6
Kinetics of Pharmacologic Response

The type of relationship that exists between the plasma concentration of a drug and a given response is generally determined by two factors: whether concentration is directly or indirectly related to response, and whether the drug interacts with the receptor in a reversible or irreversible manner. The simplest type is where there is a direct relationship between plasma concentration and response, and where the interaction of the drug and the receptor is reversible. Many drugs (e.g., antiarrythmics, digitalis glycosides, theophylline, and neuromuscular blocking agents) appear to act directly and reversibly. A second type of concentration-response relationship is where the elicited response is not directly related to the plasma drug concentration. This is generally referred to as an indirect pharmacologic response, and is best exemplified by the coumarin anticoagulants. A third type is where the drug binds to the receptor irreversibly. Anticancer agents and bactericidal antibiotics are examples of drugs that exert their effects in this manner.

KINETICS OF DIRECTLY REVERSIBLE PHARMACOLOGIC RESPONSE

One-Compartment Model

The concept of a direct and rapidly reversible response implies that a given intensity of response is associated with a particular drug concentration at the site of action. By definition in the model under consideration, the drug concentration at the receptor site C_r is proportional to the drug concentration in the plasma C, and the interaction between the drug and receptor is reversible:

$$C \rightleftharpoons C_r + \text{receptor} \rightleftharpoons \underset{\text{complex}}{\text{drug-receptor}} \rightarrow \text{response}$$

The following relationship, known as the Hill equation, has been proposed to relate plasma concentration and response R under these circumstances:

$$R = \frac{R_m C^s}{(1/Q) + C^s} \tag{6.1}$$

where R_m is the maximum intensity of the pharmacologic response (i.e., $R \to R_m$ as $C \to \infty$), Q is a constant related to the affinity of the drug for the receptor, and s is a constant that relates the change in response to the change in concentration. One should also note that the term 1/Q is equal to the drug concentration in the plasma (raised to the sth power) at which response is 50% of maximal response, (i.e., $C^s_{50\%}$). The basis for Eq. (6.1) has been discussed in detail [1]. This equation will quantitatively and fully characterize the typical sigmoid curve resulting from a log C versus R-type plot. Rearranging terms and inverting both sides of (6.1) yields

$$\frac{R_m}{R} = \frac{1 + C^s Q}{C^s Q} \tag{6.2}$$

Subtracting unity from both sides of this equation (i.e., R/R from the left side and C^sQ/C^sQ from the right side), collecting terms, and again inverting both sides of the equation gives

$$\frac{R}{R_m - R} = C^s Q \tag{6.3}$$

A linear form of this equation is

$$\log \frac{R}{R_m - R} = s \log C + \log Q \tag{6.4}$$

A plot of $R/(R_m - R)$ versus C on log-log graph paper will yield a straight line with a slope of s.

A more common approach relating response and concentration is based on the well-known empirical plot of response versus logarithm of dose, plasma concentration, or amount of drug in the body which yields the classical sigmoid curve shown in Fig. 6.1. Very often this curve manifests excellent linearity from at least 20 to 80% of the maximum attainable intensity of response, a region of particular interest and applicability under clinical conditions. This linear relationship may be expressed by

$$R = m \log C + r \tag{6.5}$$

where R and C are as described previously, m is the slope of the R versus log C plot, and r is a constant. Such linearity between response

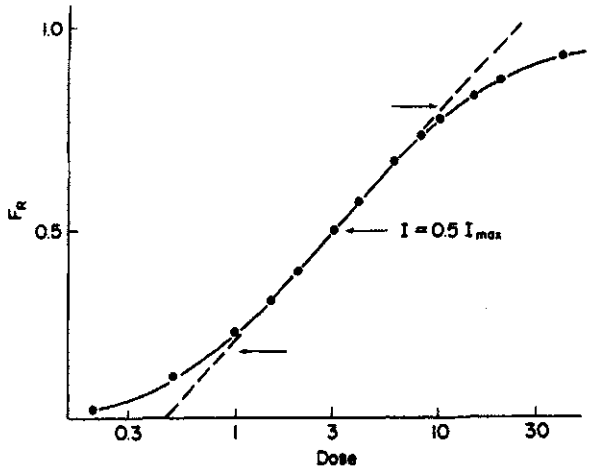

Fig. 6.1 Typical log dose-response curve calculated according to the relationship $F_R = D/(K + D)$, where K is a constant and F_R is the fraction of the maximum response of the system attained after a dose D. The plot is apparently linear in the region bounded by $F_R = 0.2$ and $F_R = 0.8$ (see arrows). A dose of 3 units is the median effective dose ED_{50} since it produces an intensity I of response that is 50% of the maximum intensity I_{max}. (Data from Ref. 2.)

and log C has been demonstrated for a number of drugs, examples of which are propranolol (Fig. 6.2) and theophylline (Fig. 6.3). Relating response to the logarithm of plasma concentration rather than the logarithm of dose should reduce the variability in the data by removing variability related to interpatient differences in drug absorption and elimination.

Rearrangement of (6.5) yields

$$\log C = \frac{R - r}{m} \tag{6.6}$$

In a one-compartment system, the plasma concentration of drug at any time following the administration of an intravenous bolus dose of a drug that is eliminated by first-order processes can be described by

$$\log C = \log C_0 - \frac{Kt}{2.303} \tag{6.7}$$

where C_0 is the plasma concentration at time zero, t is time, and K is the apparent first-order elimination rate constant of the drug. Based on the proposed model, the maximum response elicited by this dose, R_0, would be associated with a plasma concentration of C_0 [5]. Therefore, an equation analogous to (6.6) can be written:

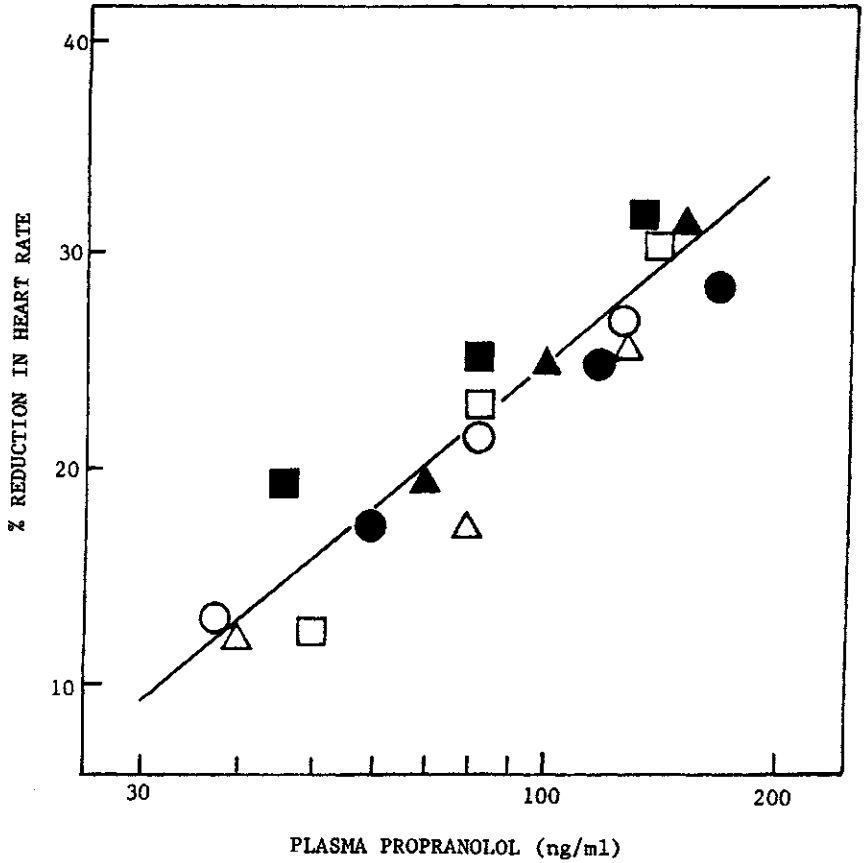

Fig. 6.2 Relationship between response (percent reduction in exercise-induced tachycardia) and propranolol concentration in plasma (log scale) after intravenous administration to healthy volunteers. (Data from Ref. 3.)

$$\log C_0 = \frac{R_0 - r}{m} \tag{6.8}$$

Substituting the values of log C and log C_0 from (6.6) and (6.8), respectively, into (6.7) yields

$$\frac{R - r}{m} = \frac{R_0 - r}{m} - \frac{Kt}{2.303} \tag{6.9}$$

This equation can be simplified to give

$$R = R_0 - \frac{mK}{2.303}t \tag{6.10}$$

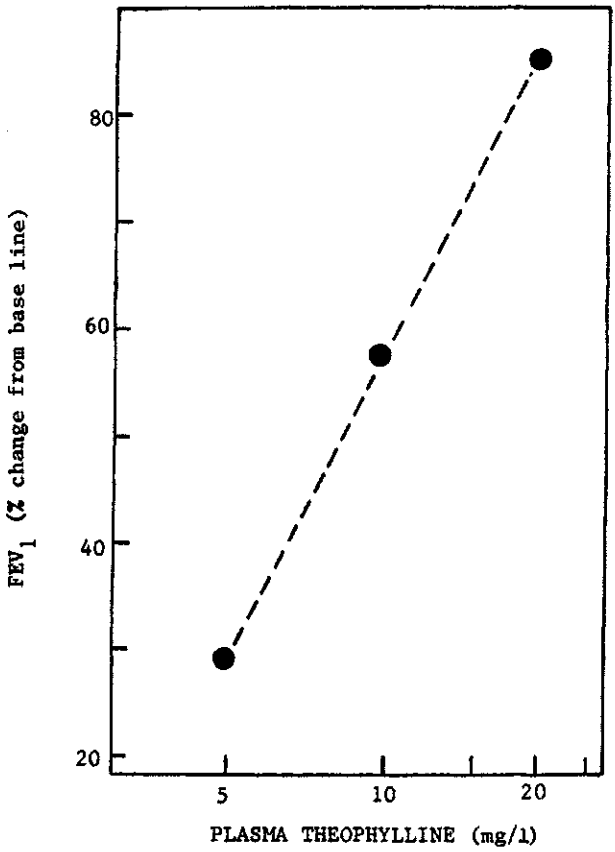

Fig. 6.3 Relationship between average response (normalized improvement in 1 s forced expiratory volume) and theophylline concentration in plasma (log scale) after intravenous administration of the drug to patients. (Data from Ref. 4.)

This equation shows that, under the conditions stated, the intensity of response decreases at a constant rate that is a function of the apparent first-order elimination rate constant K and the slope of the response versus log C curve, m. It should be noted that the rate of decline in response is zero order even though the rate of decline in plasma concentration is first order. This linear or zero-order decline in response with time has been demonstrated for a number of drugs and an example is shown in Fig. 6.4.

It is also readily shown by substituting log C from Eq. (1.94) [$C = k_a F X_0 (e^{-Kt} - e^{-k_a t})/V(k_a - K)$] into Eq. (6.5) that (6.10) also describes the decay of effect in the postabsorptive phase (i.e.,

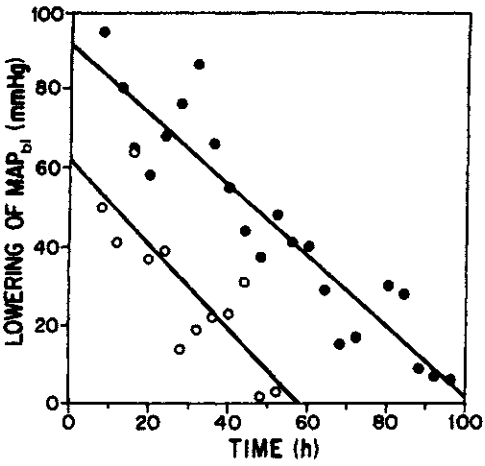

Fig. 6.4 Time course of hypotensive response (reduction in mean arterial pressure) in a patient following 10 (○) and 25 (●) mg single oral doses of minoxidil. Some time after administration, the intensity of the drug's effect declines at a constant and similar rate after each dose. (Data from Ref. 6.)

$e^{-k_a t} \to 0$) after oral or intramuscular drug administration. An example is the zero-order loss of the stimulant effect of amphetamine after intramuscular administration (Fig. 6.5). Although the decline in pharmacologic response for many drugs that act directly and reversibly is zero order, there are examples where the decline in response appears to be first order. This type of decline has been observed with the digitalis glycosides (Fig. 6.6).

This departure from theory may be related to the approximate nature of Eq. (6.5). Although (6.10) predicts a linear decline of pharmacologic response with time after intravenous administration, combination of (6.1) with the appropriate pharmacokinetic expression for drug elimination in a one-compartment model suggests that the decline of pharmacologic response is curvilinear (see Fig. 6.7). Regions of this curve may be linearized on semilogarithmic coordinates. Of particular importance is the fact that the response versus time curves are *nearly* linear in the response range 20 to 80%. Hence, for all practical purposes one would anticipate for a large number of drugs that the loss of effect would indeed be essentially linear over a very wide reponse range, as predicted by (6.10).

