_{oral}, in the lower right-hand graph. The areas under the curve now, unlike the IV data, reflect the 50% decrease in intrinsic hepatic clearance; the interaction can be seen using this oral dosing protocol. The area under the oral dosing curve divided into the oral dose is referred to as *apparent oral clearance* (CL_O or CL_{oral}) and, in this instance, it is equal to intrinsic hepatic clearance, assuming complete absorption. This value is essentially the same measure that is obtained from a test tube experiment in which the compound is incubated with enzyme and which permits determination of CL_{int}. Notice, however, that the terminal line and $t_{1/2}$ have not changed from the control experiment. This is because $t_{1/2}$ still depends on systemic clearance, and, for this compound, that value is approximately equal to hepatic blood flow, which has not changed. Thus, an interaction in metabolism for low or high hepatic clearance compounds can be seen after oral dosing. The only caveat is that there be no interaction in absorption between the test compound and the interactant.

Systemic bioavailability is used to assess the efficiency of absorption by quantitation of the rate and completeness or extent of absorption. Extent of absorption is based on measuring the total area under the plasma concentration-time curve and comparing to some standard. Rate is generally characterized by the values for C_{max} and T_{max}. There are two definitions of bioavailability: absolute and relative. Absolute bioavailability, $F_{absolute}$, compares the total area under the plasma concentration-time curve (AUC_0^∞) obtained after an oral (or any other route) dose to that obtained after an IV dose. Because, by definition, the IV dose is completely absorbed (i.e., F = 1), one determines the absolute amount of the dose absorbed by the nonvascular route. The two appropriate equations and their ratio are

$$(AUC_0^\infty)_{oral} = \frac{F \cdot dose_{oral}}{CL_S} \qquad F = \frac{(AUC_0^\infty)_{oral} \cdot CL_S}{dose_{oral}}$$

$$(AUC_0^\infty)_{iv} = \frac{(1) \cdot dose_{iv}}{CL_S} \qquad 1 = \frac{(AUC_0^\infty)_{iv} \cdot CL_S}{dose_{iv}} \quad \text{[Eq. 51]}$$

$$F_{absolute} = \frac{F}{1} = \frac{(AUC_0^\infty)_{oral} \cdot CL_S}{(AUC_0^\infty)_{iv} \cdot CL_S} \bullet \frac{dose_{iv}}{dose_{oral}}$$

The study is generally designed so that a crossover protocol is used, and, in that way, it is reasonable to make the assumption that CL_S remains the same in each subject from occasion to occasion. That being true, the basic relationship that is used to calculate bioavailability can be simplified to

$$F_{absolute} = \frac{F}{1} = \frac{(AUC_0^\infty)_{oral}}{(AUC_0^\infty)_{iv}} \bullet \frac{dose_{iv}}{dose_{oral}} \quad \text{[Eq. 52]}$$

The experimental design should attempt to maximize the correctness of the above assumption by, for example, avoiding any changes from one experiment to the other (e.g., avoid other drugs, alcohol, and so forth). The assumption of constant clearance may not be correct, and it appears to be least correct for those compounds referred to as having highly variable clearance, and, typically, they are compounds with large clearance values.

The other, more practical definition of bioavailability and the one most often used by the U.S. Food and Drug Administration in making decisions about generic drug entry into the marketplace is referred to as *relative bioavailability*, $F_{relative}$. This definition is different from absolute bioavailability in that comparison is not made with reference to an IV dose but rather to some comparable standard product that is already on the market (the innovators product). As a consequence, one only determines how much is absorbed relative to that standard, and the absolute amount absorbed is not determined. Study design and calculations are essentially the same as outlined previously and assuming constant clearance. *Test* refers to the product whose relative bioavailability is being assessed, and *reference* is the innovator's product or some other standard.

$$F_{relative} = \frac{F_{test}}{F_{reference}} = \frac{(AUC_0^\infty)_{test}}{(AUC_0^\infty)_{reference}} \bullet \frac{dose_{reference}}{dose_{test}} \quad \text{[Eq. 53]}$$

A $F_{relative}$ value of 1.0 gives no information about how completely the dose was absorbed. That value of 1.0 or 100% simply says that the test product is absorbed to the same extent as the reference, which might have an absolute bioavailability of 1% or 100%.

As noted previously, the assumption of constant clearance may not be reasonable for those compounds that have variable clearance, and, if that is the case, one needs to design a study with a large number of subjects to have sufficient statistical power to detect differences between the products. Alternatively, one may use stable or radioactive isotopic forms of the compound. The use of that approach has been reported (47), and it results in a considerable reduction in the number of subjects needed with a gain in statistical power. An example illustrating the effect of changes in the fraction of the dose absorbed on the plasma concentration-time profile was presented in Figure 42B. A good source for information about bioavailability and bioequivalence is the U.S. Food and Drug Administration Web site (http://www.fda.gov).

Intramuscular (IM) and subcutaneous dosing are often thought to result in rapid and complete absorption, comparable to IV dosing and certainly better than oral administration. This may not be the case, however, for several reasons. There are two possible rate-limiting steps to drug absorption after IM dosing. The capillary wall at the site of IM or subcutaneous injection is less of a barrier to absorption than is the GI tract membrane, because the former is more loosely knit. In general, large, polar, and charged molecules have a greater chance of being absorbed by this route than after oral absorption. Thus, this route is commonly used for drugs such as insulin, proteins (e.g., interferons), peptides, and aminoglycosides. This route is also less chemically damaging to those molecules that may be unstable at the low pH of gut fluids. Thus, one possible rate-limiting step in

absorption is blood flow to the site of administration, which, in turn, may depend on the specific site used. A good example is that of the water-soluble compound lidocaine, whose absorption is more rapid from the deltoid muscle versus the vastus lateralis. The plasma concentrations rise more rapidly and achieve greater concentrations after deltoid dosing compared to the vastus lateralis, and this results in a greater response from deltoid dosing. The reason for these differences is that there is more rapid blood flow and, therefore, a greater rate of absorption from the deltoid muscle. The buttocks are expected to provide for even a slower rate of absorption and response. There is also, in the latter case, the chance of delivering the drug to deep fat tissue, which further prolongs absorption.

Another possible rate-limiting step that applies to poorly water-soluble drugs after IM dosing is precipitation in the muscle tissue that requires redissolution to be absorbed. The rate-limiting step here, as it is for poorly water-soluble oral drugs, is rate of dissolution. A good example is phenytoin. This drug is poorly water-soluble. It is given in a solution buffered to a pH of approximately 10 or 11, to keep it in solution. On IM administration, the drug meets an aqueous environment of pH 7.4 and it precipitates. The drug then redissolves slowly, and concentrations remain quite constant over a period of several days, essentially performing as a controlled release form. The oral dose is absorbed more rapidly and has a shorter terminal $t_{1/2}$ compared to the IM dose.

Diffusion from the interstitial spaces across the blood capillary wall, as noted previously, allows movement of large, polar, and charged compounds. The upper limit for size, however, is approximately 5000. Compounds of greater molecular weight are not able to diffuse across the capillary wall and these compounds enter the blood primarily via the lymph. Because lymph flow is slow, such compounds are absorbed slowly over a prolonged period of time. Such a process has the appearance of a *flip-flop model*, the terminal phase being quite long and being controlled by lymph flow.

STEADY STATE: INFUSION AND MULTIPLE DOSING

Infusion

It is often desirable, in a clinical setting, to achieve a target plasma concentration associated with a needed response and to then maintain concentrations at or near the target value. In other words, sustain or control the plasma concentrations over a narrow range of values, especially if the drug has a narrow concentration range associated with therapeutic effect. This is the aim of all controlled release products, which may be dosed by several routes (e.g., oral, transdermal, IM, and so forth). Whereas this is most often achieved by multiple dosing, as discussed later, it is instructive to establish the principles using the IV route with continuous dosing.

To maintain precise control over plasma concentrations and desired response, *constant rate intravenous infusion* is used. Mechanically, this may be achieved with use of an infusion pump or with an IV drip. The rate of infusion or input into the body is given by a constant, k_o, with units of amount/time (e.g., mg/minute). The rate of loss of compound from the body is given by the product of clearance and plasma concentration (or the product of the first-order rate constant of elimination, apparent volume of distribution, and plasma concentration): $CL_S \cdot C$ (or, $K \cdot V \cdot C$). The rate of change of the amount of compound in the body is the difference between the rate in and the rate out; rate of change = $k_o - CL_S \cdot C$. When infusion is begun, plasma concentrations rise from a value of zero until the rate of input eventually becomes equal to the rate of loss. When that happens, the rate of change of the concentration of the compound in the body is zero, and the rate in equals the rate out. The latter is said to be a *steady state condition* and it continues for as long as the compound is administered at the same rate. A steady state plasma concentration, C_{SS}, is achieved:

$$\text{rate in} = \text{rate out} \qquad k_o = CL_S \cdot C_{SS} \qquad \text{[Eq. 54]}$$

As a consequence, the steady state plasma concentration, sometimes referred to as the average concentration, depends on the ratio of *rate in* to *rate out*:

$$C_{SS} \equiv C_{average} = \frac{\text{rate in}}{\text{rate out}} = \frac{k_o}{CL_S} \qquad \text{[Eq. 55]}$$

This is an extremely important and useful relationship, which may be expressed in a variety of ways, as illustrated under multiple dosing. There are basically two questions that need to be answered about this relationship: What determines the value of C_{SS}, and how long does it take to get there? For a given value of CL_S, the magnitude of C_{SS} depends directly only on the rate of infusion: the greater the rate of infusion, the greater the plasma concentration (double the k_o, double C_{SS}). This is, as discussed in First-Order (Linear) Kinetic Processes, the simple principle of first-order kinetics or of a linear system: double the input, double the output. Any change in CL_S for a given rate of infusion results in a different C_{SS}. This is shown in Figure 45A for three hypothetical infusion rates. Infusion rates of 10, 20, and 40 mg per hour result in C_{SS} values of 1, 2, and 4 mg/L, respectively. The ratio of any two infusion rates is identical to the ratio of the resulting steady state plasma concentrations.