Regardless of the relationship between response and concentration, one can frequently demonstrate a relationship between the duration of a given response and the dose and half-life or elimination rate constant of a drug [9]. Equation (6.7) can be readily converted to an

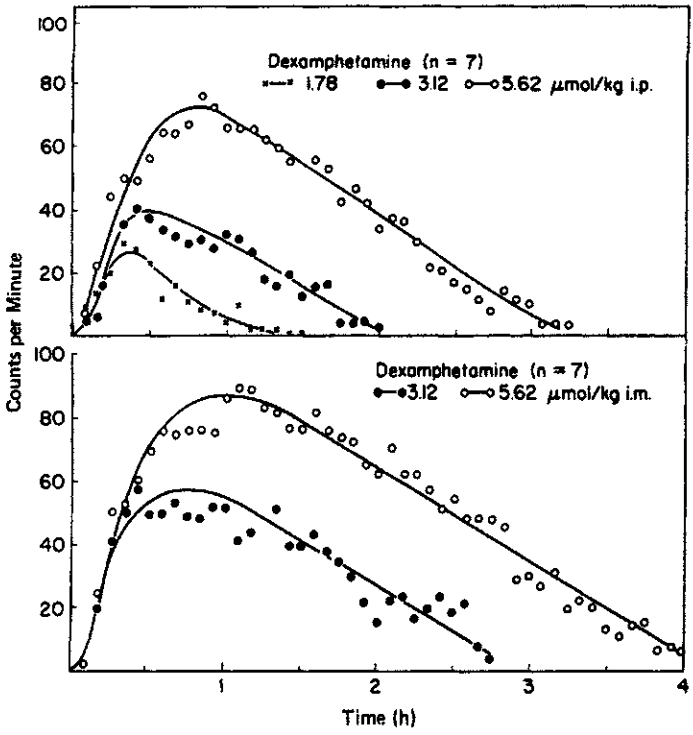

Fig. 6.5 Time course of central nervous sytem response (locomotor activity measured in counts per minute) after intraperitoneal and intramuscular administration of dexamphetamine sulfate to rats. Irrespective of dose and route of administration, the effect of the drug declines at a constant rate during the postabsorptive phase. (From Ref. 7.)

equation in terms of amount by multiplying the concentration terms by the apparent volume of distribution. This yields

$$\log X = \log X_0 - \frac{Kt}{2.303} \tag{6.11}$$

where X is the amount of drug in the body at time t and X_0 is the initial amount of drug in the body (i.e., the intravenous dose). If it is assumed that the intensity of a pharmacologic response is associated with a given amount of drug in the body, and that there is a minimum amount of drug in the body X_{min} necessary to elicit a response, the time necessary for the initial amount of drug in the body X_0 to decline to this minimum effective amount is the duration of response t_d. Substitution of X_{min} for X and t_d for t in (6.11) yields

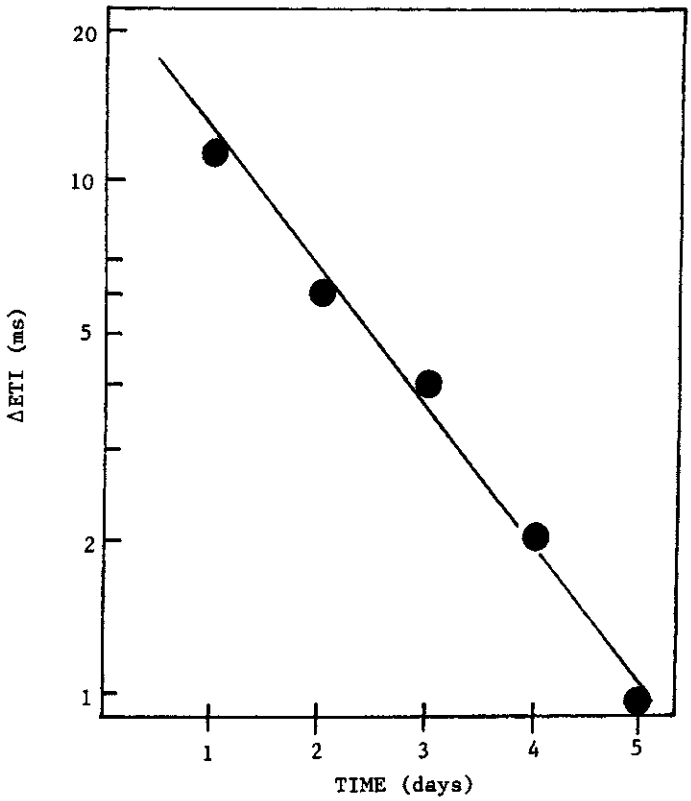

Fig. 6.6 Time course of cardiac response (change in ejection time index, plotted on log scale) after intravenous administration of digoxin. Exponential decline of response has also been observed with other cardiac glycosides, including ouabain, deslanoside C, and digitoxin. (Data from Ref. 8.)

$$\log X_{min} = \log X_0 - \frac{Kt_d}{2.303} \tag{6.12}$$

which when solved for t_d is

$$t_d = \frac{2.303}{K} \log X_0 - \frac{2.303}{K} \log X_{min} \tag{6.13}$$

Therefore, a plot of the duration of response versus the logarithm of the intravenous dose should be linear. The intercept on the log X_0 axis will be the minimum amount of drug in the body necessary to elicit a response, and the slope $-2.303/K$ will provide an estimate of the elimination rate constant. An example is shown in Fig. 6.8.

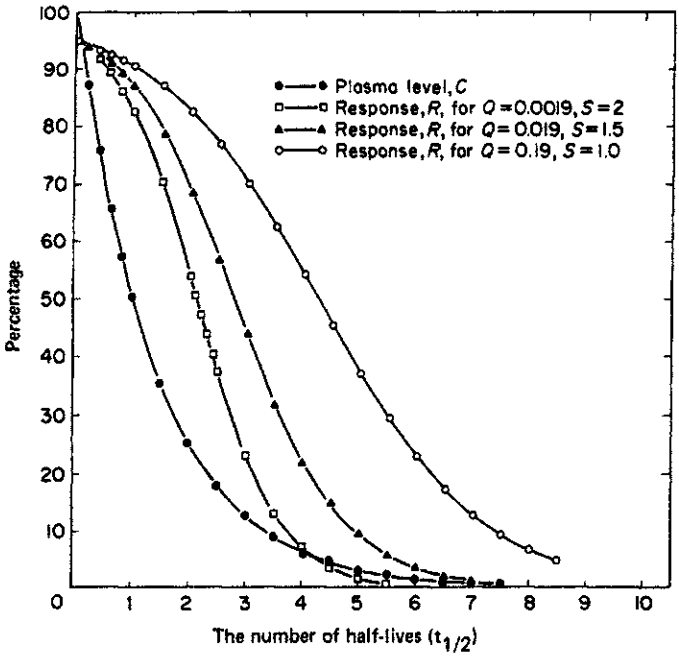

Fig. 6.7 Drug concentration in plasma and anticipated response curves under different conditions [see Eq. (6.1)] after intravenous administration. [From Ref. 1, © 1972 Academic Press, Inc. (London), Ltd., reprinted with permission.]

Equation (6.13) may be applied to determine the rate constant for drug elimination in instances where direct measurement of drug concentration as a function of time is not possible but where pharmacologic response can be measured adequately.

Under certain circumstances drugs may be dosed based on pharmacologic response. An example would be the use of neuromuscular blocking agents during anesthesia. If a drug confers on the body the pharmacokinetic properties of a one-compartment model, the administration of a second dose of a drug immediately after the apparent disappearance of the pharmacologic response from the initial dose is likely to produce a more intense and more prolonged response than the first dose. This is due to the fact that the second dose is superimposed on the minimum effective amount of drug remaining in the body from the first dose [11]. This phenomenon is readily expressed in mathematical terms by considering that the intensity of the response is related linearly to the logarithm of the amount of drug in the body (see Fig. 6.9). Hence

$$R = m(\log X - \log X_{min}) = m \log \frac{X}{X_{min}} \qquad (6.14)$$

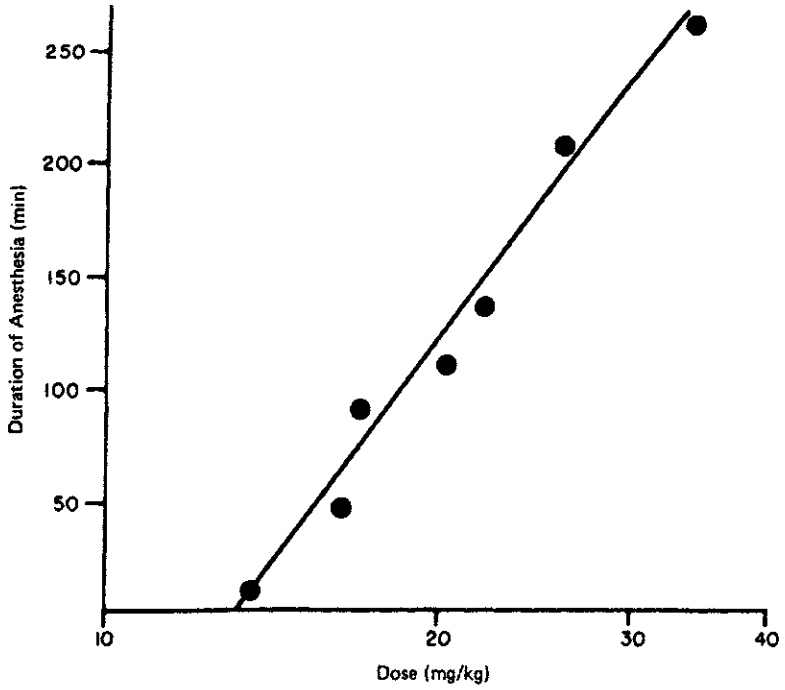

Fig. 6.8 Relationship between intravenous dose of pentobarbital (x axis) and duration of anesthesia (y axis, in minutes) in monkeys. X_{min}, the minimum dose required to elicit a measurable response, is equal to 13 mg/kg. (From Ref. 10.)

This equation may be used to estimate the maximum intensity R_{01} of the pharmacologic response elicited by an initial intravenous dose X_0:

$$R_{01} = m \log \frac{X_0}{X_{min}} \tag{6.15}$$

When a second (and equal) dose is administered immediately after disappearance of the response of the first dose (i.e., when the amount of drug in the body has declined to X_{min}), the maximum intensity of the response R_{02} would be

$$R_{02} = m \log \frac{X_0 + X_{min}}{X_{min}} \tag{6.16}$$

Obviously, $R_{02} > R_{01}$. The maximum response from a third and subsequent doses, if all were administered in the same manner as the second dose, would be equal to the maximum response from the second dose, and hence would be described by (6.16).

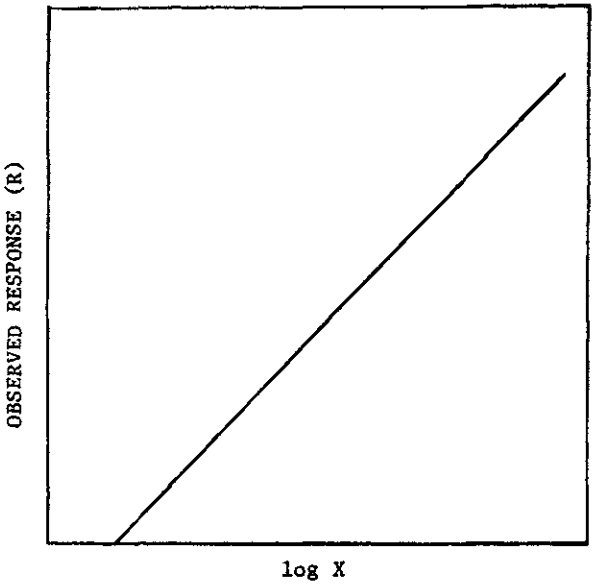

Fig. 6.9 Relationship between response and the logarithm of the amount of drug in the body X, according to Eq. (6.14). The slope (m) of the line is the same as the slope of a log concentration-response plot [see Eq. (6.5)] and the X intercept corresponds to the minimum amount of drug in the body, X_{min}, needed to elicit a measurable response.

Similar reasoning may be applied to determine the effect of a second dose on the duration of a pharmacologic response. By rearranging (6.13), the duration of effect of the first dose can be written as

$$(t_d)_1 = \frac{2.303}{K} \log \frac{X_0}{X_{min}} \tag{6.17}$$

It follows that the duration of effect of the second dose is

$$(t_d)_2 = \frac{2.303}{K} \log \frac{X_0 + X_{min}}{X_{min}} \tag{6.18}$$

Again, it is apparent that $(t_d)_2 > (t_d)_1$. Equations (6.16) and (6.18) predict that there will be no further increase in the intensity and duration of response of third and subsequent doses. The predictable "potentiating" effect may be avoided by using $X_0 - X_{min}$ as the second and subsequent doses.

The total pharmacologic activity of a single dose of a drug has sometimes been represented as the area under the intensity of response

versus time curve (i.e., $\int_0^\infty R\,dt$). This index of total activity has shortcomings for many drugs in that it does not define the maximum intensity or duration of response. It is useful, however, in quantitating such responses as diuresis, electrolyte excretion, and weight loss. Since there is frequently a nonlinear relation between the amount of drug in the body and the intensity of response [see, e.g., (6.1) and (6.5)] the *relative pharmacologic activity* of a drug (i.e., the total area under the effect versus time curve divided by the dose, which upon intravenous administration is given by $\int_0^\infty R\,dt/X_0$) usually decreases with increasing dose. Consequently, the total effect of a fixed amount of drug per day may be affected by the dosage regimen (i.e., the number of doses per day). Computer simulations using the integrated form of (6.1) have shown that when the daily dose is divided, the total 24 h response is increased [1]. The greatest increase occurs with the first subdivision of the dose (i.e., two doses a day compared with a single dose). It is of interest to note that the administration of 1 g of chlorothiazide twice a day produces a significantly greater 24 h diuretic response than that observed after administration of a single dose of 2 g [12].

Multicompartment Models

Effect in the Central or Peripheral Compartment. The time course of drug action in multicompartment systems depends on the location of the site of action. Mathematically, the site may be located in the central compartment or in the peripheral compartment or it may require representation as a separate compartment. The location of the site of action may be determined by examining the relationship between the intensity of response and the concentration of drug in the plasma or the calculated amount of drug in a peripheral compartment. A relatively simple approach to this problem has been used with tubocurarine, where effect data after several doses (over a fourfold range) were available [13]. A detailed method to correlate response with either plasma concentration or the "concentration" at some other site or hypothetical compartment after a single dose has also been suggested [14]. In essence, this method requires the following steps:

1. Measure the response and plasma concentration as a function of time until drug levels are no longer detectable.
2. By means of mathematical analysis, determine the appropriate pharmacokinetic model that rationalizes the concentration-time data.
3. Attempt to relate the response values to the instantaneous concentrations in the plasma compartment or peripheral compartments by means of some functional effect-concentration equation such as (6.1) or (6.5).

4. Once the appropriate pharmacokinetic model and functional equation are determined, *simultaneously* fit the observed drug concentration in the plasma, response, and time data, using a suitable nonlinear least-squares estimation program and a digital computer (Appendix H).

The significance of response correlations with drug "levels" in hypothetical *peripheral* compartments of multicompartment models is subject to challenge. Westlake [15] has demonstrated the large degree of error that may be involved in calculating the amount of drug in the peripheral compartment of a two-compartment model from drug concentration in the plasma versus time data after intravenous administration, which can be rigorously fit to a biexponential equation. Still greater error is involved if a more complex pharmacokinetic model is required to rationalize the plasma concentration-time data. Additional error is introduced when one considers that the quantitative assessment of response is often imprecise. Also, no single "response-concentration" relationship has been universally accepted; rectilinear, log-linear, or log-log plots have been used in arriving at these correlations. Finally, the calculated time course of drug in a hypothetical peripheral compartment reflects a type of weighted average of at least several tissues. It is quite possible that the time course of drug at the site of action and at some noneffector tissue having a relatively high capacity for the drug may be significantly different, yet from a kinetic point of view both the site of action and the noneffector tissue may appear to be part of the same peripheral compartment.

If the site of action is associated with the central compartment, a plot of response versus the logarithm of plasma concentration should yield the same sigmoid-type curve as that shown in Fig. 6.1. A similar relationship should also be observed when the response is associated with a peripheral compartment and response is plotted against the logarithm of the calculated amount of drug in a peripheral compartment. Examples of these two possible situations are illustrated in Figs. 6.10 and 6.11, respectively. When the site of action is associated with a peripheral compartment, and response is plotted as a function of the logarithm of plasma concentration, response will increase with decreasing plasma concentration during the distributive phase, reach a peak, then decrease during the postdistributive phase. This type of response-concentration profile is depicted in Fig. 6.12. The maximum response observed following a given dose will occur when maximum drug levels are attained in the peripheral compartment.

In multicompartment systems the rate of decline of response is likely to occur at a constant rate independent of dose during the postdistributive phase, irrespective of the apparent site of effect. However, drug concentrations in the postdistributive phase may be too

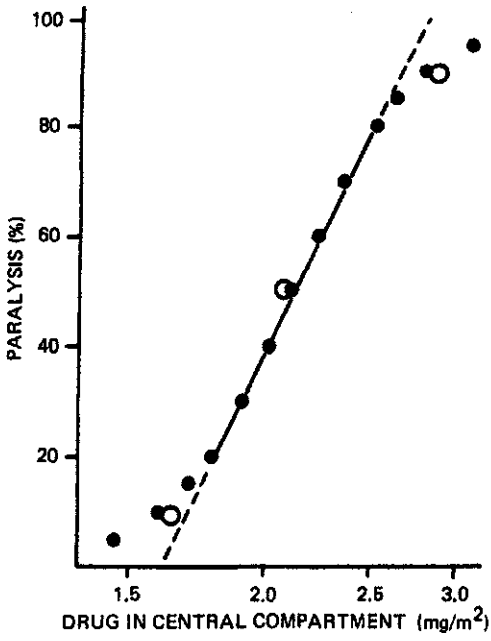

Fig. 6.10 Relationship between neuromuscular response (percent paralysis) and amount of drug in the central compartment of a multicompartment system (log scale) after intravenous administration of tubocurarine. The closed circles were calculated based on a pharmacokinetic model and the open circles represent experimental data from normal volunteers. (From Ref. 16, reprinted with permission.)

low to be of clinical consequence. When the site of action is associated with the central compartment the maximum response will be observed shortly after administration of the intravenous dose (i.e., during the distributive phase). Since drug concentration during the distributive phase does not decline in a monoexponential fashion, one would not expect response to decline in a linear manner. Theory suggests that the decline of response to a drug showing multicompartment characteristics and apparently acting in the central compartment will be a curvilinear function of time after intravenous administration. Interestingly, the decline of effect of certain drugs such as tubocurarine which show pronounced multicompartment characteristics is apparently linear after a given dose, but the apparent zero-order rate of decay of effect decreases with increasing dose (see Fig. 6.13). This linearity merely reflects the fact that over the limited concentration range associated with the range of intensities of pharmacologic effect, the curvilinear log C versus time plot can often be approximated by a straight line. The dose dependence results from the changing slope

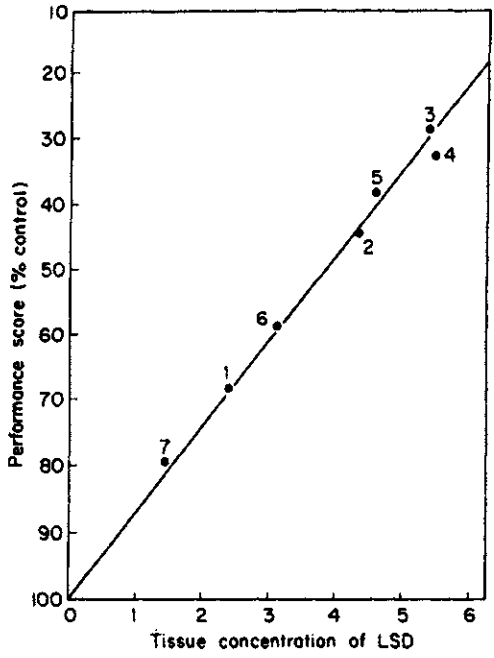

Fig. 6.11 Relationship between behavioral response (average performance scores on arithmetic tests) and amount of drug in the peripheral compartment of a two-compartment open model (or "tissue concentration") after intravenous administration of d-lysergic acid diethylamide (LSD) to volunteer subjects. The number associated with each data point denotes the blood sample number after drug administration (e.g., number 1 represents the "tissue concentration" calculated from the drug concentration found in the first blood sample taken after injection). (From Ref. 14.)

of the log C versus time curve in this concentration range as a function of dose (see Fig. 6.14).

In contrast to the relationships developed for the one-compartment model in the first section of this chapter, the duration of effect of a drug conferring multicompartment characteristics to the body is not a linear function of the logarithm of the intravenous dose. Examples are shown in Figs. 6.15 and 6.16. Apparently, linear relationships between duration of effect and logarithm of dose can be obtained in a restricted dose range, but the slope of the line is dependent on the intensity of the effect used as the end point [18]. Moreover, for a so-called two-compartment drug the slope of this apparently linear relationship after intravenous administration may approximate $1/\lambda_1$, $1/\lambda_n$, or some other intermediate value. An additional observation is

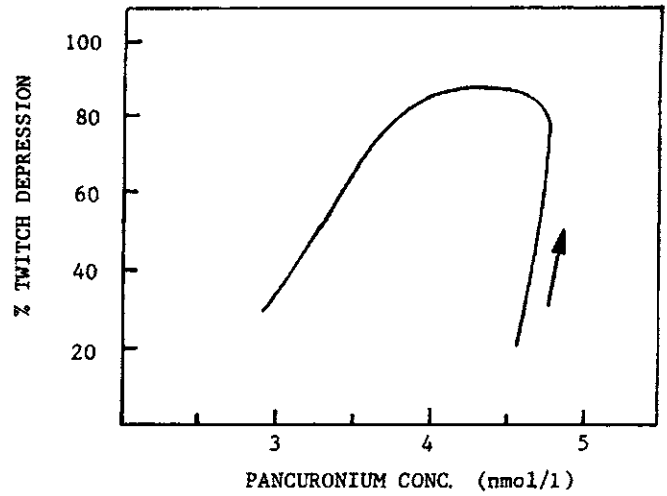

Fig. 6.12 Relationship between neuromuscular response (percent twitch depression) and pancuronium concentration in the plasma after intravenous administration of the drug. The arrow denotes the time course of the response. The results suggest that the locus of drug effect is at a site peripheral to the central compartment. (From Ref. 17, © 1978 Macmillan Journals Ltd., reprinted with permission.)

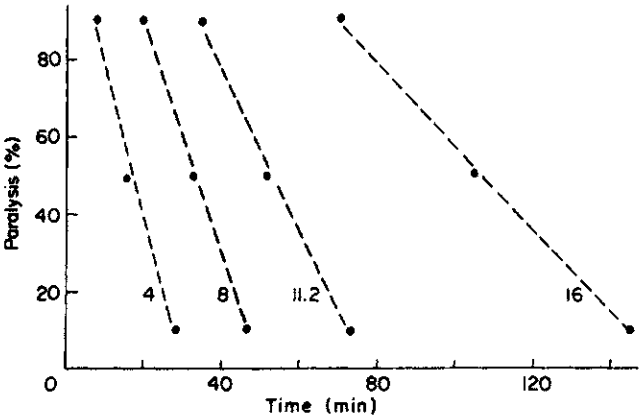

Fig. 6.13 Decline of neuromuscular blocking effects after intravenous administration of different doses of d-tubocurarine to human volunteers. Although the loss of effect is zero order, the rate is dose dependent. (From Ref. 16, reprinted with permission.)

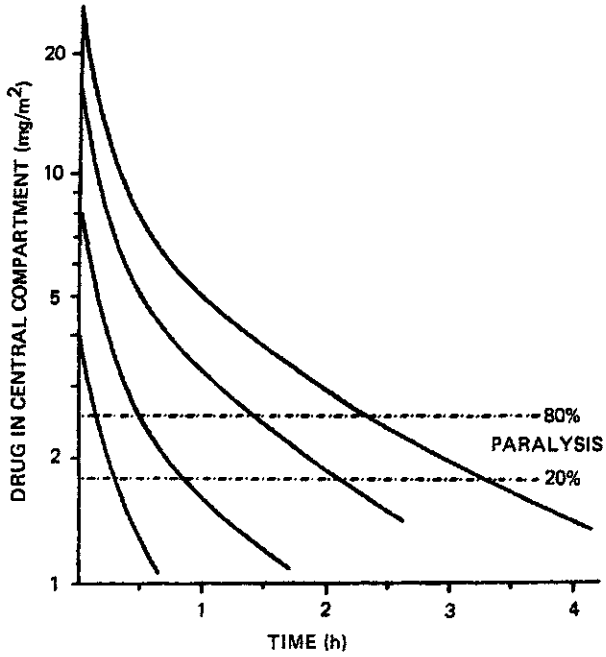

Fig. 6.14 Time course of tubocurarine in the central compartment of a multicompartment system after intravenous administration of different doses to healthy volunteers. The horizontal lines denote drug levels required to elicit 20% and 80% paralysis of the thumb adductor muscle. Although the deline of drug levels between 80% response and 20% response is approximately log linear in each case, the slope is dose dependent. (From Ref. 16, reprinted with permission.)

that the duration of a response associated with the central compartment of a multicompartment system will increase with successive doses when the drug is dosed according to response alone (Fig. 6.17). This is in contrast to a one-compartment system, where the duration of response increases from the first to the second dose but does not increase on subsequent doses. The maximum response increases from the first to the second dose in both systems but does not increase thereafter.

It is of theoretical interest to consider drug effects in a peripheral compartment of a multicompartment system which is poorly accessible to the central compartment. Drug moves in and out of such deep compartments rather slowly. If the site of drug action is in the deep compartment, the pharmacologic effect will be delayed and prolonged, and the relationship between drug levels in the plasma and effect may not be readily apparent. With this type of drug, repeated intravenous

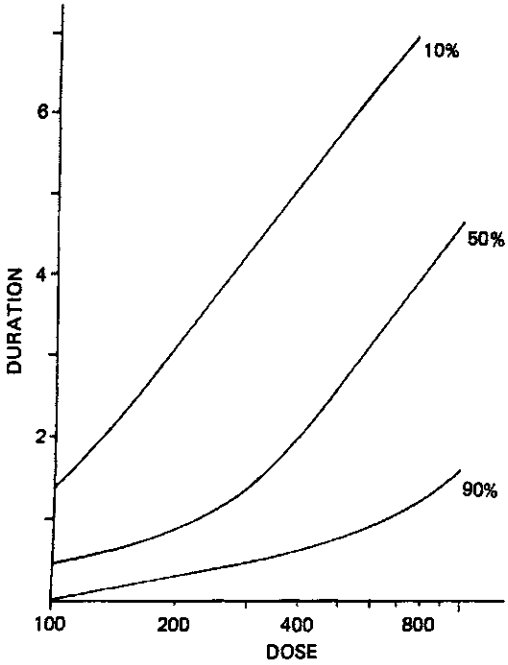

Fig. 6.15 Relationship between duration of response and intravenous dose (log scale), assuming that the site of effect is in the central compartment of a two-compartment model. The duration is measured in terms of the time required after administration of a given dose for the peak effect to decline to 90%, 50%, or 10% of the maximum attainable effect of the drug. It is evident that the shape of the curve depends on the end point. (From Ref. 18.)

administration of equal doses at constant time intervals will yield the concentration versus time patterns shown in Fig. 6.18 for the central and deep peripheral compartments. This simulation, with the assumed minimum detectable drug concentration in the central compartment and minimum pharmacologically effective drug concentration in the deep compartment, suggests certain clinically interesting characteristics. The pharmacologic effect appears only after the third dose, and the intensity of this effect increases beyond the tenth dose since drug levels in the deep compartment do, in fact, accumulate. When drug administration is stopped, the effect persists well beyond the last dose. There are pronounced pharmacologic effects at a time when there is no detectable drug concentration in the plasma. Thus the effects of drugs that act directly and reversibly in a deep compartment may sometimes be mistaken for indirect and/or irreversible drug effects.