How long does it take to reach a steady state? Take any of the exponentially increasing plasma concentration-time curves shown in Figure 45A and turn it upside down and a typical exponential decreasing curve just as that seen after an IV bolus dose is seen. The parameter that determines the decline (i.e., slope) of the exponential decreasing curve is the same parameter that determines the rise of an infusion curve, $t_{1/2}$. The time necessary to achieve any fraction of steady state is simply a function of $t_{1/2}$, regardless of rate of infusion. This can be visualized by taking the three curves in Figure 45A, dividing each by infusion rate, and a single superimposed curve is obtained. This is the same idea, superposition, discussed previously for single IV bolus doses, and it is a characteristic of first-order kinetics. Because these infusion rate-normalized curves superimpose, it takes the same amount of time for any of those infusion curves to achieve the same fraction of steady state. It takes one $t_{1/2}$ for an exponential declining curve to reach 50% of the starting concentration; it takes one $t_{1/2}$ for an exponential increasing infusion curve to achieve 50% of its final steady state concentration. After two $t_{1/2}$s, an exponential declining curve has declined by 75% of its starting value; after two $t_{1/2}$s, an infusion curve achieves 75% of its final steady state concentration. After three $t_{1/2}$s, an exponential declining curve has declined to 88% of its starting value; after three $t_{1/2}$s, an infusion curve achieves 88% of its final steady state concentration. This continues for each subsequent $t_{1/2}$. The rise in the infusion curve after a certain number of $t_{1/2}$s (as percentage of the final steady state concentration) is exactly equal to the decline (as percentage of the starting concentration) in an IV bolus plasma concentration-time curve at the same number of $t_{1/2}$s. As a practical general rule, it takes approximately four $t_{1/2}$s to achieve a steady state (actually, 94% of C_{SS}).

The exact equation that describes the concentration-time curve after constant rate IV infusion to steady state, assuming a one-compartment model, is

$$C = \frac{k_0}{CL_S} \cdot (1 - e^{-K \cdot t}) = C_{SS} \cdot (1 - e^{-K \cdot t}) \qquad \text{[Eq. 56]}$$

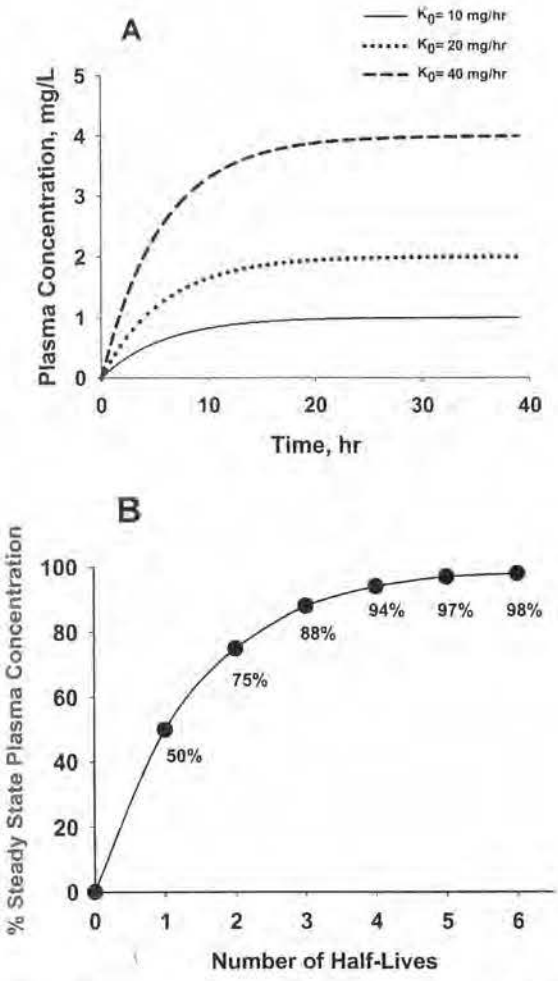


Figure 45. **A:** Plasma concentration-time profiles for a hypothetical compound given by constant rate intravenous infusion at rates of 10, 20, and 40 mg/hour. The resulting steady state plasma concentrations are directly proportional to the infusion rates: 1, 2, and 4 ng/ml. **B:** The percentage of steady state as a function of the number of half-lives of infusion. The values on the line indicate the percentage steady state achieved at each half-life. (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

At time zero, the concentration is zero, and, at time infinity, the steady state concentration is reached, and it is equal to k_o/CL_S. This equation describes the curves illustrated in Figure 45A. Once the infusion is stopped, whether a steady state is achieved or not, the concentrations decline in an exponential fashion just as it does after an IV bolus dose. The slope of the line describing the decline is equal to $-K/2.3$.

The percentage of the steady state plasma concentration that is ultimately achieved after any infusion rate is illustrated in Figure 45B as a function of the number of $t_{1/2}$s of infusion. The values for percentage of steady state achieved are noted on the line for each $t_{1/2}$.

The idea of a steady state plasma concentration applies as much to endogenous biochemicals as it does to exogenously administered compounds. The only difference is that the numerator, rather than being an infusion rate, is a formation or synthesis rate:

$$C_{SS} = \frac{\text{formation rate}}{CL_S} \qquad \text{[Eq. 57]}$$

For example, creatinine is formed from muscle metabolism, and the resulting steady state serum creatinine concentrations are a function of its formation rate from muscle and creatinine renal clearance. This idea applies to any biochemical for which there is a source of production, such as serum albumin.

Multiple Dosing

Constant rate IV infusion is useful for establishing the two basic ideas of steady state: What determines the value of the steady state concentration and how long does it take to achieve a steady state. Furthermore, infusion has a place in therapy although its use is limited by the need for a clinical facility and experienced personnel. In some instances, a portable infusion pump can be attached to a patient and thereby permit ambulatory activities to continue. Far and away, however, the most frequent approach to continual therapy and to achieving a steady state is with use of a *multiple dosing regimen*. Although such therapy might involve multiple IV infusions or multiple IV bolus doses (again, in a clinic or hospital setting), other routes, especially oral or subcutaneous administration, are the rule. A multiple dosing regimen requires a maintenance dose (D_M) and, perhaps, a loading dose (D_L), a dosing interval (τ; tau), a route of administration, and a specific drug product. The dosing interval determines the frequency of dosing. Issues of exposure to environmental compounds have identical considerations when it comes to accumulation in the body.

Consider a route of administration that requires absorption into the body, as this results in the most general relationships. The basic relationship, with one alteration, is the same as that developed for constant rate IV infusion. The only difference is that rather than a constant rate infusion, a dose rate is dealt with here. A *dose rate* is the amount of substance that reaches the systemic circulation ($F \cdot D_M$) per dosing interval, τ; dose rate equals $(F \cdot D_M)/\tau$. Therefore, the steady state concentration is given by

$$C_{SS} = C_{average} = \frac{\text{dose rate}}{CL_S} = \frac{F \cdot D_M}{CL_S \cdot \tau} \qquad \text{[Eq. 58]}$$

As with the previous relationship, this is an especially useful equation and it can be written in a number of equivalent forms.

$$C_{SS} = C_{average} = \frac{\text{dose rate}}{CL_S} = \frac{F \cdot D_M}{CL_S \cdot \tau} = \frac{F \cdot D_M}{\lambda_n \cdot V \cdot \tau} = \frac{F \cdot D_M \cdot t_{1/2} \cdot (1.44)}{V \cdot \tau} \qquad \text{[Eq. 59]}$$

A change in any one variable at a time should lead to a change in C_{SS} that makes sense. Thus, if $t_{1/2}$ were to increase, holding all other variables constant, one would expect the steady state concentration to increase, as the equation predicts. The reason that the term $C_{average}$ is used is because, unlike constant rate IV infusion, multiple dosing actually produces a fluctuating and not a constant steady state, as is illustrated.

Another idea that is different for multiple dosing is that of *accumulation*. As long as one administers a dose of the compound before the prior dose is completely eliminated from the body, the amount of compound in the body continues to accumulate with additional doses until a steady state is reached. What determines the value for C_{SS}? Dose rate and clearance. How long does it take to achieve a steady state? The answer is approximately four $t_{1/2}$s, and it does not matter how often the compound is administered. To illustrate these ideas, consider Figures 46 and 47. A typical multiple dosing plasma concentration-time profile involving absorption is shown in Figure 46A. The compound has a $t_{1/2}$ of 4 hours and it is being dosed every 4 hours. If only the first dose was given, the plasma concentrations continue to decline after reaching a maximum (C_{max}). Also shown is the area under the first dose curve. However, if a sec-

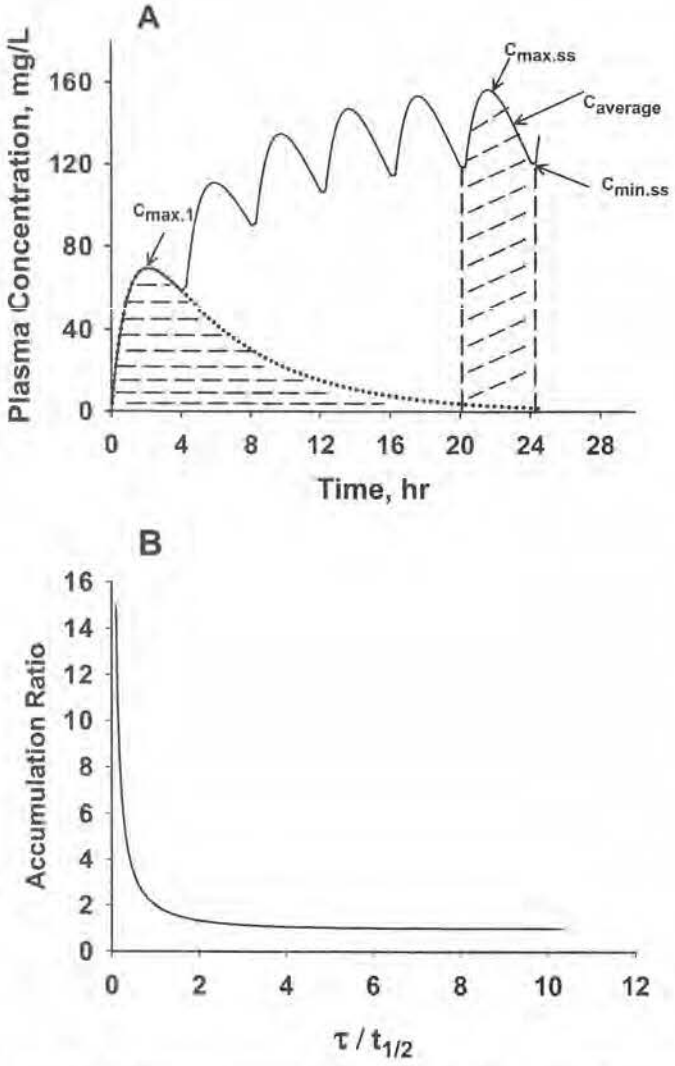


Figure 46. **A:** Plasma concentration-time profile after the multiple dosing of a compound that undergoes absorption to gain access to the body. The compound has a terminal half-life of 4 hours and is being dosed at a dosing interval (τ) of 4 hours. The concentrations increase with dosing as a result of accumulation, and a steady state concentration is achieved within approximately four half-lives. The first dose is characterized by a maximum plasma concentration ($C_{max\cdot1}$), and the total area under the curve for the first dose is indicated. At steady state there is a maximum and minimum steady state plasma concentration ($C_{max\cdot ss}$ and $C_{min\cdot ss}$), and an area under the curve during the dosing interval at steady state is indicated. An average steady state concentration ($C_{average}$ or $\bar{C}$) between the maximum and minimum value may also be calculated. **B:** The accumulation ratio as a function of the ratio of dosing interval to half-life, $\tau/t_{1/2}$. The more frequent the dosing (left side of graph), the smaller the value for $\tau/t_{1/2}$ and the greater the compound accumulates. The less frequent the dosing (right side of graph), the greater the value for $\tau/t_{1/2}$ and the smaller the accumulation. Note that when $\tau/t_{1/2} = 1$, the accumulation ratio is 2.0. (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

ond and subsequent doses are given every 4 hours, the plasma concentrations rise as a consequence of accumulation. This rise continues until a steady state is achieved and this is seen after approximately four $t_{1/2}$s. All subsequent curves during a dosing interval simply repeat the identical concentration-time pattern (in fact, they are superimposable). Any concentration-time curve during a dosing interval at steady state is characterized by a maximum ($C_{max\cdot ss}$), a minimum ($C_{min\cdot ss}$), and an average ($C_{average}$ or $\bar{C}$; read as *C-bar*) steady state plasma concentration. There are exact equations that may be used to calculate those values. The