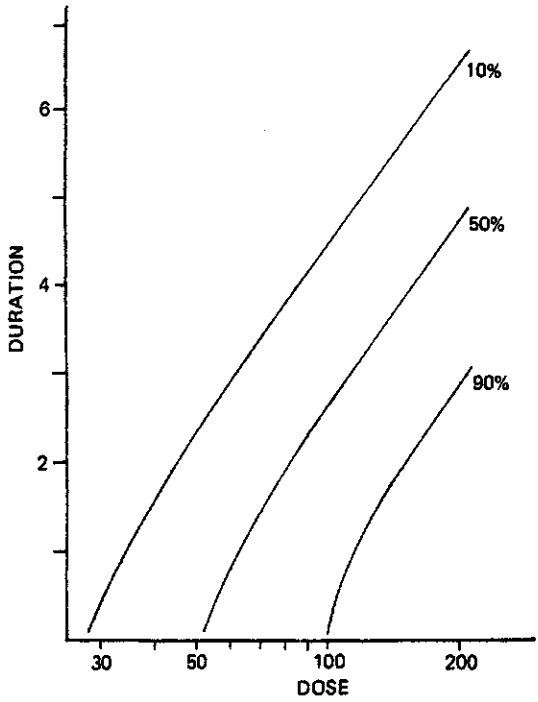

Fig. 6.16 Relationship between duration of response and intravenous dose (log scale), assuming that the site of effect is in the peripheral compartment of a two-compartment model. The end points used to determine duration of response are the same as in Fig. 6.15. For this particular simulation the curves are approximately linear and parallel. (From Ref. 18.)

Other Sites of Effect. A particular shortcoming of the pharmacodynamic modeling discussed in the preceding sections of this chapter is the required assumption that the plasma, central compartment, or some other pharmacokinetically identifiable compartment is associated with the pharmacologic effect. However, pharmacokinetic models concern themselves with the disposition of mass of drug in the body; a site receiving little mass is not described. There is no a priori reason to assume that the active site corresponds, kinetically, with a site receiving a large mass of drug. Accordingly, there is little reason to hope that the kinetics of drug in plasma, or another pharmacokinetically determined site, will parallel those at the active site. It has recently been proposed that the effect compartment be modeled as a separate compartment linked to the plasma compartment by a first-order process, and be one that receives a negligible mass of drug [19,20]. Therefore, one does not enter an additional exponential term into the phar-

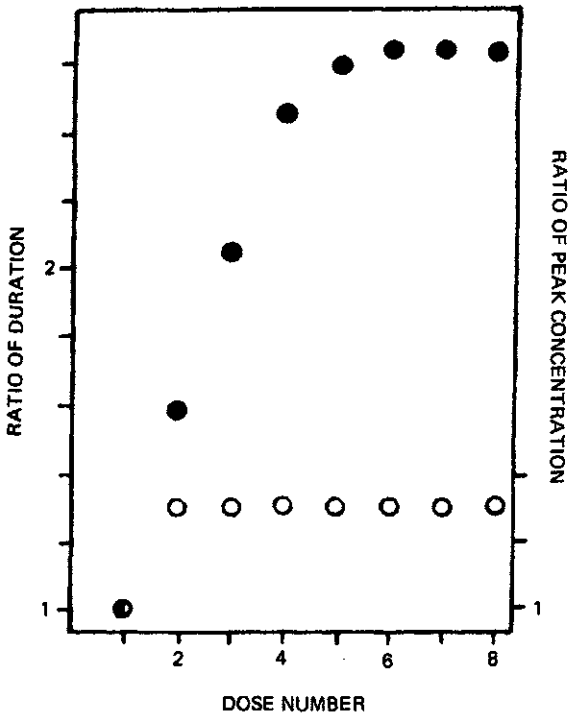

Fig. 6.17 Relative duration of response (●) and peak concentration (○) for a situation where equal intravenous doses are given repetitively as soon as a certain effect end point is reached, assuming that the site of effect is in the central compartment of a two-compartment model. (From Ref. 18.)

macokinetic solution for the mass of drug in the body to account for the effect compartment. The model is illustrated in Fig. 6.19. In this model a first-order rate constant k_{1e} connects the central to the effect compartment. Drug leaves the effect compartment by means of a first-order rate constant k_{e0}. By assuming k_{1e} to be very small relative to the magnitude of any other rate constant in the model (Fig. 6.19), the transfer of mass to the effect compartment is negligible, and consequently does not influence the plasma concentration versus time curve. Since a negligible amount of drug is transferred to the effect compartment, its return to the central compartment is inconsequential, and therefore may be taken to the outside rather than back into the system. The rate constant for drug removal from the effect compartment, k_{e0}, characterizes the temporal aspects of equilibrium between plasma concentration and response.

The following differential equation can be written for the amount of drug in the effect compartment, X_e:

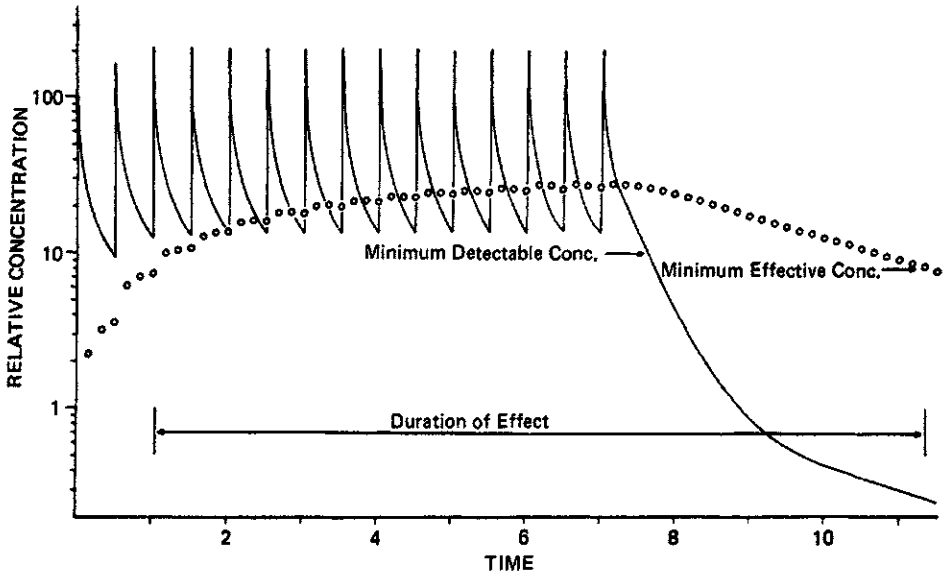

Fig. 6.18 Relative concentrations of a drug in the central (solid line) and deep peripheral (O) compartments of a multicompartment system during repetitive intravenous administration of equal doses at equal time intervals. (From Ref. 18.)

$$\frac{dX_e}{dt} = k_{1e}X_c - k_{e0}X_e \tag{6.19}$$

where k_{1e} and k_{e0} are as defined above and X_c is the amount of drug in the central compartment. The Laplace transform of (6.19) (see Appendix B) is

$$s(a_{s,e}) = k_{1e}a_{s,c} - k_{e0}a_{s,e} \tag{6.20}$$

Solving for $a_{s,e}$ and substituting the value of $a_{s,c}$ as given in (2.3) [i.e., $a_{s,c} = X_0 \prod_{i=2}^{n} (s + E_i)/\prod_{i=1}^{n} (s + \lambda_i)$] yields

$$a_{s,e} = \frac{k_{1e}X_0 \prod_{i=2}^{n} (s + E_i)}{(s + k_{e0}) \prod_{i=1}^{n} (s + \lambda_i)} \tag{6.21}$$

The anti-Laplace (see Appendix B) of (6.21) gives the following equation for the amount of drug in the effect compartment as a function of time:

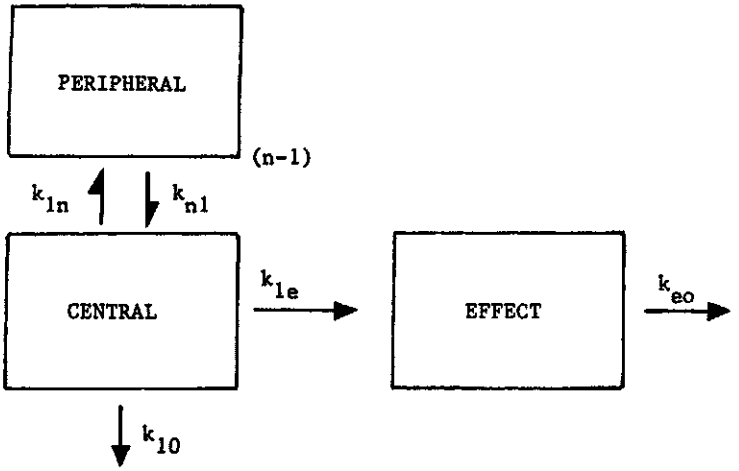

Fig. 6.19 Pharmacokinetic-pharmacodynamic model to describe that situation where the site of effect does not correspond to a pharmacokinetic compartment. (Data from Refs. 19 and 20.)

$$X_e = k_{1e}X_0 \frac{\prod_{i=2}^{n}(E_i - k_{e0})}{\prod_{i=1}^{n}(\lambda_i - k_{e0})} e^{-k_{e0}t} + k_{1e}X_0 \sum_{\ell=1}^{n} \frac{\prod_{i=2}^{n}(E_i - \lambda_\ell)}{(k_{e0} - \lambda_\ell)\prod_{\substack{i=1 \\ i\neq\ell}}^{n}(\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t} \qquad (6.22)$$

where X_0 is the intravenous dose, E_i the sum of the exit rate constants from the ith compartment, n the number of compartments in the n-compartment mammillary model, and λ_i and λ_ℓ are disposition rate constants. Assuming that the amount of drug in the effect compartment is proportional to the concentration in this compartment, C_e:

$$X_e = V_e C_e \qquad (6.23)$$

where V_e is the apparent volume of the effect compartment, we can write (6.22) in terms of concentration as follows:

$$C_e = \frac{k_{1e}X_0}{V_e} \frac{\prod_{i=2}^{n} (E_i - k_{e0})}{\prod_{i=1}^{n} (\lambda_i - k_{e0})} e^{-k_{e0}t} + \frac{k_{1e}X_0}{V_e} \sum_{\ell=1}^{n} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{(k_{e0} - \lambda_\ell) \prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t} \quad (6.24)$$

By assuming that the rates of appearance of drug in and removal of drug from the effect compartment are governed by the same process, it follows that the clearance from the central to the effect compartment and the clearance out of the effect compartment are equal, and therefore

$$V_c k_{1e} = V_e k_{e0} \quad (6.25)$$

Rearrangement of (6.25) to solve for k_{1e}/V_e (i.e., $k_{1e}/V_e = k_{e0}/V_c$) and substitution of k_{e0}/V_c for k_{1e}/V_e in (6.24) gives

$$C_e = \frac{k_{e0}X_0}{V_c} \frac{\prod_{i=2}^{n} (E_i - k_{e0})}{\prod_{i=1}^{n} (\lambda_i - k_{e0})} e^{-k_{e0}t} + \frac{k_{e0}X_0}{V_c} \sum_{\ell=1}^{n} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{(k_{e0} - \lambda_\ell) \prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t} \quad (6.26)$$

Multiexponential plasma concentration-time data after intravenous administration can be described by

$$C = \frac{X_0}{V_c} \sum_{\ell=1}^{n} \frac{\prod_{i=2}^{n} (E_i - \lambda_\ell)}{\prod_{\substack{i=1 \\ i\neq\ell}}^{n} (\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t} \quad (6.27)$$

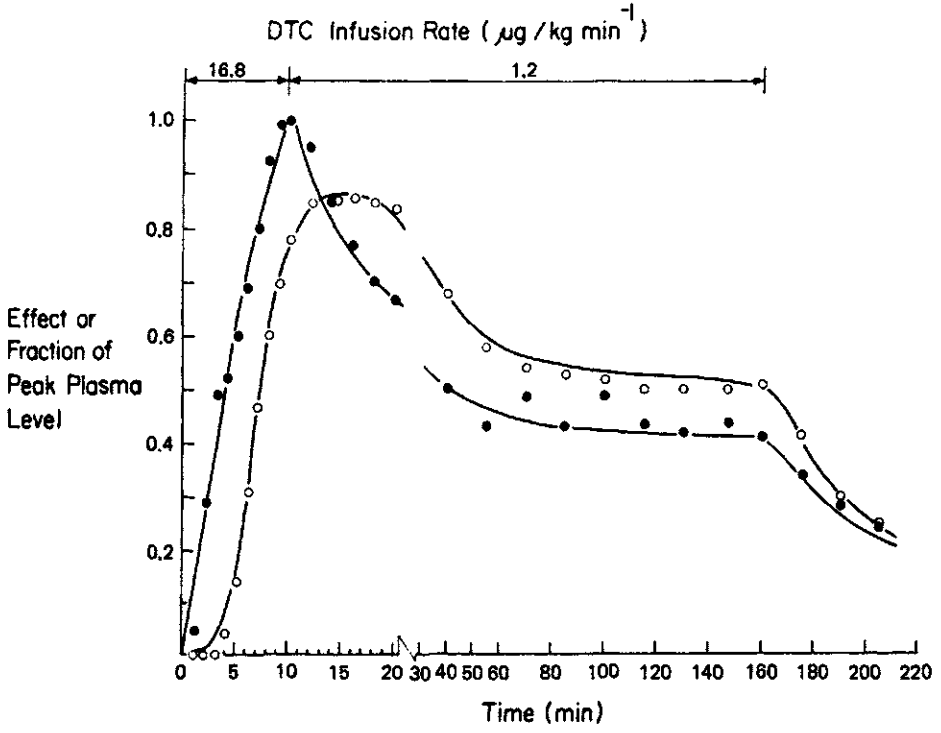

Fig. 6.20 Plasma concentration (●) and effect (○) relationships during and after intravenous infusions of d-tubocurarine to a patient. The solid lines represent the best fits of the proposed model to the data. Note break in graph at 20 to 30 min, due to change of scale on time axis. (From Ref. 19.)