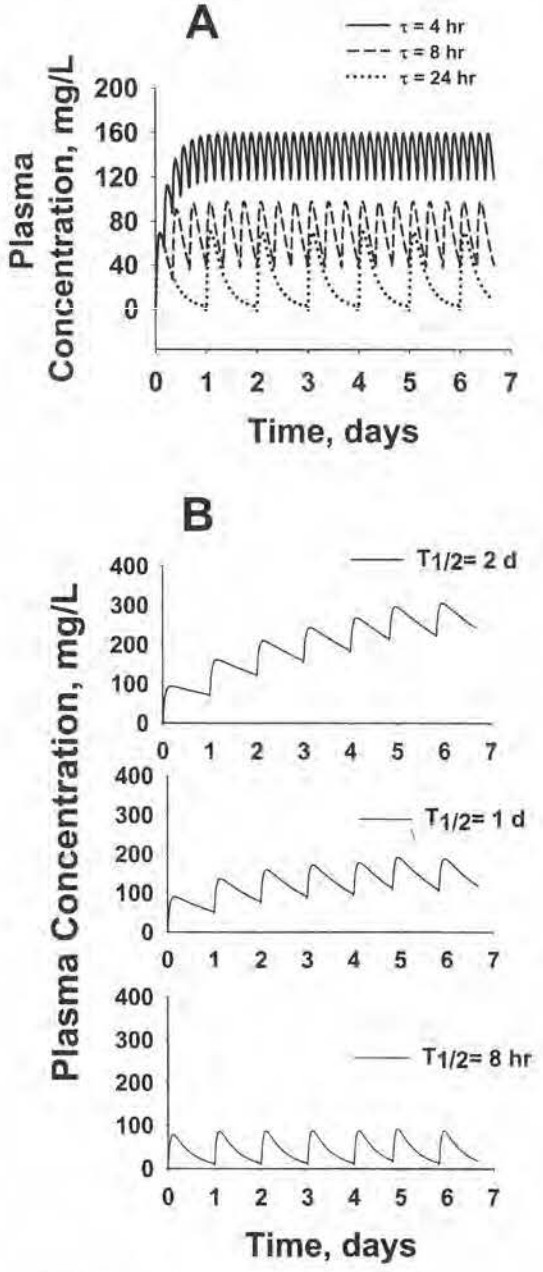


Figure 47. **A:** Plasma concentration-time profiles for a drug administered in a multiple dosing fashion by a route that requires absorption into the body. The same maintenance dose of the same drug ($t_{1/2}$ = 4 hours), is administered at different dosing intervals (τ = 4, 12, and 24 hours), giving rise to different dose rates and different steady state plasma concentrations. Note that accumulation is greatest for the smallest ratio of $\tau/t_{1/2}$ (i.e., τ = 4 hours). **B:** Plasma concentration-time profiles for different drugs administered in a multiple dosing fashion by a route that requires absorption into the body. Each drug is given at the same dosing interval, τ = 1 day. The half-lives of the drug are 2 days (*top*), 1 day (*middle*), and 8 hours (*bottom*). Note that accumulation is greatest for the smallest ratio of $\tau/t_{1/2}$ (i.e., $t_{1/2}$ = 2 days). (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

$C_{average}$ is not the mean of the maximum and minimum concentrations, but rather it is defined as the area under the steady state plasma concentration during a dosing interval divided by the dosing interval, $C_{average} = (AUC_0^{\tau})_{ss}/\tau$. The degree of accumulation is judged by examining the concentration obtained from the first dose and comparing it to the concentration obtained on multiple dosing. For example, the ratio of $C_{max\cdot ss}$ to $C_{max\cdot1}$ gives an estimate of accumulation. In the example illustrated, the

value is approximately 2.0; the drug accumulates to the extent of approximately twofold. The degree of accumulation as judged by the accumulation ratio is illustrated in Figure 46B. Accumulation is a function of the ratio of dosing interval to $t_{1/2}$, $\tau/t_{1/2}$. Thus, the smaller this ratio, the more frequently the dose is given (e.g., τ = 4 hours; $t_{1/2}$ = 24 hours), the greater the accumulation. In contrast, less frequent dosing (e.g., τ = 24 hours; $t_{1/2}$ = 4 hours) gives a large value on the x-axis and little accumulation. A useful index value is an accumulation ratio of 2.0, associated with a $\tau/t_{1/2}$ ratio of 1. That is, dose the drug at a time equal to its $t_{1/2}$ and accumulation is twofold.

The latter ideas are also expressed in Figure 47. Figure 47A illustrates the multiple dosing plasma concentration-time data for a drug that undergoes absorption and that is administered at three different dosing intervals. With a $t_{1/2}$ of 4 hours, this hypothetical drug undergoes greater accumulation when it is given most frequently (i.e., τ = 4 hours) and least accumulation when given infrequently (i.e., τ = 24 hours). Figure 47B illustrates a similar idea except that the dosing interval is held constant (τ = 24 hours) for three different hypothetical drugs with different half-lives (from top to bottom, 2 days, 1 day, and 8 hours). The greater the $t_{1/2}$, the greater the accumulation.

Dosing regimens that use the same dose rate provide identical average steady state plasma concentrations. Thus, the following equivalent dose rates result in identical values for $C_{average}$: 1000 mg/24 hours = 500 mg/12 hours = 250 mg/6 hours. However, the range of maximum to minimum concentrations is different. The least frequent dosing (1000 mg/24 hours) results in a much larger range of concentrations at steady state compared to more frequent dosing (i.e., 250 mg/6 hours). These ranges of concentrations during a dosing interval at steady state for different dosing intervals are illustrated in Figure 48.

One of the most useful applications of clearance concepts is their incorporation into the multiple dosing relationships. Based on the category of clearance of the compound (low or high), one can predict what should happen at steady state as a result of alterations due to, for example, drug-drug interactions or as a result of disease states. In the same way, one can evaluate the results of studies to determine the correct mechanism(s) responsible for the observed changes. This is especially true when trying to understand changes in total and unbound plasma concentrations and $t_{1/2}$ as a result of alterations in plasma protein binding.

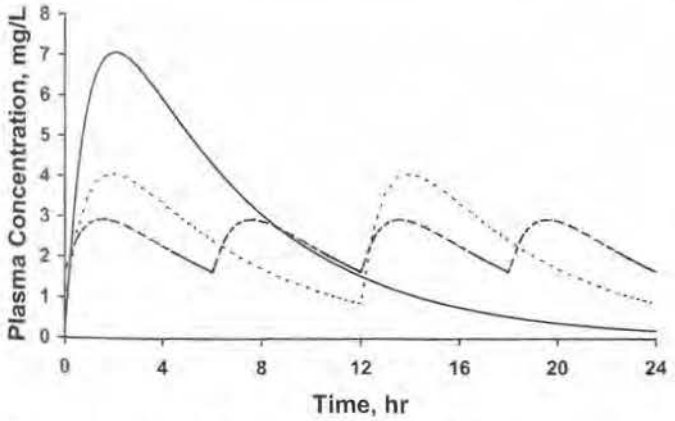


Figure 48. Steady state plasma concentrations of a drug administered in a multiple dosing fashion by a route that requires absorption into the body. The same drug (half-life, 4 hours) was given at different dosing intervals but using equal dose rates. The three dose rates are 1000 mg/24 hours; 500 mg/12 hours; 250 mg/6 hours. Note that the same average steady state plasma concentration is achieved; however, there is a wide range of concentrations when the dosing interval is long. (From M. Mayersohn, *unpublished*, with permission from Saguaro Technical Press, Inc, Tucson, AZ, 2002.)

What effect will a change in plasma protein binding have on total and unbound plasma concentrations? The change in plasma protein binding may be the result of an alteration in plasma protein (e.g., albumin) concentrations or as a consequence of being displaced by another highly bound compound. Total steady state plasma concentration, C_{TOTAL}, is a function of dose rate and clearance, whereas the unbound concentration is that value multiplied by the unbound fraction:

$$C_{TOTAL} = \frac{\text{dose rate}}{CL_S}$$

$$C_{UNBOUND} = f_U \cdot C_{TOTAL} = \frac{f_U \cdot \text{dose rate}}{CL_S} \qquad \text{[Eq. 60]}$$

The exact relationship depends on the category of clearance: low or high. For a *low clearance* compound, $CL_S \equiv f_U \cdot CL_{U,int}$, and, therefore,

$$C_{TOTAL} \cong \frac{\text{dose rate}}{f_U \cdot CL_{U,int}}$$

$$C_{UNBOUND} = f_U \cdot C_{TOTAL} \cong \frac{f_U \cdot \text{dose rate}}{f_U \cdot CL_{U,int}} = \frac{\text{dose rate}}{CL_{U,int}} \qquad \text{[Eq. 61]}$$

Total plasma concentration is affected by changes in plasma protein binding (e.g., an increase in the unbound fraction results in a decrease in total concentration). In sharp contrast, a change in plasma protein binding has *no* effect on unbound plasma concentrations. This important conclusion is sometimes thought to be counter-intuitive, especially when it is stated that *plasma protein binding has no effect on the unbound plasma concentration*. The unbound plasma concentration is influenced only by the $CL_{U,int}$, whereas the total concentration is affected by total clearance. The only way to change the unbound plasma concentration is to alter the $CL_{U,int}$. For example, if the drug is metabolized, any drug-drug interaction causing an increase (induction) or decrease (inhibition) in $CL_{U,int}$ results in a change in the unbound plasma concentration. Because it is the unbound plasma concentration that is in equilibrium with tissues (the likely sites of action), that type of interaction is expected to affect response and/or toxicity. In fact, it is generally correct to state that drug displacement interactions have little if any clinical significance (48).