Once plasma concentration-time data have been fitted, all the parameters in (6.27) and (6.26) (except for k_{e0}) can be generated. Substitution of C_e for C in (6.1) yields the following equation, which relates the observed pharmacologic response to concentrations in the effect compartment:

$$R = \frac{R_m C_e^s}{(1/Q) + C_e^s} \qquad (6.28)$$

where C_e is given by (6.26). Therefore, either response-time data can be fitted after the concentration-time data have been fitted, generating values of R_m, s, Q, and k_{e0} [Eqs. (6.26) and (6.28)], or response-time and concentration-time data can be fitted simultaneously [Eqs. (6.26) to (6.28)], generating all pharmacokinetic and pharma-

codynamic parameters. This approach to the quantitative description of response-plasma concentration-time data has been used in the quantitative analysis of d-tubocurarine and disopyramide pharmacodynamics [19–21]. An example is presented in Fig. 6.20.

KINETICS OF INDIRECT PHARMACOLOGIC RESPONSE

The intensity of a pharmacologic response may not be due to a direct effect of the drug on the receptor; rather, it may be the net result of several processes only one of which is influenced by the drug. Under such circumstances a direct relationship between the plasma concentration of the drug and the measured pharmacologic response can generally not be obtained. If this is the case, the process that is influenced by the drug must be identified and an attempt made to relate plasma drug concentrations to changes in this process. A good example is the anticoagulant (hypoprothrombinemic) effect of the coumarin drugs, which inhibit the synthesis of certain vitamin K-dependent clotting factors (i.e., factors II, VII, IX, and X), but have no effect on the physiologic degradation of these factors. Thus the real effect of these drugs is inhibition of synthesis rate, and any correlation with plasma concentration must be based on this effect rather than on the degree of inhibition of clotting time [22]. Administration of warfarin or bishydroxycoumarin rapidly blocks the synthesis of prothrombin complex activity P [23], but significant anticoagulant effect will not be observed until normal circulating levels of P are reduced sufficiently. Hence it is not surprising that although peak levels of warfarin in the plasma are observed within several hours after oral administration, the maximum hypoprothrombinemic response does not appear until several days after administration (see Fig. 6.21).

The degree of anticoagulation is generally measured in terms of a prothrombin time PT. PT is a measure of the net effect of the rate of synthesis and the rate of degredation of the appropriate clotting factors. Prothrombin time is generally expressed as the percent of the normal prothrombin complex activity, and will be denoted by the symbol P. P can be determined employing the following relationship:

$$P = 100\left(1 - \frac{PT_0 - PT_n}{PT_n}\right) \tag{6.29}$$

where PT_0 is the observed prothrombin time and PT_n is the normal prothrombin time. For example, if a prothrombin time of 19 s was measured, the prothrombin complex activity P would be 42% of normal, assuming a normal prothrombin time of 12 s.

The net rate of change of P at any time (i.e., dP/dt or R_{net}) may be described by

$$R_{net} = R_{syn} - R_{deg} \tag{6.30}$$

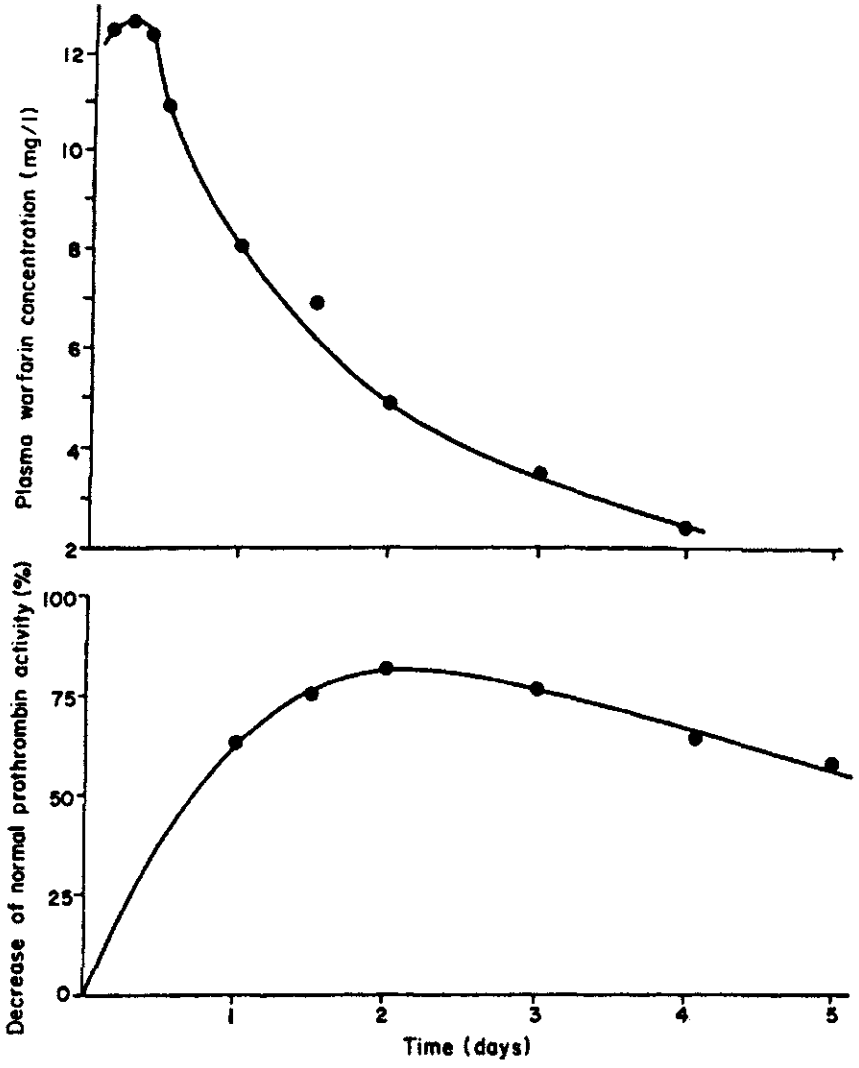

Fig. 6.21 Average warfarin concentration in plasma and depression of prothrombin complex activity after oral administration of warfarin to healthy subjects. (From Ref. 22.)

where R_{syn} and R_{deg} are the rates of P synthesis and degradation, respectively. The R values are measured in terms of percentage of normal activity per day since P is measured relative to the average P level of normal subjects.

As noted, the direct effect of coumarin anticoagulants is not reflected by changes in P but rather by changes in R_{syn} relative to its

normal value. R_{syn} may be calculated from (6.30) if R_{deg} can be determined, since R_{net} is readily obtained from P (i.e., $R_{net} = dP/dt$). If it is assumed that the degradation of P is describable by first-order kinetics, then

$$R_{deg} = k_d P \tag{6.31}$$

where k_d is the apparent first-order degradation rate constant. This constant can be obtained experimentally from the slope of a log P versus time plot after administration of a synthesis blocking dose of a coumarin anticoagulant. Under these conditions R_{syn} in (6.30) equals zero. Therefore,

$$\frac{dP}{dt} = R_{net} = -R_{deg} \tag{6.32}$$

and hence

$$\frac{dP}{dt} = -k_d P \tag{6.33}$$

Integration of (6.33) yields

$$P = P_0 e^{-k_d t} \tag{6.34}$$

which in logarithmic terms is

$$\log P = \log P_0 - \frac{k_d t}{2.303} \tag{6.35}$$

where P_0 is the level of P prior to medication. Therefore, a plot of log P versus time should be a straight line, the slope of which will yield k_d (Fig. 6.22). In one study where a synthesis blocking dose of 1.5 mg/kg of warfarin was administered orally, an average value of k_d of 1.21 per day was determined [22]. This corresponds to an average half-life of 13.7 h.

Solving (6.30) for R_{syn} and substituting $k_d P$ for R_{deg} according to (6.31) and dP/dt for R_{net} according to (6.32) yields

$$R_{syn} = \frac{dP}{dt} + k_d P \tag{6.36}$$

Therefore, by knowing k_d and P as a function of time, R_{syn} can be determined.

The magnitude of response R at any given time can be expressed as the difference between the synthesis rate before medication R°_{syn} and R_{syn} at time t:

$$R = R^{\circ}_{syn} - R_{syn} \tag{6.37}$$

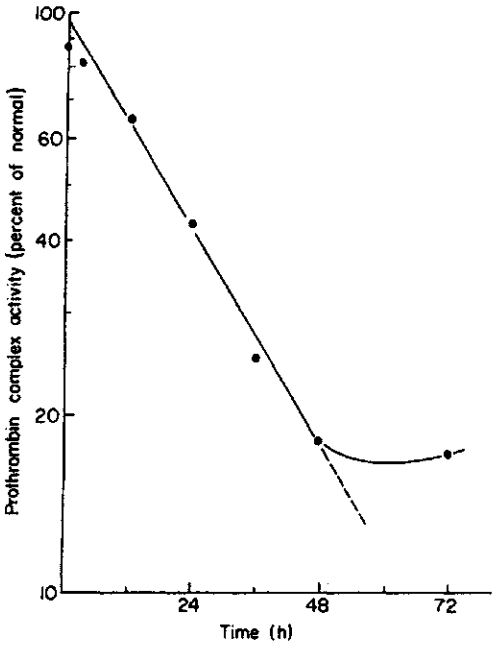

Fig. 6.22 Plasma prothrombin complex activity in a normal subject after oral administration of 1.5 mg/kg dose of warfarin. (From Ref. 22.)

As discussed above, the magnitude of many types of pharmacological response is related to the logarithm of the plasma concentration of the drug. Equation (6.14) can be converted to a concentration equation by dividing by volume of distribution to yield

$$R = m(\log C - \log C_{min}) \tag{6.38}$$

where C_{min} is the minimum effective plasma concentration. Substituting $R^{\circ}_{syn} - R_{syn}$ for R according to (6.37) in (6.38) and solving for R_{syn} gives

$$R_{syn} = R^{\circ}_{syn} + m \log C_{min} - m \log C \tag{6.39}$$

Therefore, a plot of R_{syn} versus log C should yield a straight line with a slope of $-m$ (Fig. 6.23). According to (6.39), when R_{syn} equals R°_{syn}, C equals C_{min}.