For a *high clearance* compound, clearance is approximately equal to organ blood flow, $CL_S \equiv Q$, and, therefore,

$$C_{TOTAL} \cong \frac{\text{dose rate}}{Q}$$

$$C_{UNBOUND} = f_U \cdot C_{TOTAL} \cong \frac{f_U \cdot \text{dose rate}}{Q} \qquad \text{[Eq. 62]}$$

In this instance, total plasma concentrations remain unchanged, but the unbound concentration increases if the unbound fraction increases. This is one of the few categories of drug in which a drug displacement interaction might have clinical relevance (e.g., lidocaine).

An excellent example of the use of these concepts in evaluating literature claims and in examining possible mechanism(s) of interactions is the classical interaction between warfarin and phenylbutazone. It was known that the coadministration of those two compounds resulted in incidents of bleeding. It was also known that both compounds bound extensively to plasma proteins, and displacement from binding sites could be seen in *in vitro* studies. The conclusion reached, which was held for a long time, was that phenylbutazone was displacing warfarin from its plasma protein binding sites. All that is needed to know to assess the correctness of this conclusion is the clearance rate-

gory of warfarin. Because that compound is totally metabolized by the liver, and its clearance is approximately 100 ml/minute, it is in a low clearance category (ER ≡ 0.067). Equation 61 offers an approximation of total and unbound plasma concentrations for a low clearance compound and it suggests that total concentration should decrease. In fact, total warfarin concentrations were found to decrease in the presence of phenylbutazone in a clinical study. Therefore, that finding is consistent with the suggested mechanism of the interaction being a displacement interaction. However, why would a *decrease* in the concentration of the drug cause an *increased* response (i.e., more bleeding)? Equation 61 also predicts that there should be no change in the unbound plasma concentrations. In fact, in the clinical study, the unbound plasma concentrations were found to *increase* in the presence of phenylbutazone. That increase is consistent with an enhanced response, but how does one explain that change? The only way to explain the findings is to conclude that the $CL_{U,int}$ has decreased, and this is the cause of the increase in the unbound plasma concentrations,

$$\uparrow C_{UNBOUND} \equiv \frac{\text{dose rate}}{\downarrow CL_{U,int}} \qquad \text{[Eq. 63]}$$

In other words, there are actually two interactions occurring, but the clinically important one is a result of phenylbutazone inhibiting the metabolism of warfarin, causing a decrease in the $CL_{U,int}$ (49).

These concepts can also be applied in an attempt to predict or interpret the effect of altered plasma protein binding on the terminal $t_{1/2}$. This becomes somewhat more complex because $t_{1/2}$ depends on both apparent volume of distribution and clearance, and both may be affected by plasma protein binding, depending on the clearance category. To conduct this analysis in a practical way, one needs to simplify the volume and the clearance terms: small or large volume, small or large clearance. For example, what effect would an increase in the unbound fraction in plasma have on the terminal $t_{1/2}$ of a small volume and small clearance compound (e.g., warfarin)?

$$t_{1/2} = \frac{0.693 \cdot V_d}{CL_S} \equiv \frac{0.693 \cdot (7 + 8 \cdot f_U)}{f_U \cdot CL_{U,int}} \qquad \text{[Eq. 64]}$$

This analysis would conclude that, because the numerator and denominator contain a term for f_U, any change in that value has little if any effect on $t_{1/2}$. Perhaps being a bit more precise (even though this is an approximation only), the numerator goes up in a nonproportional way with an increase in the unbound fraction, whereas the denominator goes up directly, leading to an overall decrease in $t_{1/2}$. This type of simplified analysis is useful and goes a long way in explaining unexpected results and in making reasonable experimental predictions.

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GLOSSARY

A

Absorption: The process of a substance moving from an extravascular (i.e., nonintravenous) site of dosing across one or more biologic membranes (usually down a concentration gradient) and appearing in the systemic (i.e., blood) circulation after administration.

Absorption rate constant: The apparent first-order absorption rate constant describes the relationship between the rate of absorption and the concentration or amount of substance being absorbed from the absorption site; rate of absorption = $k_a \cdot$ amount. Usual symbol is k_A (units, 1/time).

Absolute bioavailability: See *Bioavailability*.

Accumulation: The process of drug amount (and plasma concentration) increasing in the body after multiple dosing. Accumulation occurs when the next dose is given before all drug from the previous dose has been eliminated from the body. Measured by the accumulation ratio.

Accumulation ratio: The extent to which a drug accumulates in the body after a multiple dosing regimen. This value is determined by the ratio of the dosing interval (τ) to elimination half-life ($t_{1/2}$); the smaller that ratio is, the greater the extent of accumulation. Symbol often used is R_C (unitless). For a simple model,

$$R_c = \frac{1}{1 - e^{-K \cdot \tau}}$$

Active tubular reabsorption: The active process requiring metabolic energy that is responsible for the movement of a substance from the urine back into the blood. As with all active processes, a specific transport system is required. Such systems are important for homeostasis of required nutrients such as monosaccharides, amino acids, and vitamins. The renal clearance of such substances is approximately zero until the process becomes saturated and at a maximum approaches glomerular filtration. This process is characterized by a V_{max} or T_{max} (transport maximum) and k_m, concentration to achieve one-half T_{max}.

$$CL_{reabs} = \frac{T_{max}}{k_m + C_{urine}} \qquad CL_{reabs} \to 0, \text{ as } C_{urine} \to \infty$$

Active tubular secretion (or transport): When used in the context of the kidney, this refers to the passage of drug directly from the bloodstream (efferent arteriole) into the renal tubule, without going through the glomerulus. The process is *active*, because it requires the input of energy to push the drug from a low concentration in the bloodstream to a high concentration in the renal tubule. Such active processes also have characteristics of site specificity, structural specificity, and may be competitively inhibited. Penicillin is a drug example (inhibited by probenecid; a classic drug-drug interaction). Renal clearance associated with active tubular secretion (approximately 1200 blood/minute or 600 ml plasma/minute) exceeds that of glomerular or passive filtration (approximately 100 to 120 ml plasma/minute). Mathematically, this process can be described by the same relationship as for Michaelis-Menten enzyme kinetics. This process is characterized by a V_{max} or T_{max} (transport maximum) and k_m, concentration to achieve one-half T_{max}. The renal clearance of such substances used to measure renal blood flow (e.g., p-aminohippuric acid) approaches renal blood flow at low plasma concentrations. Clearance approaches zero at high plasma concentrations. At high plasma concentrations, renal clearance approaches glomerular filtration.

$$CL_{secretion} = \frac{T_{max}}{k_m + C_{plasma}} \qquad CL_{secretion} \to 0, \text{ as } C_{plasma} \to \infty$$

ADME: The mnemonic used for *a*bsorption, *d*istribution, *m*etabolism, and *e*xcretion.

p-Aminohippurate (PAH): See *Para-aminohippurate*.

Apparent oral clearance: Determined after an oral dose from CL_O = dose/$(AUC)_0^\infty$. Sometimes referred to as intrinsic clearance (see *intrinsic clearance*). Apparent oral clearance equals systemic clearance if the fraction of the dose absorbed (F) is equal to 1. Under all other circumstances, oral clearance is greater than systemic clearance (units, volume/time).

Apparent volume of distribution: See *Volume of distribution*. Symbol is V, usually with a subscript to indicate which volume it represents (units, volume).

Area under the curve (AUC): A shorthand term for the area under the plasma concentration-time curve. Unless otherwise specified, AUC_0^∞ is the area from time 0 to infinity. This important measure is directly related to dose (assuming first-order kinetics) and is used to calculate several other important values such as clearance, apparent volume of distribution, and bioavailability. The mathematical equivalent of this graphical area is the integral of the equation that describes the curve (from time 0 to infinity); $AUC_0^\infty = \int_0^\infty C \cdot dt$. The area may be determined by fitting the data (e.g., nonlinear regression analysis), or it may be

approximated with any of several techniques (e.g., trapezoidal rule, spline function, and so forth). This area is sometimes referred to as the *zeroth moment*. Conceptually, the AUC_0^∞ may be considered (as it is by pharmacologists and toxicologists) as an index of exposure to the drug. Thus, the greater the area is, the greater the exposure to the drug (units, concentration × time).

B

Bile: A liquid produced by the liver and secreted into the duodenum; it contains water, bile salts, bile pigments, cholesterol, lecithin, and ions. Bile salts make bile a micellar solution. The primary function of bile is to emulsify fats, through micellar solubilization, and it appears to increase the water-solubility and dissolution rate of poorly water-soluble drugs.

Biliary recycling (enterohepatic recirculation): The process whereby a drug or endogenous substance is taken up by the liver, incorporated into bile, secreted into the gut, and reabsorbed back into the systemic circulation. So effective is reabsorption and recycling of bile salts, that greater than 95% of these molecules are reabsorbed from the gut. Biliary recycling of a drug is often observed as a secondary peak in the plasma concentration-time curve, often in association with ingestion of a meal. Disruption of this process increases systemic clearance. The long half-life of phenobarbital (approximately 4 days) appears to be due to enterohepatic recycling. The half-life is reduced dramatically after oral charcoal administration, which disrupts the recycling process.

Bioavailability: A term used to define and quantitate the rate and efficiency of the extravascular absorption process. As a parameter, there are two types of bioavailability: (A) *absolute bioavailability* refers to the fraction of a dose reaching the systemic circulation intact (in reference to an intravenous dose); and (B) *relative bioavailability* is the fraction of a dose of drug reaching the systemic circulation relative to a reference product (*innovator's* product). As an adjective, *bioavailability* refers to the rate and extent of drug absorption (as in a bioavailability study). The symbol F is often used for bioavailability (fraction of the dose absorbed), and the maximum plasma concentration (C_{max}) and the time of occurrence of the maximum concentration (T_{max}) are often used to reflect rate of absorption.

Bioequivalence: The property of two or more dosage forms, which contain the same amount of drug, producing equivalent biologic responses. Regulatory agencies (e.g., U. S. Food and Drug Administration) customarily assume dosage forms are bioequivalent when, from a statistical point of view, they are equally bioavailable. Hence, the term *bioequivalence* is frequently interchanged with bioavailability equivalence. The basis for this determination is often AUC_0^∞ or the amounts of drug excreted into the urine. Numerous statistical approaches are used for this judgment. The Food and Drug Administration has guidances available to define and test bioequivalence.

Biologic half-life: Often used interchangeably with elimination half-life. This term should *not* be used as it is often confused with a response half-life. Symbol $t_{1/2}$ (units, time).

Biopharmaceutics: The study of the influence of physical chemical and formulation factors on the *in vitro* (e.g., dissolution rate) and *in vivo* performance (e.g., absorption) of a drug dosage form. Frequently, however, biopharmaceutics is also used to characterize formulation factors affecting only dissolution.

Biophase: The presumed site of action in which the receptor is located. Drug is thought to bathe this site and be in equilibrium with unbound drug concentration in the blood (see *Effect site*).

Biotransformation: See *Metabolism*.

Bolus: Refers to instantaneous drug input, as an intravenous bolus injection. In veterinary medicine, a bolus refers to a large tablet administered to animals. Symbol often used for an intravenous bolus dose is X_{iv}^0 (units, mass).