Prothrombin Complex Activity Versus Time. Although the direct effect of the coumarin anticoagulants is on R_{syn}, the time course of P is of interest since this is the actual response being measured. This information can be obtained by incorporating the concepts expressed

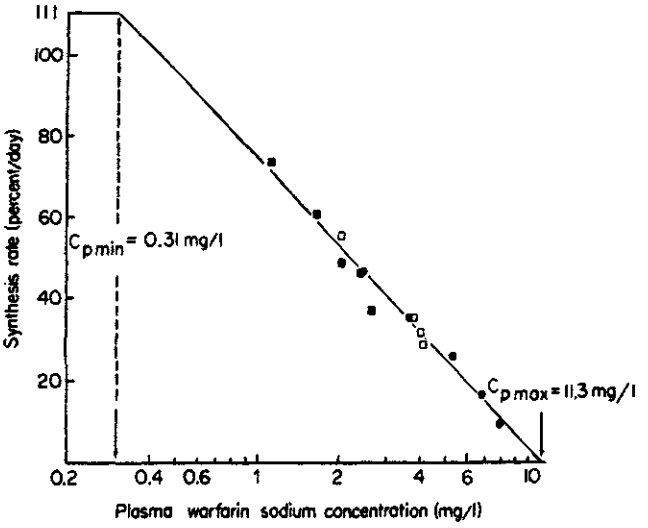

Fig. 6.23 Average synthesis rate of prothrombin complex activity as a function of plasma warfarin concentration in normal volunteers. Warfarin sodium dosing schedules: ●, a single oral dose of 1.5 mg/kg; ■, daily oral doses of 10 mg for 5 days; □, daily oral doses of 15 mg for 4 days. $C_{p\,min}$, the apparent minimum effective plasma warfarin sodium concentration; $C_{p\,max}$, the concentration of warfarin sodium in the plasma which apparently suppresses totally the synthesis of prothrombin complex activity. (From Ref. 22.)

in the preceding paragraphs into a single mathematical expression that permits the determination of P as a function of time and the initial plasma concentration (or dose) of the drug. Substitution of $dP/dt + k_dP$ for R_{syn} according to (6.36) in (6.39) and rearrangement yields

$$\frac{dP}{dt} = R^{\circ}_{syn} + m \log C_{min} - m \log C - k_dP \tag{6.40}$$

Prior to the initiation of anticoagulant therapy, the circulating levels of P are constant at P°, and at that time R°_{syn} is given by

$$R^{\circ}_{syn} = k_dP^{\circ} \tag{6.41}$$

[see (6.36)]. Substituting this value of R°_{syn} in (6.40) results in

$$\frac{dP}{dt} = k_dP^{\circ} + m \log C_{min} - m \log C - k_dP \tag{6.42}$$

It has been shown that after intravenous administration,

$$\log C = \log C_0 - \frac{Kt}{2.303} \tag{6.7}$$

Accordingly,

$$\frac{dP}{dt} = k_d P^\circ - m \log \frac{C_0}{C_{min}} + \frac{mK}{2.303} t - k_d P \tag{6.43}$$

Since the first two terms of (6.46) are constant for a given dose, they may be combined, and upon rearrangement,

$$\frac{dP}{dt} + K_d P = A_0 + \frac{mK}{2.303} t \tag{6.44}$$

where $A_0 = k_d P^\circ - m \log (C_0/C_{min})$. Multiplying through by dt yields

$$dP + k_d P\, dt = A_0\, dt + \frac{mK}{2.303} t\, dt \tag{6.45}$$

The solution to this differential expression requires the use of an integrating factor.† In this case the appropriate integrating factor is $e^{\int k_d t}$, which is equivalent to $e^{k_d t}$. Multiplying through by this term yields

$$e^{k_d t}\, dP + k_d P e^{k_d t}\, dt = A_0 e^{k_d t}\, dt + \frac{mKt e^{k_d t}}{2.303} dt \tag{6.46}$$

Since

$$d(Pe^{k_d t}) = e^{k_d t}\, dP + k_d P e^{k_d t}\, dt \tag{6.47}$$

we may substitute $d(Pe^{k_d t})$ for the left-hand side of (6.46). Hence upon substitution and rearrangement, (6.46) may be rewritten as

$$d(Pe^{k_d t}) = \left(A_0 + \frac{mKt}{2.303}\right) e^{k_d t}\, dt \tag{6.48}$$

The indefinite integral of this expression is

$$Pe^{k_d t} = \int \left(A_0 + \frac{mKt}{2.303}\right) e^{k_d t}\, dt + i \tag{6.49}$$

where i is an integration constant. Upon rearrangement,

$$P = e^{-k_d t}\left[\int \left(A_0 + \frac{mKt}{2.303}\right) e^{k_d t}\, dt + i\right] \tag{6.50}$$

---

†See L. M. Kells, *Elementary Differential Equations*, 6th ed. McGraw-Hill, New York, 1965, chap. 3, sec. 24, pp. 63–68.

The integral term of (6.50) may be expressed as

$$A_0 \int e^{k_d t}\, dt + \frac{mK}{2.303} \int te^{k_d t}\, dt$$

The first term of this expression is readily solved since

$$A_0 \int e^{k_d t}\, dt = \frac{A_0}{k_d}\, e^{k_d t} + i' \tag{6.51}$$

but the solution of the second term requires some effort. Considering the general relationship

$$xy = \int d(xy) = \int (x\, dy + y\, dx) = \int x\, dy + \int y\, dx \tag{6.52}$$

it follows that

$$\int x\, dy = xy - \int y\, dx \tag{6.53}$$

Now returning to the second term of the integral,

$$\frac{mK}{2.303} \int te^{k_d t}\, dt$$

and letting $t = x$ and $e^{k_d t}\, dt = dy$, it follows that $y = e^{k_d t}/k_d$.

Substituting these relationships in the second term of the integal yields

$$\int te^{k_d t}\, dt = \frac{te^{k_d t}}{k_d} - \int \frac{e^{k_d t}}{k_d}\, dt \tag{6.54}$$

which upon integration yields

$$\int te^{k_d t}\, dt = \frac{te^{k_d t}}{k_d} - \frac{e^{k_d t}}{k_d^2} + i'' \tag{6.55}$$

Upon further simplification,

$$\int te^{k_d t}\, dt = \frac{e^{k_d t}}{k_d^2}(k_d t - 1) + i'' \tag{6.56}$$

Accordingly,

$$\frac{mK}{2.303} \int te^{k_d t}\, dt = \frac{mKe^{k_d t}}{2.303k_d^2}(k_d t - 1) + i'' \tag{6.57}$$

Summing (6.51) and (6.57) yields the integral term of (6.50):

$$\int\left(A_0 + \frac{mKt}{2.303}\right) e^{k_d t}\, dt = \frac{A_0}{k_d} e^{k_d t} + \frac{mKe^{k_d t}}{2.303k_d^2}(k_d t - 1) + i' + i'' \tag{6.58}$$

Substituting the right-hand side of (6.58) for the integral terms in (6.50) and collecting the integration constants such that $i + i' + i'' = I$ yields

$$P = e^{-k_d t}\left[\frac{A_0}{K_d} e^{k_d t} + \frac{mKe^{k_d t}}{2.303k_d^2}(k_d t - 1) + I\right] \tag{6.59}$$

Upon simplification,

$$P = Ie^{-k_d t} + \frac{A_0}{k_d} - \frac{mK}{2.303k_d^2} + \frac{mK}{2.303k_d} t \tag{6.60}$$

Evaluation of I at $t = 0$, where $C = C_0$ and $P = P°$, yields

$$I = P° - \frac{A_0}{k_d} + \frac{mK}{2.303k_d^2} \tag{6.61}$$

Substituting for I and A_0 in (6.60) and simplifying the results gives

$$P = P° - a(1 - e^{-k_d t}) + bt \tag{6.62}$$

where

$$a = \frac{m \log (C_0/C_{min})}{k_d} + \frac{mK}{2.303k_d^2} \quad \text{and} \quad b = \frac{mK}{2.303k_d}$$

Equation (6.62) has a number of interesting features. Shortly after drug administration, when t is relatively small, the second term predominates over the third term and P decreases with time. At later times, the third term predominates and P increases with time. At some time later, $e^{-k_d t} \to 0$ and P increases linearly with time. Values of P calculated as a function of time after warfarin administration, by means of (6.62), agree exceedingly well with clinically observed values (see Fig. 6.24). A pharmacokinetic analysis by this method of the effect of a barbituate on the anticoagulant action of warfarin and bishydroxycoumarin has shown that the reduced efficacy of these drugs in

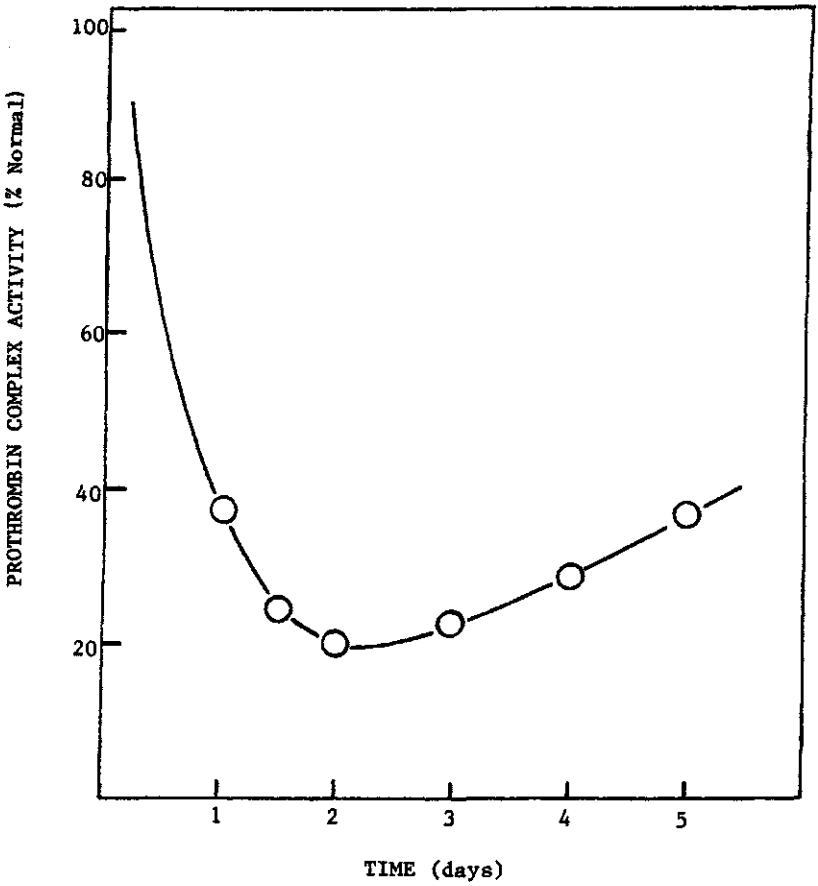

Fig. 6.24 Calculated (——) and observed (O) prothrombin complex activity in healthy human subjects after a single oral dose of 1.5 mg/kg warfarin sodium. (From Ref. 22.)

humans during barbiturate administration is due to enhanced biotransformation of the coumarin drugs rather than to changes in distribution or affinity to the pharmacologic receptors. Thus, whereas the biologic half-life of the coumarins was decreased significantly with the barbiturate, the relationship between effect and plasma-drug concentration remained unchanged [24,25]. On the other hand, phenylbutazone, which also enhances the elimination of warfarin, has a pronounced effect on the relationship between synthesis rate of prothrombin complex activity and plasma-warfarin concentration [26]. These observations are consistent with the assumption that phenylbutazone competitively displaces warfarin from nonspecific binding sites in the plasma and tissues and thereby increases the interaction

of the anticoagulant with its pharmacologic receptor and metabolizing enzyme system.

KINETICS OF IRREVERSIBLE PHARMACOLOGIC RESPONSE

Although most drugs produce a response that is reversible, certain antibiotics and anticancer agents cause cell death (an irreversible effect) by the irreversible or covalent incorporation of drug into a metabolic pathway of a cell. When discussing the kinetics of irreversible pharmacologic response, it is appropriate to consider two classes of drugs, each of which affects the cell cycle and mitosis in a different manner, one class which is nonphase specific in its cytoxic effect and the other class which is phase specific.

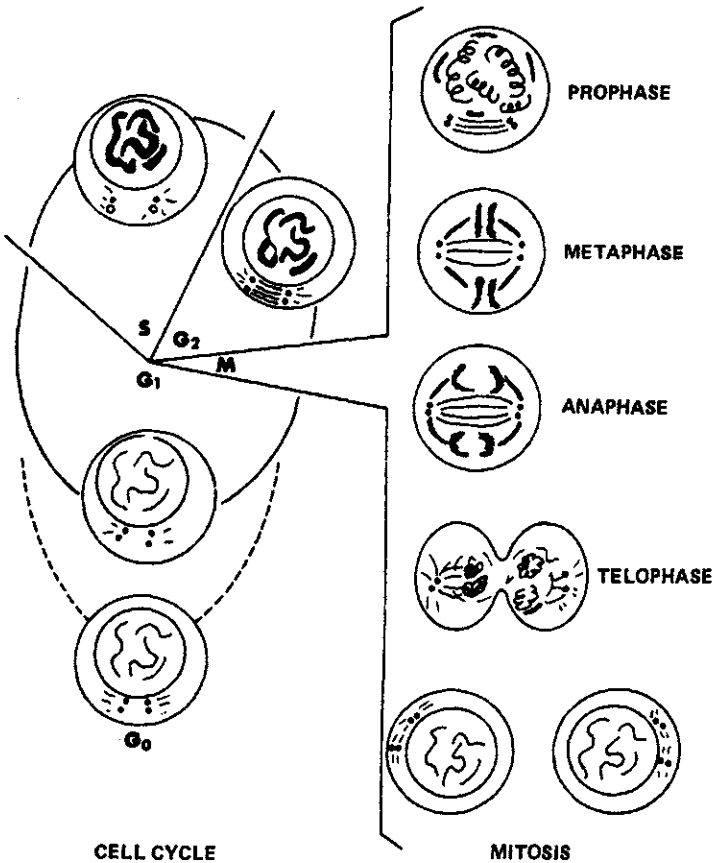

Fig. 6.25 Segments of the cell cycle and mitosis (see Ref. 27).