Blood: The fluid that forms the major communication system within the body. Blood is comprised of a fluid (plasma) that is suspended proteins and formed elements (e.g., various cells). Blood is the fluid that delivers and removes drug from tissues that it bathes.

Brush border: See *Microvilli*.

C

Central (or initial) compartment: The compartment or region of a multicompartment model that receives drug and often is the site of elimination of drug. This compartment is *central* to all other compartments in a mammillary model (all others *feed-off* of this compartment) and contains the blood and all other highly blood-perfused tissues. The exact tissues located in this compartment also depend on the drug. Often called the initial compartment.

Clearance: A primary pharmacokinetic parameter characterizing the rate at which drug is removed from plasma. In general, clearances are additive, as, for example, (total) clearance equals metabolic clearance plus renal clearance plus biliary clearance, and so forth. Clearance has units of volume/time. If clearance equals 20 ml/minute, this denotes that total elimination of drug is such that every minute an equivalent amount of drug is irreversibly removed (eliminated) as is contained in 20 ml of plasma (or blood). Clearance may also be viewed as the proportionality constant between plasma concentration and rate of elimination (i.e., plasma concentration × clearance = rate of elimination). When the term *clearance* is used, it refers to total clearance (total body clearance, TBC, or systemic clearance, CL_S), unless specifically denoted otherwise. Clearance is one of if not the most important pharmacokinetic parameters, as it characterizes the functional ability of an eliminating organ and it determines steady-state plasma concentrations resulting from multiple dosing. The fundamental mathematical relationship for clearance is CL = rate of elimination/C_{PLASMA} (units, volume/time).

Compartment: A part of a system, which may be a substance or a space. If a drug and metabolite occupy the same body, there are two compartments, one for the drug and the other for the metabolite. If a drug occurs in two distinct sites in the body, there are two compartments for that drug. The latter, differentiating space or location, is the most frequently used definition. Compartmental models arise from the need to describe measurable rates of drug distribution in the body. Compartmental models are usually arranged in a mammillary format, such that there is a *central* compartment from which all other compartments feed.

Concentration gradient: The difference in concentration of a substance at two different locations. For example, a concentration gradient across a membrane is the driving force for movement across that membrane. When the gradient is zero (i.e., no difference in concentrations on two sides of the membrane), transport ceases. In first-order processes, compounds move down a gradient. Only in active or specialized transport processes is a compound able to go up or against a gradient (e.g., active tubular secretion).

Concentration maximum: See *Maximum plasma concentration*.

Constant of elimination or disposition: See *Disposition rate constant*.

Creatinine (clearance): Creatinine is an endogenous waste product of muscle metabolism. Creatinine is almost completely eliminated by the kidney by glomerular filtration without tubular secretion or reabsorption. Hence, creatinine clearance is a good approximation of glomerular filtration rate. Creatinine clearance is extensively used, because it does not require exogenous drug administration. The value of creatinine clearance may

be estimated from a measure of serum creatinine concentration with the aid of one of several equations that incorporate age, body weight, and gender (Cockcroft-Gault equation or Siersback-Nielsen equation).

$$\text{CLCr, ml/min (males)} = \frac{(\text{ideal weight, kg})(144 - \text{age, yr})}{72 \cdot \text{Scr (mg\%)}}$$

$$\text{CLCr, ml/min (females)} = \frac{0.86(\text{ideal weight, kg})(144 - \text{age, yr})}{72 \cdot \text{Scr (mg\%)}}$$

in which CLCr is creatinine clearance and Scr is serum creatinine concentration (units, volume/time).

Cytochrome P-450: A large family of enzymes that is responsible for the metabolism of many drugs. Such metabolic processes are described as phase I metabolism. There are numerous isozymes or isoforms, some of which are under genetic control. Also referred to as CYP450.

D

Disintegration: The breaking apart of a dosage form, observed as when an aspirin tablet is placed in water. The tablet initially breaks up into clumps of granules, followed by granules, and then primary particles. This is *not* the same as dissolution, which is a prerequisite step for absorption. Consider a tablet made of granules of cement; the tablet disintegrates but never dissolves.

Distal: Further away from some reference point. For example, the reference point of the gastrointestinal tract is the juncture of the esophagus and stomach. Therefore, the large intestine is more distal than the small intestine.

Disposition: The simultaneous processes of drug distribution and elimination.

Disposition half-life: A term used to describe the terminal log-linear phase of a plot of plasma concentration versus time (or any other plot from which half-life or the rate constant may be determined). This is the preferred term (compared with biologic or elimination half-life) because it implies properly that this half-life is a function of all dispositional processes (i.e., a function of distribution and elimination). The most appropriate relationship for half-life, which shows the dependent and independent variables, is $t_{1/2} = (0.693 \cdot V)/CL$ (units, time).

Disposition rate constant: A constant that acts as a proportionality constant between a rate and the amount or concentration of drug. This rate constant refers to the log-linear terminal phase of a semilog plot of blood concentration versus time. This constant, which has units of reciprocal time, may be viewed as the fractional (or percentage) rate of loss from the body, which involves both processes of distribution and elimination. Symbols often used are K, β, λ_n, or λ_{last}. The disposition half-life is obtained from the value $t_{1/2} = 0.693/K$ (units, 1/time).

Dissolution: The process of dissolving (i.e., changing state from a solid to a liquid). Dissolution rate is often the rate-limiting step in the extravascular absorption process, especially for poorly water-soluble drugs. Dissolution and disintegration are *not* the same processes (see *Disintegration*).

Distribution: Translocation from the plasma to tissues, and *vice versa*.

Distribution equilibrium: This occurs when the ratio of drug concentration in plasma to concentration in tissue remains constant as a function of time. If distribution is instantaneous (which results in a one-compartment model), the plasma/tissue concentration ratios are constant at all times after dosing. If distribution occurs at a measurable rate (leading to a multicompartment model) the plasma/tissue ratios continue to change until an equilibrium is achieved.

Distribution phase: The initial rapid portion of a drug concentration-time profile after an IV bolus dose, which primarily reflects the distribution of drug or movement into other tissues. When this distributive phase occurs, the drug may be described by a multicompartment model. This is often called the α-*phase*.

Dosage form: The physical form in which the drug is dispersed and used for delivery to humans (e.g., tablet, capsule, solution, and so forth).

Dosage regimen: The dosage form, amount, frequency, and route of administration of a multiple dosing scheme (e.g., one 300 mg oral tablet taken every 6 hours).

Dose-dependency: This condition exists whenever drug concentration-time profiles, divided by dose, are not superimposable. A dose-dependent or nonlinear system is one in which there is not a linear relationship between input and output. This process denotes one or more types of nonlinearity. Other terms used are: nonlinearity, capacity-limited, zero-order (but incorrectly), saturable. An example is Michaelis-Menton enzyme kinetics. Dose-dependent generally refers to the relationship between a parameter (e.g., half-life, clearance, volume) and dose. Other forms of nonlinearity are time-dependent.

Dose-response curve: Any linear or (semi)logarithmic plot of drug response (either therapeutic or toxic) as a function of dose. More commonly in pharmacokinetics, concentration-response curves are used.

Dosing interval: Time interval between consecutive doses. Often symbolized by τ (tau) (units, time).

Drug: A substance given for the treatment, cure, or amelioration of disease or physiologic disorders. It may be synthetic, semisynthetic, or derived from natural sources.

Drug metabolism: See *Metabolism*.

E

Effect site: The actual, presumed, or hypothetical site within the body in which receptors generating the pharmacologic effect are located. This site is often called a *biophase* (see *Biophase*).

Elimination: The sum of (bio)chemical and physical removal of drug from the body.

Elimination half-life (or rate constant): A term used to describe the terminal log-linear phase of a plot of plasma concentration versus time (or any other plot from which half-life or the rate constant may be determined). Although this is a commonly used term, it is *not* the preferred term, which is disposition or terminal half-life. See *Disposition half-life*.

Enterohepatic recycling or recirculation: See *Biliary recycling*.

Enzyme: An organic catalyst, frequently a protein.

Enzyme induction: The process whereby exposure to an agent increases the concentration of a drug-metabolizing enzyme, which results in an increase in metabolic clearance. Smoking induces certain forms of cytochrome P-450, which increases the metabolic clearance of certain drugs (e.g., theophylline).

Enzyme inhibition: The reverse of enzyme induction; the process whereby enzyme activity is reduced. This process results in a reduction in metabolic clearance (e.g., cimetidine is a common enzyme inhibitor).

Epithelial cells: These are cells covering internal or external surfaces of the body. Epithelial cells line the villi of the gastrointestinal tract (one layer thick); they are joined and held together by small amounts of a cement-like substance. The junction between any two cells is termed the *tight junction*. Leakage through the tight junction is the major route of drug absorption of dissociated (ionized) molecules. A layer of epithelial cells is termed an *epithelium*.

Ex vivo: Away or removed from life, oftentimes a combination of *in vivo* and *in vitro*. For example, one could study enzyme induction by administering the inducer to rats *in vivo*, then preparing liver homogenates and studying enzymic activity *in vitro*.

Exogenous: Not naturally present in the body. Most drugs are exogenous agents; exceptions are agents like thyroxine, sodium bicarbonate, progesterone, estradiol, and so forth.
Exponential: In pharmacokinetics, referring to any mathematical expression with the number *e* (the base of natural numbers; 2.71828 . . .) or 10 raised to a power. In general, an exponent is the power to which a base is raised (e.g., 10^2; 2 is the exponent of the base 10). Exponential terms most frequently arise in pharmacokinetics as a result of a first-order kinetic process. First-order disposition could be characterized as exponential disposition. Exponential processes occur frequently in nature (e.g., growth of cells). In pharmacokinetics, absorption from an extravascular site is often described by an exponential input of drug into the body; elimination of drug from the body is often described by exponential loss.
Extraction ratio (ER): The fraction of molecules entering an organ or tissue that is irreversibly eliminated from blood as it passes through that organ. For example, a hepatic ER of 0.2 indicates that 20% of all molecules entering the liver are irreversibly eliminated through metabolism, biliary excretion, and so forth. This fraction remains constant with each passage through the eliminating organ assuming first-order kinetics. ER is determined from the following measurement:

$$ER = \frac{C_{in} - C_{out}}{C_{in}}$$

in which C_{in} is the arterial drug concentration entering the eliminating organ and C_{out} is the venous concentration exiting the organ. ER may also be determined from a knowledge of the organ clearance (CL) and with an estimate of organ blood flow (Q): ER = CL/Q.
Extravascular: External to the bloodstream. Any route of administration that does not provide direct entry into the bloodstream. Thus, oral, rectal, pulmonary, transdermal, and so forth are pathways or routes of administration that require passage across one or more biologic membranes before gaining access to the bloodstream.