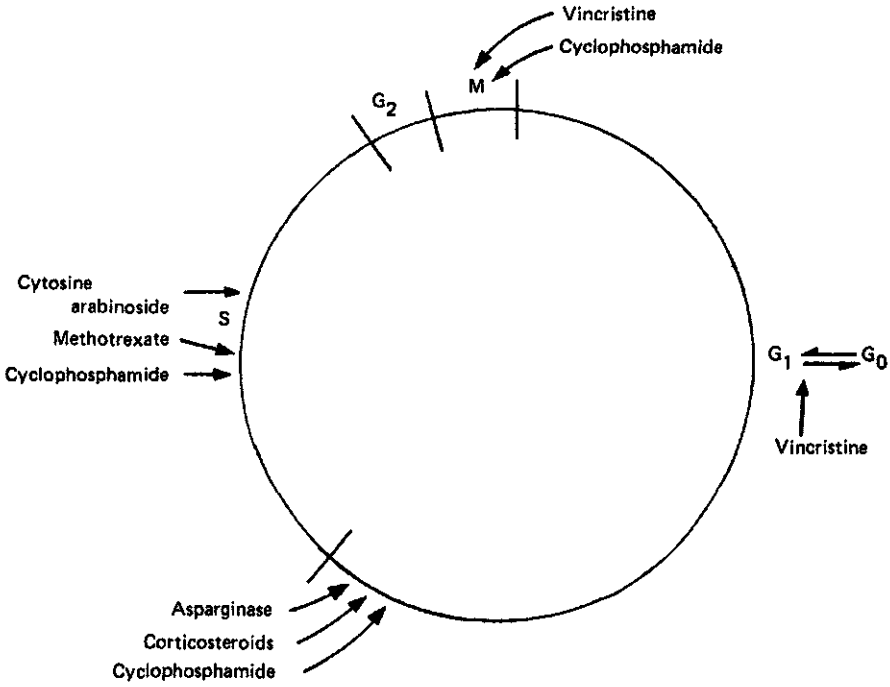

Fig. 6.26 Effect(s) of various chemotherapeutic agents on phases of the cell cycle. (From Ref. 28, reprinted with permission.)

The various segments of the cell cycle and mitosis are depicted in Fig. 6.25. Briefly, at the completion of mitosis M, the cells spend a variable period of time in a resting phase G_1. This is followed by the DNA synthesis period, the S phase. The cells cease DNA synthesis during the G_2 phase before reentry into mitosis. Each cytotoxic agent exerts its effect by disrupting one or more phases of the cell cycle. For example (see Fig. 6.26), methotrexate and cytosine arabinoside appear to inhibit DNA synthesis, while corticosteroids and L-asparginase inhibit the entry of cells into the S phase. Vincristine arrests mitosis and blocks the entry of resting cells into the mitotic cycle. Cyclophosphamide, on the other hand, appears to have several effects: inhibition of DNA synthesis, arrest of cells in mitosis, and inhibition of cells from entering DNA synthesis.

Nonphase Specific Drugs

The proposed model in Fig. 6.27 is an expansion of the model in Fig. 6.19, and is a slight modification of one presented previously [29]. This model permits an evaluation of the influence of cell cycle non-

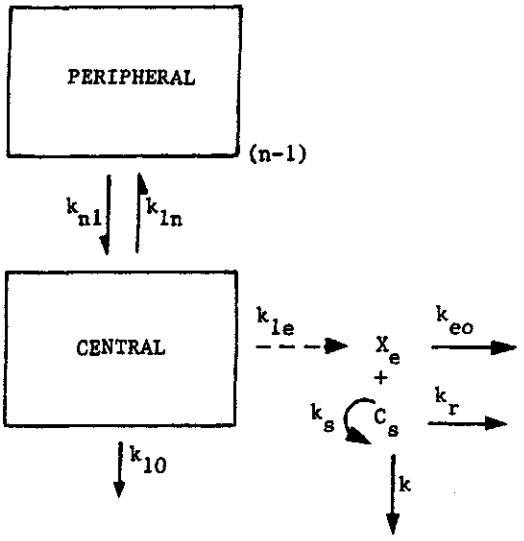

Fig. 6.27 Pharmacokinetic-cytotoxic model for nonphase specific drugs. (Data from Ref. 29.)

specific drugs on cell cytotoxicity. In this model X_e is the amount of drug in the effect compartment, C_s the concentration of proliferating target cells, k_s the rate constant for natural mitotic growth, k_r the rate constant for normal physiologic degradation, and k the rate constant for cell kill. All other parameters are as defined previously. As with the model in Fig. 6.19, the effect compartment is assumed to receive a negligible amount of the total drug in the body (i.e., k_{1e} is very small) and therefore does not influence the plasma concentration versus time curve. Nor does it enter into the pharmacokinetic solution for the amount of drug in the body.

Based on the model in Fig. 6.27, the following equation can be written for the rate of change of target cells:

$$\frac{dC_s}{dt} = k_s C_s - k_r C_s - k C_s X_e \tag{6.63}$$

Rearrangement yields

$$\frac{dC_s}{C_s} = (k_s - k_r)\, dt - k X_e\, dt \tag{6.64}$$

which when integrated becomes

$$\ln C_s = (k_s - k_r)\, t - k \int_0^t X_e\, dt + i \tag{6.65}$$

where i is a constant of integration. At $t = 0$, $i = \ln C_s^\circ$, where C_s° is the concentration of target cells before the initiation of therapy. Substitution of $\ln C_s^\circ$ for i in (6.65) and rearrangement produces the following relationship:

$$\ln \frac{C_s}{C_s^\circ} = (k_s - k_r)t - k\int_0^t X_e \, dt \tag{6.66}$$

Since most anticancer drugs have relatively short half-lives, it is suggested that the pharmacokinetic events (i.e., absorption, distribution, and elimination) are essentially over before much happens to the cells. Therefore,

$$\int_0^t X_e \, dt = \int_0^\infty X_e \, dt \tag{6.67}$$

The amount of drug in the effect compartment as a function of time is given by

$$X_e = k_{1e}X_0 \frac{\prod_{i=2}^{n}(E_i - k_{e0})}{\prod_{i=1}^{n}(\lambda_i - k_{e0})} e^{-k_{e0}t} + k_{1e}X_0 \sum_{\ell=1}^{n} \frac{\prod_{i=2}^{n}(E_i - \lambda_\ell)}{(k_{e0} - \lambda_\ell)\prod_{\substack{i=1 \\ i\neq\ell}}^{n}(\lambda_i - \lambda_\ell)} e^{-\lambda_\ell t} \tag{6.22}$$

Integration of (6.22) from zero to infinity yields

$$\int_0^\infty X_e \, dt = k_{1e}X_0 \left[\frac{\prod_{i=2}^{n}(E_i - k_{e0})}{k_{e0}\prod_{i=1}^{n}(\lambda_i - k_{e0})} + \sum_{\ell=1}^{n} \frac{\prod_{i=2}^{n}(E_i - \lambda_\ell)}{\lambda_\ell(k_{e0} - \lambda_\ell)\prod_{\substack{i=1 \\ i\neq\ell}}^{n}(\lambda_i - \lambda_\ell)} \right] \tag{6.68}$$

The same solution for $\int_0^\infty X_e\,dt$ [Eq. (6.72)] results regardless of the value of n. Therefore, arbitrarily setting n = 2 in (6.68) gives

$$\int_0^\infty X_e\,dt = k_{1e}X_0\left[\frac{E_2 - k_{e0}}{k_{e0}(\lambda_1 - k_{e0})(\lambda_2 - k_{e0})} + \frac{E_2 - \lambda_1}{\lambda_1(k_{e0} - \lambda_1)(\lambda_2 - \lambda_1)} + \frac{E_2 - \lambda_2}{\lambda_2(k_{e0} - \lambda_2)(\lambda_1 - \lambda_2)}\right] \tag{6.69}$$

Bringing (6.69) to a common denominator, expanding the resulting numerator, canceling common terms, substituting k_{21} for E_2, and factoring out k_{21} produces

$$\int_0^\infty X_e dt = k_{1e}k_{21}X_0\,\frac{\lambda_1^2\lambda_2 - \lambda_1\lambda_2^2 + \lambda_2^2k_{e0} - \lambda_2k_{e0}^2 - \lambda_1^2k_{e0} + \lambda_1k_{e0}^2}{\lambda_1\lambda_2k_{e0}(\lambda_1 - \lambda_2)(k_{e0} - \lambda_1)(k_{e0} - \lambda_2)} \tag{6.70}$$

Recognizing that the numerator of (6.70) is equal to $(\lambda_1 - \lambda_2)(k_{e0} - \lambda_1)(k_{e0} - \lambda_2)$ permits (6.70) to be simplified to

$$\int_0^\infty X_e\,dt = \frac{k_{1e}k_{21}X_0}{\lambda_1\lambda_2k_{e0}} \tag{6.71}$$

Since $\lambda_1\lambda_2 = k_{21}k_{10}$ [Eq. (2.100)], $k_{21}k_{10}$ can be substituted for $\lambda_1\lambda_2$ in (6.71) and k_{21} canceled to give

$$\int_0^\infty X_e\,dt = \frac{k_{1e}X_0}{k_{e0}k_{10}} \tag{6.72}$$

Substitution of $k_{1e}X_0/k_{e0}k_{10}$ for $\int_0^t X_e\,dt$, according to (6.67) and (6.72), in (6.66) yields

$$\ln\frac{C_s}{C_s^\circ} = (k_s - k_r)t - \frac{kk_{1e}}{k_{e0}k_{10}}X_0 \tag{6.73}$$

or

$$\log\frac{C_s}{C_s^\circ} = \frac{k_s - k_r}{2.303}t - \frac{kk_{1e}}{2.303k_{e0}k_{10}}X_0 \tag{6.74}$$

Equation (6.74) can be given as

$$\log \frac{C_s}{C_s^\circ} = \frac{k_s - k_r}{2.303} t - K_L X_0 \tag{6.75}$$

where

$$K_L = \frac{kk_{1e}}{2.303 k_{e0} k_{10}} \tag{6.76}$$

Therefore, a plot of the logarithm of the fraction of surviving cells (C_s/C_s°) versus dose should be linear. An example is presented in Fig. 6.28. The slope of the line K_L is a function of the affinity of the target cell for the drug, k, the elimination rate constant of the drug, k_{10}, and the constants responsible for the appearance and disappearance of drug in the effect compartment.

The reciprocal of K_L (i.e., $1/K_L$) has been defined as a lethality constant ED_{90}, which is the dose increment of drug required to reduce the fraction of surviving cells (C_S/C_S°) by one order of magnitude [29]. This lethality constant can be used to compare the cytotoxic effects of a drug on various cell systems or effects of various drugs on a single-cell system. For example, a comparison of the curves in Fig. 6.28 would suggest that cyclophosphamide has a smaller lethality constant for or is more potent against osteosarcoma cells than chimera spleen cells.

Cell-Cycle-Specific Drugs

There are some anticancer drugs which are cytotoxic only during a specific phase of the cell cycle. For this class of drugs the model in Fig. 6.29 is proposed. Again, this model is slightly modified from one presented previously [30]. C_s represents the concentration (or number) of cells sensitive to the drug, and C_r is the concentration (or number) of insensitive cells. Cells in each group are interconvertible with transformation rate constants k_{rs} and k_{sr}. All other terms are as defined previously. As can be seen from the model, the cell proliferation rate constant k_s is assumed to act only on C_s cells, and the rate constant for cell loss k_r acts only on C_r cells. This model is analogous to systems in which C_S and C_r represent proliferative and resting cells, respectively.

The rate of change in the number of target or proliferating cells and insensitive or resting cells can be written as the following differential equations:

$$\frac{dC_s}{dt} = k_s C_s - kX_e C_s - k_{sr} C_s + k_{rs} C_r \tag{6.77}$$

and

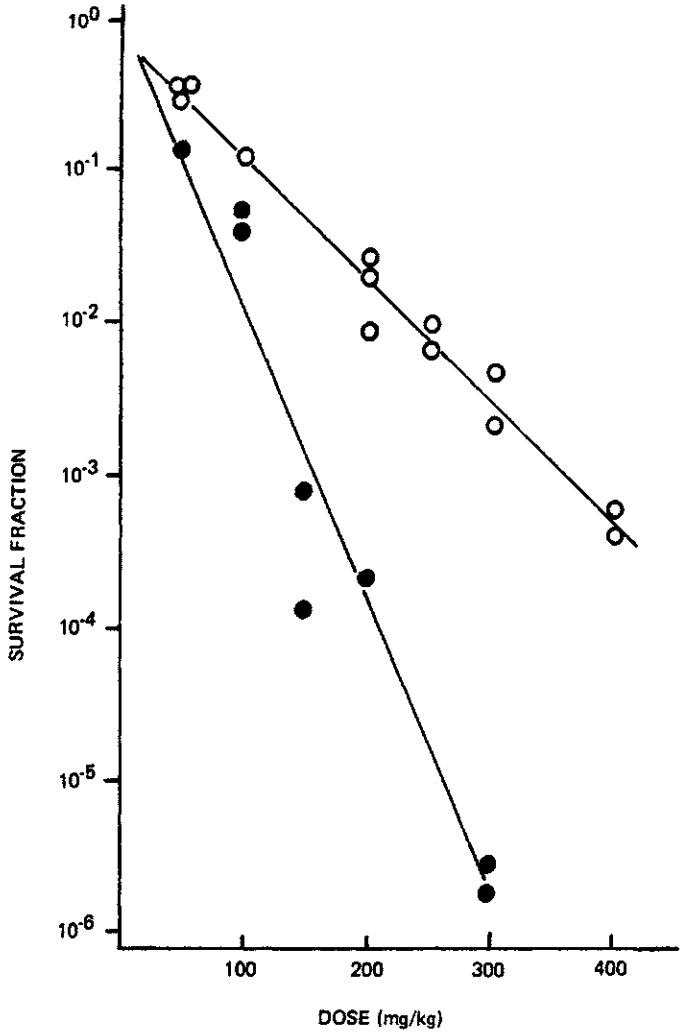

Fig. 6.28 Survival curves for chimera spleen cells (O) and osteosarcoma cells (●) after intraperitoneal administration of single doses of cyclophosphamide. (From Ref. 29, reprinted with permission.)