F

Filtration: See *Glomerular filtration*.
Filtration fraction: The fraction of plasma flow that is filtered through the glomerulus (approximately 20%).
First-order: Denoting direct proportionality between rate and concentration or amount of substance (rate ∝ concentration). For example, elimination could be first-order (i.e., directly proportional to plasma drug concentration). The proportionality is represented by a rate constant (rate = K × concentration). This is an important kinetic process that is used to describe the behavior of most drugs. This process is often referred to as linear or dose-independent kinetics. Such pharmacokinetic parameters as half-life, clearance, and volume are dose-independent. See also *Order*.
First-pass effect (presystemic elimination): Drug degradation and/or metabolism after extravascular administration and which occurs before systemic absorption. Oral first-pass effects include lumen degradation/metabolism, gut wall metabolism, and hepatic metabolism before systemic appearance of drug. Oral hepatic first-pass metabolism occurs subsequent to passage into the hepatoportal vein in the *first pass* of drug molecules through the liver, before reaching the heart. The magnitude of the latter is governed by the value of hepatic clearance (or hepatic extraction ratio). This first pass after oral dosing is more significant than after IV dosing because in the latter case the drug is distributed and diluted before its first appearance in the liver (therefore a small mass is cleared). This effect may be avoided by buccal or sublingual administration (e.g., organic nitrates, methyltestosterone). There may also be a pulmonary first-pass effect after IV dosing, dermal first-pass, and so forth. The fraction of the absorbed dose that escapes any of these sequential metabolic processes is given by $(1\text{-}ER_i)$. See *Hepatic first-pass effect*.
Flip-flop (model): This occurs when rate of drug absorption is slower than disposition, and hence the shape of the plasma concentration-time curve reflects absorption rather than disposition. Penicillin has a disposition half-life of approximately 1 hour; when administered as a depot intramuscular injection, the plasma concentration-time curve decays with a much longer half-life, reflecting the (flip-flop) half-life of absorption. Sustained release products are formulated such that elimination is governed by slow absorption. The slowest step in a sequence of steps (e.g., absorption to blood to elimination) governs the terminal slope of the plasma concentration versus time plot (this is the idea of a *rate-limiting step*).
Fraction unbound: The unbound (or free) fraction of drug in plasma (f_U). See *Unbound fraction*.
Free fraction: Same as fraction unbound. See *Unbound fraction*.

G

Gastric emptying: The process that describes movement out of the stomach and into the small intestine (see *Gastric emptying rate*).
Gastric emptying rate (GER): The rate at which materials (especially food) leave the stomach and enter the small intestine. This rate is different for liquids and solids and is affected by such factors as fat and carbohydrate content, osmotic pressure, position, and so forth. Often measured as a gastric emptying half-time because the process may not be exponential (see *Half-time*). GER may be a limiting factor in controlling rate of absorption because drugs are best absorbed from the small intestine.
Generic: Refers to a product marketed under the pharmaceutical name, as opposed to a proprietary (trade) name.
Genetic polymorphism: A type of genetic variation in which individuals with sharply distinct qualities coexist as normal members of a population. The study of genetic variations in response to drugs falls under the broad heading of *pharmacogenetics*. For example, rapid and slow acetylation of the drug isoniazid represents a pharmacogenetic polymorphism. In such instances a frequency-distribution diagram of clearance or half-life illustrates at least a bimodal shape rather than the usual normal distribution. One CYP-450 isoform that is under genetic control is 2D6.
GI tract: Gastrointestinal tract (or *gut*).
Glomerular filtration: The passive process whereby blood is filtered through the glomerulus of the nephron. All formed elements (e.g., cells) and proteins are not able to penetrate this membrane (this may not be true under disease conditions such as nephritis or nephrosis). As a result, drugs bound to proteins and cellular components are not filtered, and the resulting clearance is less than that for filtration (which is approximately equal to creatinine clearance, approximately 100 to 120 ml/minute). The glomerular filtration clearance of a compound bound to plasma proteins is given by $CL_{FILTRATION} = f_U \cdot CLCr$, in which f_U is the unbound fraction of drug in plasma and CLCr is creatinine clearance (units, volume/time).
Glomerulus: That part of the kidney nephron associated with the passive filtration of unbound substances in plasma (see *Glomerular filtration*).
Gut: Nickname for the gastrointestinal tract.

H

Half-life: An important pharmacokinetic parameter most often used to describe the rate at which a drug is lost from the body.

Although all kinetic processes may be described by a half-life (e.g., absorption half-life, distribution half-life, and so forth), it invariably refers to a first-order process. Half-life describes the time it takes for one-half of the material to be lost from the body (or the site of dosing; absorption half-life) or the time it takes for concentration to decline by one-half. The term strictly applies when there is only one process occurring. Thus, for a drug whose disposition is described by a multicompartment model, after an IV bolus dose half-life refers to the time associated with loss in the terminal or final phase; see *Disposition half-life* and *Terminal half-life* (units, time).

Half-time: Most often used to describe rate of loss by a non–first-order process. Thus, for a saturable elimination process (e.g., ethanol), it is the time it takes for the initial amount or concentration to decline by one-half. Sometimes used to describe gastric emptying rate (gastric emptying half-time) (units, time).

Hematocrit: The volume fraction of blood that is red blood cells. The usual hematocrit (HCT) in humans is approximately 0.45.

Hepatic: Referring to the liver.

Hepatic artery: The major artery supplying blood to the liver.

Hepatic clearance: Clearance of drug by hepatic pathways (also metabolic clearance).

Hepatic first-pass effect: The presystemic elimination or first-pass effect due to hepatic metabolism. After an oral dose the drug moves through the liver via the portal circulation where it undergoes metabolism. The extent of this first-pass effect is directly dependent on the value of hepatic extraction ratio or hepatic clearance, thus, the fraction of the dose escaping this first-pass effect (assuming complete gastrointestinal absorption) is given by

$$1 - ER_{HEPATIC} = 1 - \frac{CL_{HEPATIC}}{Q_{HEPATIC}}$$

See *First-pass effect*.

Hepatoportal: Referring to the blood circulation via the portal vein that enters the liver. Drug absorbed from the gastrointestinal tract first goes to the liver via the portal vein. This movement is what gives rise to the hepatic first-pass effect.

Housekeeper wave: See *Migrating motility complex*.

Hybrid rate constant: A rate constant, usually first-order, that is dependent on other (often micro-) rate constants. For example, the rate constants associated with a two-compartment model (α and β, or λ_1 and λ_2) are hybrid rate constants as they are a function of the micro-rate constants associated with distribution and elimination (units, 1/time).

I

Indocyanine green (ICG): A diagnostic dye used to estimate liver blood flow. Any diagnostic agent used for measurement of organ blood flow must have a high organ extraction ratio or clearance.

In silico: Theoretical experiments or simulations conducted with use of a computer program and computer.

Intramuscular (IM): Route of drug administration whereby the drug is injected into a muscle. The formulation may be a solution, suspension, oil, and so forth.

Inulin: A polysaccharide used to assess glomerular filtration.

In vitro: Literally, *in glass*. It is applied to altered biologic samples studied outside the organism. For example, hepatic enzymes could be purified and studied in a test tube (i.e., *in vitro*).

In vivo: Literally, *in life* or within the living body. Clinical studies in humans are *in vivo* studies.

Intravascular administration: Administration directly into the bloodstream [e.g., intravenous (IV), intra-arterial (IA)].

Intrinsic clearance: The intrinsic or inherent clearance (CL_{int}) of a substance in the absence of any flow (i.e., blood flow delivery to the organ) restrictions. For low clearance drugs, intrinsic clearance is equal to that seen after IV bolus dosing (i.e., systemic clearance). For all drugs that undergo hepatic first-pass metabolism, apparent oral clearance (CL_O) is equal to intrinsic clearance. May be determined experimentally in a test-tube containing enzyme (units, volume/time).

Intrinsic clearance of unbound drug: The maximum hepatic drug metabolism clearance, indicative of access to enzymes and enzymatic activity; theoretically, this occurs when there is no protein binding and hepatic blood flow is nonlimiting (i.e., infinite). Also called *unbound intrinsic clearance* ($CL_{U,INT}$). This clearance is not limited to hepatic enzyme activity, as every clearing process has associated with it an intrinsic unbound clearance (e.g., renal excretion, pulmonary excretion, and so forth). This parameter is simply related to intrinsic clearance and the unbound fraction of drug in plasma: $CL_{int} = f_U \times CL_{u,int}$ or $CL_{u,int} = CL_{int}/f_U$ (units, volume/time).

Isozyme: One of several forms of an enzyme, especially cytochrome P-450. Has the same meaning as *isoform*. See *Cytochrome P-450*.

J

Jejunum: The major portion of the small intestine (following the duodenum) from which most gastrointestinal absorption occurs.

K

Ki: The enzyme inhibition constant that is used to characterize the inhibition of a substrate-enzyme interaction. This value is approximately the concentration needed to reduce the rate of metabolism by 50% (similar in concept to the Michaelis constant) (units, concentration). As an approximation only and assuming competitive inhibition, the percentage inhibition is given by:

$$\%\ \text{inhibition} = \frac{100 \cdot (I)}{(I) + k_i}$$

in which (I) is the inhibitor concentration. Thus, 50% inhibition is seen when the inhibitor is present at a concentration equal to its k_i.

K.I.S.S. principle: Keep it simple, stupid. See *Parsimony, rule of* and *Ockham's razor*.

Km (or Kmm): The Michaelis constant that is used to characterize the substrate-enzyme interaction. This value is the concentration needed to obtain one-half of the maximal rate of metabolism (V_{max}). See *Michaelis-Menten enzyme kinetics* (units, concentration).

L

Lag time: The time delay between the time of administration and the first appearance of drug in the bloodstream (T_{LAG}). This value is associated with disintegration and dissolution processes after an oral dose or the time needed for a compound to reach the small intestine and/or be absorbed into the blood (units, time).

Linearity: In pharmacokinetics, this occurs when drug concentrations, divided by dose, are superimposable. This is another statement of or a characteristic of first-order kinetics. Nonlinearity occurs when the curves are not superimposable. In a linear system, there is a direct relationship between input and output. (See *Dose-dependency* and *First-order kinetics*.)

Loading dose: An initial dose (D_L) given a patient to rapidly achieve a concentration near that to be achieved at steady-state after multiple dosing (units, mass).

M

Maintenance dose: The dose (D_M) that is given repetitively at the dosing interval. This dose (in conjunction with the fraction absorbed and clearance) determines the steady-state plasma concentration (units, mass).

Maximum plasma concentration: The maximum value of the plasma concentration-time curve (C_{MAX}). After an extravascular dose, this value is a function of dose, fraction absorbed, the rate constants of absorption and elimination, and the apparent volume of distribution. The time at which this occurs is referred to as the time of maximum concentration. T_{MAX} (units, concentration).

Metabolic clearance (or metabolite formation clearance): Clearance (CL_M) of drug by enzymatic pathways in the liver (also hepatic clearance). This process represents the formation clearance of the metabolite (units, volume/time).

Metabolism (biotransformation): The biochemical alteration of a drug. Generally metabolism is divided into phase I and phase II processes. Phase I involves some chemical alteration, usually the addition of a group that increases the water-solubility of the parent compound (e.g., hydroxylation, *N*-methylation, and so forth). The resulting compound may be less, equal, or have more activity than the parent compound. Phase II processes are referred to as conjugation reactions because the compound is conjugated with any of several species (e.g., glucuronidation, sulfation). These derivatives are always more water-soluble than the parent compound, and they are usually but not always less active than the parent compound (e.g., morphine glucuronide is more active than morphine).

Metabolite elimination clearance: The clearance of the metabolite (CL_{ME}) by any of several possible pathways (further metabolism, urinary excretion, and so forth). Most directly determined after an IV bolus dose of metabolite. It is more difficult to determine this clearance value after metabolite formation from the parent drug (units, volume/time).

Metabolite induction of metabolism: This occurs rarely when the formed metabolite from the parent drug is able to induce the further metabolism of the parent drug. An example is carbamazepine metabolism in humans.

Metabolite inhibition of metabolism: This occurs rarely when the formed metabolite from the parent drug is able to inhibit further metabolism of the parent drug. An example appears to be phenytoin metabolism in the dog.

Michaelis-Menten elimination (enzyme) kinetics: A kinetic process whose rate may become independent of concentration beyond a certain concentration, unlike first-order kinetics. Such a kinetic process is described by the following relationship (Michaelis-Menten equation):

$$\text{Rate of elimination} = \frac{V_{max} \cdot C}{k_m + C}$$

in which V_{max} is the maximum rate (velocity) of the reaction and k_m is the Michaelis constant (concentration at one-half of V_{max}; note that this is *not* a rate constant but a concentration). The relationship is approximately first-order when $C << k_m$, and it approaches a constant, V_{max}, when $C >> k_m$. The latter situation is referred to as zero-order kinetics (rate does not depend on concentration). Michaelis-Menten kinetics is also referred to as dose-dependent, saturable, capacity-limited, nonlinear, and zero-order kinetics (the latter is not correct at all concentrations). Note the similarity in form to the equation used to define a pharmacodynamic model.

Microconstant: The first-order rate constant in a multicompartment model used to describe an irreversible movement of drug from one location to another (e.g., K_{12}, K_{21}, K_{10}) (units, 1/time).

Microvilli: Hair-like projections on the outer surface of intestinal epithelial cells. Collectively, microvilli look like the bristles of a brush; consequently, the total microvilli on an epithelial cell are termed the *brush border*.

Migrating motility complex (MMC): A band of regular contractions, migrating slowly (6 to 8 cm per minute) from the proximal stomach to the ileocecal valve. This complex only occurs in the fasting state. Each cycle lasts approximately 100 to 120 minutes and has four phases. Phase III is the most intense and is nicknamed the *housekeeper wave*, sweeping undissolved particles greater than 4 to 10 mm in diameter from the stomach into the duodenum. When an enteric-coated tablet is ingested in a fasting state, it must await the phase III housekeeper to pass into the duodenum. When an enteric-coated tablet is ingested in a fed state, it must await gastric emptying and initiation of phase III of the MMC complex before being passed into the duodenum. An enteric-coated tablet administered after a fatty meal usually takes in excess of 12 hours to pass into the duodenum. The MMC is also called the interdigestive myoelectric complex and the migrating motor complex.

Model: One thing that stands for another. A more formal definition is as follows: If the study of system A leads to an understanding of system B, then system A is a model for system B. Hence, for example, a model could be a pictorial representation of the liver, an equation for clearance or volume of distribution, a hydrodynamic analogy, and so forth. In modeling, one deliberately distorts one aspect of reality to enhance another. For example, one could distort the biophysics of the body (dividing it into two homogeneous compartments, blood and tissues), thereby permitting the easy calculation of the plasma concentration-time on multiple dosing. A model must have two properties: it must be sufficiently simple to explain a system, but, at the same time, it must adequately reflect the behavior of the system (i.e., explain the data). This is a balancing act (simplicity vs. reality). The rule of parsimony suggests that one should always select the simplest model, unless there is sufficient information to the contrary (the KISS principle; keep it simple, stupid). All models are wrong; some models are useful.

Mucosa: The inner surface of the gastrointestinal tract that consists of three layers. From the inside out, they are (a) a single layer of epithelial cells termed the *epithelium*, (b) the lamina propria, and (c) the muscularis mucosae. The epithelial cells are the primary diffusional barrier to drug absorption. The lamina propria consists primarily of connective tissue embedded with blood vessels and lymph nodes. The muscularis mucosae are responsible for gastrointestinal motility.

Multiple dosing: The process whereby a drug is given to a patient as a constant (maintenance) dose every dosing interval.

N

Nephron: The functional unit of the kidney. It consists of a glomerulus (filtering apparatus) and tubule.

Nonlinear kinetics (nonlinearity): See *Dose-dependency*.

Nonrestrictive clearance: Clearance that is not affected by plasma protein binding. Such compounds have a high organ extraction ratio (approximately ER > 0.67) and high organ clearance. Examples include diagnostic agents used to assess organ blood flow (e.g., indocyanine green for liver blood flow and p-aminohippurate for renal blood flow). The latter agents have organ ER values of 1.0. For such compounds, CL ≡ Q (units, volume/time).

O

Ockham's razor: After William of Ockham (b. 1280 England). *Entia non sunt multiplicanda praeter necessitate*; entities should not be multiplied unnecessarily. In other words, simpler is better.

When competing theories lead to the same result, the least complicated is preferred. The simplest most parsimonious (see *Parsimony, rule of*) explanation for a phenomenon is likely to be the correct one. When seeking to explain a phenomenon, start with the simplest theory. This is opposite a *Rube Goldberg*, in which the most complex methods are used for completing a task. The *razor* probably represents cutting out the unnecessary details. Einstein's rejoinder, *Everything should be made as simple as possible, but not simpler.*

Oral clearance: See *Apparent oral clearance.*

Order: If rate of change (e.g., metabolism, excretion, and so forth) is proportional to plasma concentration raised to a power, that power is the order. For example, if rate of metabolism is proportional to plasma concentration raised to the power of 1, the system is first-order. If rate of metabolism is proportional to plasma concentration raised to the power of zero, the system is zero order (because anything to the zero power is unity, rate of metabolism in this example is equal to a constant only and is independent of plasma concentration). One frequent goal of formulating a sustained-release product is to achieve zero-order absorption by providing a constant rate of drug release (i.e., a constant absorption rate independent of the amount of drug remaining in the formulation or in the gut).

P

Para-aminohippurate: Diagnostic agent used to assess renal blood flow. As with any such agent, it must have a high organ extraction ratio and high organ clearance.

Parameter: A variable constant (e.g., disposition half-life is a constant, although it varies day-to-day within a subject and also varies between subjects).

Parsimony, rule of: The idea, useful in modeling, that one should always choose the simplest possibility (or model) unless there is information to do otherwise. Also referred to as the K.I.S.S. principle (keep it simple, stupid). See *Ockham's razor.*

Partition coefficient: The concentration ratio of drug between two immiscible or distinct phases or entities. *In vitro*, the most common partition coefficient is the concentration ratio of drug between octanol and water. *In vivo*, the most common partition coefficient is the concentration ratio of drug between tissue and blood. The latter is primarily a reflection of drug binding to the two different tissues.

Per os (po): Latin for *by mouth.*

Percutaneous: Indicates application to the skin. Most percutaneous applications of drugs result in some transdermal absorption.

Perfusion: Usually referring to the flow of blood through a tissue or organ. Tissues are often classified with respect to perfusion: highly perfused lean tissue (e.g., kidney, liver); poorly perfused lean tissue (e.g., muscle, skin); poorly perfused fat tissue (e.g., adipose); negligibly perfused tissue (e.g., nails, hair).

Peripheral: Refers to any body location other than plasma or blood. The *peripheral* compartment in a multicompartment model is a lumping of several different tissues or fluids and does not represent a single real tissue.

Permeability coefficient: Characterization of the rate of movement of a molecule through or across a defined distance and a defined phase (e.g., cell, gut wall, and so forth). The greater the permeability coefficient (P), the more rapidly the compound traverses the membrane. This rate or velocity is often in units of cm/second. Rate of diffusion = $P \cdot (\Delta C)$, in which ΔC is the concentration gradient.

pH partition hypothesis: The hypothesis that only undissociated (unionized) molecules can be absorbed from the gastrointestinal tract. Due to pH, weak organic acids are only undissociated (unionized) in the stomach (pH 1 to 4) and are, therefore, presumably only absorbed there. On the other hand, weak organic bases are only undissociated (unionized) at the pH of the intestine (pH 6 to 8) and are only absorbed there. The pH partition hypothesis is a useful concept, but it is incorrect when applied to the gut. However, it is true that undissociated molecules cross the gastrointestinal membrane approximately 1000 to 10,000 times faster than dissociated molecules. This hypothesis was generated in the 1950s and 1960s from scientists at the U.S. National Institutes of Health to help explain drug absorption (e.g., B.B. Brodie). All drugs, acids or bases, are best absorbed from the small intestine regardless of degree of ionization, as a consequence of the large absorbing surface area there. A further critical consideration of this concept is the fact that the pH, which increases ionization, increases dissolution rate, which may be the limiting step for absorption.

Pharmacodynamics: The study of drug responses, frequently as a function of time and/or concentration of drug or metabolite at a presumed active site (but usually in the blood). There is an aphorism that states, *pharmacokinetics is what the body does to the drug, whereas pharmacodynamics is what the drug does to the body.*

Pharmacogenetics: Heredity variations in reactions to drugs and other exogenous compounds. See also *Genetic polymorphism.*

Pharmacokinetics: The kinetics of drug absorption, distribution, metabolism, and excretion of a drug and its metabolites, oftentimes abbreviated ADME, and sometimes KADME. The study of pharmacokinetics often includes examination of the response-time relationship (i.e., pharmacodynamics). The term was coined by the German scientist Gladtke in 1953 in his book *Der Blutspiegel.*

Pharmacokinetic/pharmacodynamic model: A model that attempts to combine the pharmacokinetic (plasma concentration-time data) and pharmacodynamic (response-time data) behaviors of a drug into a single model.

Phase I (metabolism): Those metabolic or biotransformation processes that involve the chemical alteration of a molecule. The resulting molecule is often, but not always, more water-soluble. The metabolite may have less, similar, or greater pharmacologic or toxicologic activity than the parent compound.

Phase II (metabolism): Those metabolic or biotransformation processes that involve the conjugation reactions with a molecule. The resulting molecule is always more water-soluble. The metabolite is usually less active than the parent compound, but there are exceptions (e.g., morphine glucuronide).

Physiologic pharmacokinetic model (PPM) or physiologically based pharmacokinetic model (PB/PK): A pharmacokinetic model that divides the body into real compartments (tissues and organs) that are connected by real blood flows, wherein drug disposition is characterized in terms of blood flow, partitioning, and elimination from each compartment. PPMs are also referred to as physiologically based pharmacokinetic models (PB/PK). This approach has been used by physiologists, anesthesiologists, and chemical engineers. It is attractive to many because it is *real*: There are no artificial compartments that have no physiologic relevance. Furthermore, this approach permits what chemical engineers refer to as *scale-up*, the ability to scale results from a small animal to humans. The latter is attractive in drug development, toxicity, and risk assessment.

Plasma: Fluid in blood in which all material and formed elements are suspended. A plasma sample represents blood devoid of cells but which is anticoagulated so that it contains the coagulation factors. (Compare with serum.)

Plasma protein binding: See *Protein binding.*

Presystemic elimination: The loss of parent drug, usually by chemical breakdown or metabolism, before the parent drug reaching the systemic circulation. Often called the *first-pass effect.* See *First-pass effect.*

Primary pharmacokinetic parameter: Parameters that depend only on protein binding, enzymatic activity, blood flows, and partitioning, and are not dependent on other primary parameters. The most common primary pharmacokinetic parameters are volume of distribution and clearance.
Protein binding: The reversible complexation of drug with plasma proteins. The most common plasma binding proteins are albumin and α_1-acid glycoprotein. Often characterized by the equilibrium association constant (K_{ASSN}) and the unbound fraction (f_U; see *Unbound fraction*).
Proximal: Nearer or closer to some reference point. For example, the reference point of the gastrointestinal tract is the juncture of the esophagus and stomach. Therefore, the small intestine is more proximal than the large intestine. (Also see *Distal*).

R

Rate constant of elimination or disposition: See *Disposition rate constant*.
Rate-limiting step: The slowest step in any sequence of events, which controls/restricts the rate of the overall process. For example, oral absorption may be restricted/controlled (rate-limited) by dissolution, because absorption cannot occur until drug is in solution.
Reabsorption: See *Active tubular reabsorption*.
Receptor: The specific binding site of a drug, which elicits a given response. Receptors are generally believed to be proteins. Drug that binds to a receptor is referred to as substrate.
Relative bioavailability: See *Bioavailability*.
Renal: Refers to the kidney.
Renal clearance: Clearance (CL_R) of a substance from the kidney. This is the sum of clearance as a result of glomerular filtration, active tubular secretion, and active tubular reabsorption (units, volume/time).
Restrictive clearance: Usually applied to hepatic clearance that is directly proportional to unbound fraction in plasma. Protein binding is said to *restrict* clearance. (Unrestricted or nonrestrictive clearance is independent of unbound fraction of drug). Such compounds have a low clearance relative to organ blood flow (or low extraction ratio; usually ER <0.33). In general: $CL \equiv f_U \times CL_{U\,INT}$ (units, volume/time).

S

Secondary pharmacokinetic parameter: Parameters that derive from two or more primary pharmacokinetic parameters. The most common secondary parameter is disposition half-life, which is dependent on volume of distribution and clearance:

$$T_{1/2} = \frac{0.693 \cdot V}{CL_S}$$

Secretion: See *Active tubular transport*.
Semilogarithmic plot: Any plot in which one axis is linear and the other is logarithmic. The most common semilog or semilogarithmic plot is log plasma concentration versus time (linear scale). Such graph paper used to be called *ratio* paper, because the distance between any two numbers in the same ratio (e.g., 5/1, 10/2, 100/20) was the same distance apart on the log scale. Also, pairs of numbers that increase or decrease by the same fraction or percentage are the same distance apart (e.g., 100 to 90; 50 to 45; 2 to 1.8; all decrease by 10% and are the same distance apart on the log scale).
Serum (blood serum): Fluid that is obtained from blood after letting the blood coagulate. Thus, this is the same as plasma except that it is devoid of coagulation factors.
S.H.A.M. parameters: The most fundamental parameters used to describe the disposition of a substance. The letters stand for slope, *h*eight, *a*rea, and *m*oment. The latter measures are used to describe a plasma concentration-time profile and from which one can estimate most if not all parameters of disposition.
Steady state: Strictly speaking, steady state exists when rate of input into a system is exactly equal to rate of output from the system; under these conditions, the amount or concentration of drug in the system is constant. In pharmacokinetics, a looser interpretation is applied. Pharmacokinetic steady state exists when a plasma concentration-time pattern repeats itself continuously, as for example when a drug is administered at a constant dose over a constant interval and ceases to accumulate any further. This is actually a fluctuating steady state. Steady state concentration is always expressed as rate in/rate out. In terms of drug dosing, rate in is the dose rate and rate out is clearance. For endogenous compounds, rate in is actually a production rate and rate out is clearance.
Subcutaneous: Underneath the skin (especially, subcutaneous injection, SC).
Sustained-release (SR): Denotes relatively slow release and absorption of a drug from a dosage form relative to a conventional dosage form. Most forms of *extended* release and *controlled* release products are essentially SR products.
Systemic: Referring to a central region; in pharmacokinetics, once a drug molecule has reached the heart, it is systemically available to the body.

T

Terminal rate constant or slope: Along with disposition rate constant or slope, perhaps the best term to apply to the description of the data that appear in the terminal log-linear phase of a semilog plot of plasma concentration versus time. This terminal or last slope from which a rate constant (and half-life) is derived represents the slowest process in a sequence of events. As with the term *disposition*, the word *terminal* does not permit confusion with *elimination* (units, 1/time).
Time invariance: An idea used extensively by engineers to indicate that a given system is invariant or unchanging with time. In completely defining a linear system, the properties of superposition and time invariance should strictly apply. The former is discussed under *Dose-dependency*. Some systems may be nonlinear by virtue of violating the idea of time invariance. For example, a circadian rhythm that changes drug behavior with time; metabolite inhibition of elimination causes a different behavior of parent compound with time and may provide concentration-time profiles that are log-linear or first-order (they are not superimposable, however).
Time of (occurrence) maximum plasma concentration: The time at which the maximum plasma concentration is achieved (see *Maximum plasma concentration*). This value, T_{MAX}, is a function of the rate constants of absorption and elimination and is often used to assess the rate of absorption of a drug in a bioequivalence study (units, time).
Topical: Pertaining to a particular area. In common usage, this almost always refers to a relevant portion of skin.
Total body (or systemic) clearance: Clearance of a substance from the body by all possible routes of elimination ($TBC = CL_S = CL_{RENAL} + CL_{HEPATIC} + CL_{OTHER}$). Calculated as

$$CL_S = \frac{IV\ dose}{AUC_0^\infty} \quad \text{or as} \quad CL_S = \frac{F \cdot dose}{AUC_0^\infty}$$

Toxicokinetics: The application of pharmacokinetics to the understanding and interpretation of toxicity studies.
Transdermal: Through the skin. Percutaneous indicates application to the skin. Most percutaneous applications of drugs result in some transdermal absorption.

Tubular reabsorption: See *Active tubular reabsorption.*
Tubular secretion: See *Active tubular transport.*

U

Unbound fraction: The unbound or free fraction of drug in the plasma (f_U), which is the ratio of unbound or free concentration to the total (i.e., unbound plus bound) concentration. For most drugs, this fraction is constant and independent of plasma drug concentration.
Unbound intrinsic clearance: See *Intrinsic clearance of unbound drug.*
Unbound volume of distribution: The apparent volume of distribution corrected for plasma protein binding, $V_{unbound} = V/f_U$.

V

Volume of distribution (apparent volume of distribution): A primary pharmacokinetic parameter reflecting the reversible uptake of drug by tissues from the blood. The fictitious space or volume that a drug appears to occupy in the body relative to the concentration of drug in the blood. Volume of distribution is the imaginary volume the drug occupies if it is present throughout the body in the same concentration as plasma. Because the reference fluid is always blood, the larger the volume of distribution, the more drug is in tissue relative to plasma. Volume of distribution has units of volume, but is commonly normalized to body weight, as, for example, liters/kg or V/m^2. Volume of distribution multiplied by plasma concentration equals the amount of drug in the body (but with some limitations). This parameter may, therefore, exceed the real volume of the body. There are numerous apparent volumes used in pharmacokinetics, including $V_{extrapolated}$, V_β or V_{AREA}, V_C or V_1, V_T or V_2, V_{SS}. The apparent volume serves two purposes: gives an indication of the magnitude of distribution or movement out of the blood and into tissues (the greater the apparent volume, the less drug is in the blood and more is in tissues); acts as a proportionality constant between the amount of drug in the body and the concentration in the blood.

Z

Zero-order: A rate is zero-order when it is constant, independent of concentration or amount. See *Order.*

CHAPTER 80

Role of the Laboratory in the Diagnosis and Management of Poisoning

Robert J. Flanagan

Analytical toxicology is concerned with the detection, identification, and measurement of drugs and other foreign compounds (xenobiotics) and their metabolites in biologic and related specimens. The analytical toxicologist can play a useful role in the diagnosis and management of poisoning, but to do so, he or she should have a basic knowledge of emergency medicine and intensive care and must be able to communicate effectively with physicians. In addition, a good understanding of clinical chemistry, pharmacology, and toxicology is desirable. The analyst's dealings with a case of suspected poisoning are usually divided into preanalytical, analytical, and post-analytical phases (Table 1).

Many acutely poisoned patients are treated successfully without any contribution from the laboratory other than routine clinical laboratory tests. The analytical toxicologist can only contribute to diagnosis and management if a physician, pathologist, or other person first suspects poisoning. Close collaboration between the analyst and the physician is then important if anything other than the simplest of analyses is to be useful. Many requests for emergency analytical toxicologic investigations are, in fact, requests for advice on the diagnosis or management of poisoning and are best handled by staff of a poisons information service, at least in the first instance.

Toxicologic analyses can play a useful role if the diagnosis of poisoning or the nature of any poison(s) present is in doubt, the administration of antidotes or protective agents is contemplated, or the use of active elimination therapy is being considered. All relevant information about a particular patient should be communicated to the analyst and appropriate specimens must be collected and properly labeled. Information to enable the analyst to assign the appropriate priority to the analysis in such cases is especially vital because, in general, specific therapy is only started when the nature and the amount of the poison(s) involved are known. At the least, a request form should be completed to accompany the specimens to the laboratory.

TABLE 1. Steps in undertaking an analytical toxicologic investigation

Preanalytical	Obtain details of current (suspected) poisoning episode, including any circumstantial evidence of poisoning, and the results of biochemical and hematologic investigations, if any. Also obtain the patient's medical and occupational history, if available, and ensure access to the appropriate samples. Decide the priorities for the analysis.
Analytical	Perform the agreed analysis.
Postanalytical	Interpret the results in discussion with the physician looking after the patient. Perform additional analyses, if indicated, using either the original samples or further samples from the patient. Save any unused or residual samples in case they are required for additional tests.