$$\frac{dC_r}{dt} = k_{sr}C_s - k_{rs}C_r - k_rC_r \qquad (6.78)$$

The problem encountered in trying to solve (6.77) and (6.78) is the time-dependent nature of X_e. This problem can be overcome by numerical integration of the specific differential equations that describe

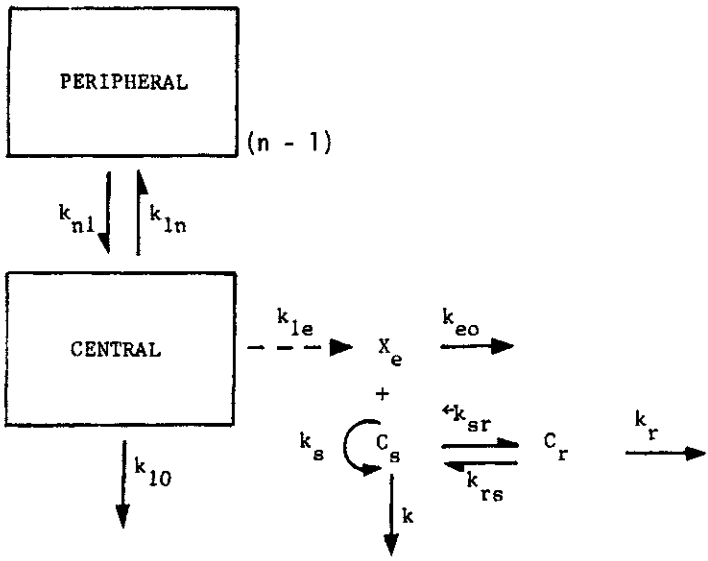

Fig. 6.29 Pharmacokinetic-cytotoxic model for cell-cycle-specific drugs. (Data from Ref. 30.)

the model [i.e., Eqs. (6.77) and (6.78), plus the differential equations for X_e and other compartments (see Fig. 6.29)]. Such an approach has been applied to arabinosylcytosine data (see Fig. 6.30).

If X_e in (6.77) is assumed to remain constant, a specific equation for (6.77) can be obtained quite readily. Assuming that X_e can be approximated by the average amount of drug in the effect compartment during a dosing interval at steady state, $\bar{X}_e$, where

$$\bar{X}_e = \frac{\int_0^\tau X_e \, dt}{\tau} \tag{6.79}$$

(see Chap. 3), then

$$X_e \simeq \frac{\int_0^\tau X_e \, dt}{\tau} \tag{6.80}$$

where τ is the dosing interval and $\int_0^\tau X_e \, dt$ is the area under the X_e versus t curve during a dosing interval at steady state. Since $\int_0^\tau X_e \, dt$ equals $\int_0^\infty X_e \, dt$ (see Chap. 3), $k_{1e}X_0/k_{e0}k_{10}$ can be substituted for $\int_0^\tau X_e \, dt/\tau$ in (6.80) [see Eq. (6.72)] to give

$$X_e \simeq \frac{k_{1e}X_0}{k_{e0}k_{10}\tau} \tag{6.81}$$

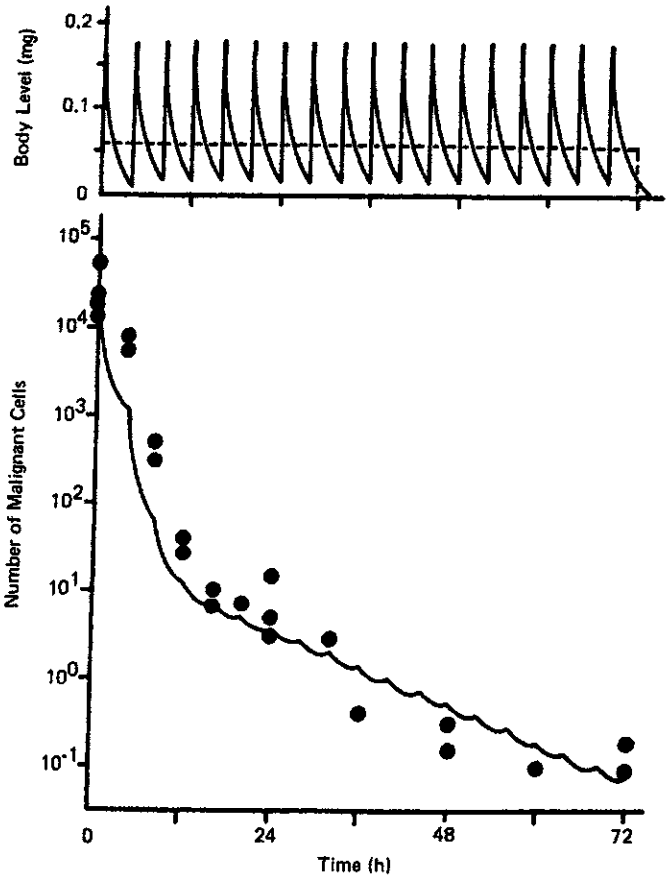

Fig. 6.30 Time course of drug levels and survival of lymphoma cells in mouse femur on multiple dosing of arabinosylcytosine (Ara-C). The upper graph shows the calculated body levels of Ara-C when doses of 0.167 mg are given every 4 h (assuming a biologic half-life of 1 h) as well as the average body level of Ara-C (dashed line). The solid line in the lower graph is calculated from the model using numerical integration. (From Ref. 30, © 1971 Plenum Publishing Corp.)

Substitution of this value of X_e for X_e in (6.77) yields

$$\frac{dC_s}{dt} = k_s C_s - \frac{k k_{1e} X_0 C_s}{k_{e0} k_{10}^{\tau}} - k_{sr} C_s + k_{rs} C_r \qquad (6.82)$$

The solutions for C_s and C_r are provided in the appendix to this chapter.

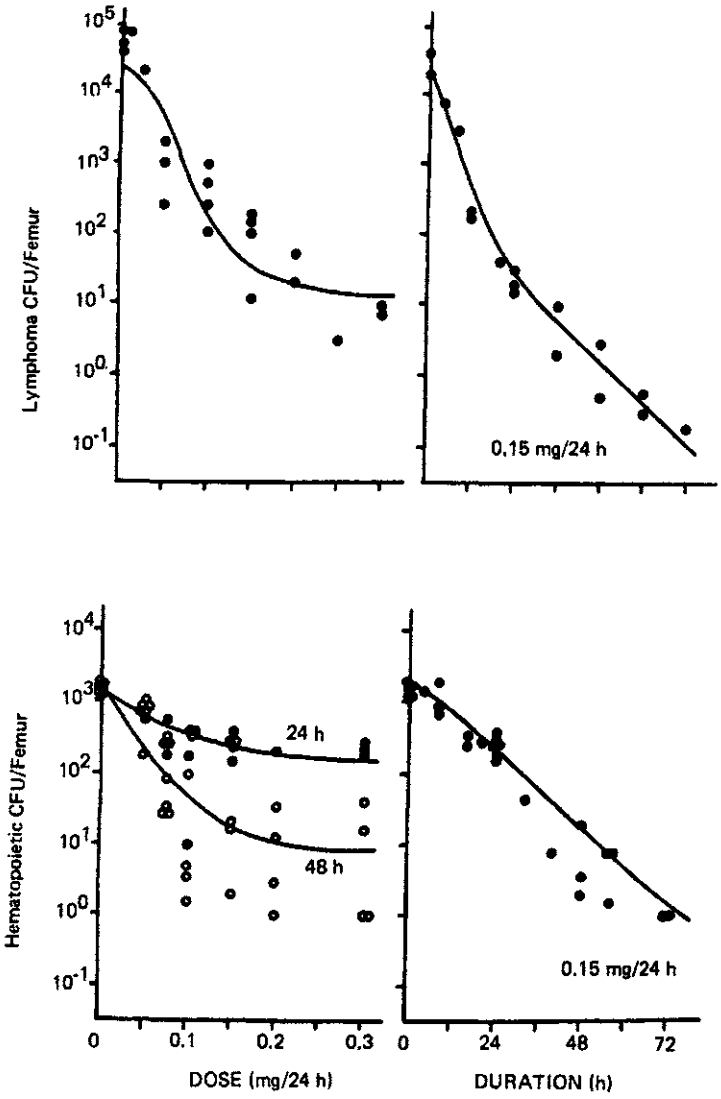

Fig. 6.31 Dose- and time-dependent cell survival curves for the effects of vinblastine on hematopoietic and lymphoma cells in the mouse femur. (From Ref. 30, © 1971 Plenum Publishing Corp.)

Of interest is the total number of cells in the system C_T as a function of time and of dose. This is given by

$$C_T = A_1 e^{-\alpha_1 t} + A_2 e^{-\alpha_2 t} \tag{6.83}$$

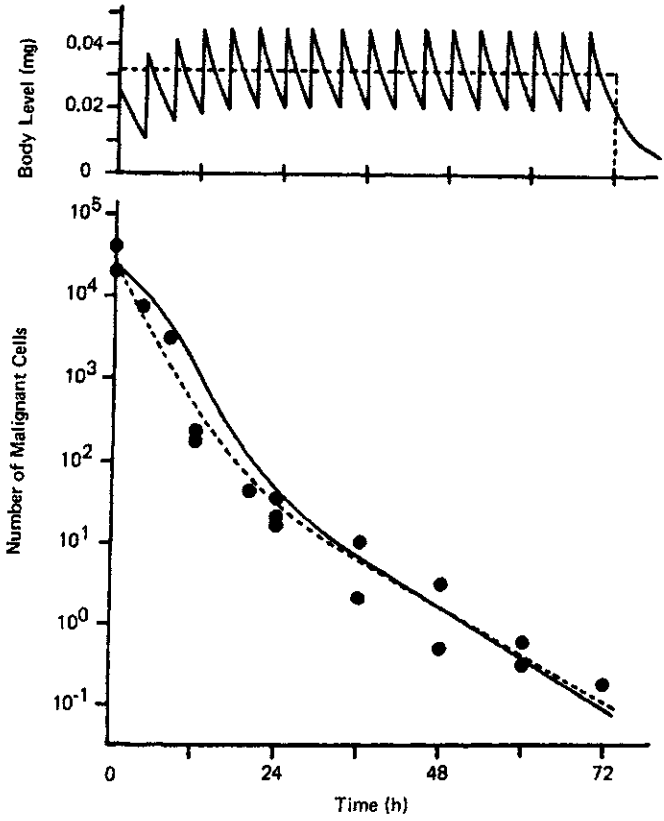

Fig. 6.32 Time course of drug levels and survival of lymphoma cells in mouse femur on multiple dosing of vinblastine. The upper graph shows the calculated body levels (solid line) of vinblastine when doses of 0.025 mg are given every 4 h (assuming a biologic half-life of 3.5 h) as well as the average body level of vinblastine at steady state (dashed line). The solid line in the lower graph is calculated from the model using numerical integration; the dashed line is based on average body levels. (From Ref. 30, © 1971 Plenum Publishing Corp.)

where t is time, α_1 and α_2 are disposition rate constants,

$$A_1 = \frac{C_s^\circ(k_{rs} + k_r + k_{sr} - \alpha_1) + C_r^\circ(KX_0 + k_{sr} - k_s + k_{rs} - \alpha_1)}{\alpha_2 - \alpha_1} \tag{6.84}$$

and

$$A_2 = \frac{C_s^\circ(k_{rs} + k_r + k_{sr} - \alpha_2) + C_r^\circ(KX_0 + k_{sr} - k_s + k_{rs} - \alpha_2)}{\alpha_1 - \alpha_2} \tag{6.85}$$

and C_s° and C_r° are the respective concentrations or numbers of sensitive and insensitive cells at time zero. Derivations of these equations may also be found in the appendix to this chapter.

The approximation that resulted in the solution for (6.83) allows the characterization of the average effect of a given dose of a drug, rather than the time course of effect of the dose, and is precise only at the instant that all of the drug has been lost from the body and tumor site [30]. An example of the application of Eq. (6.83) with regard to the effect of dose and time on hematopoietic and lymphoma cells in the mouse femur is illustrated in Fig. 6.31. Figure 6.32 demonstrates the good agreement between the approximate solution and a more rigorous kinetic treatment.

Although the data are limited, there are examples in the literature, as illustrated above, that demonstrate the application of the relationships developed in cancer chemotherapy. Unfortunately, there remains a paucity of information concerning the effect of duration of antibiotic therapy and dose on bacterial cell growth.

APPENDIX: SOLUTIONS FOR C_s, C_r, AND C_T FOR CELL SYSTEMS SENSITIVE TO DRUGS THAT ARE CELL CYCLE SPECIFIC

The differential equations for C_s and C_r [Eqs. (6.86) and (6.81), respectively] are

$$\frac{dC_s}{dt} = k_s C_s - KX_0 C_s - k_{sr} C_s + k_{rs} C_r \tag{A6.1}$$

and

$$\frac{dC_r}{dt} = k_{sr} C_s - k_{rs} C_r - k_r C_r \tag{A6.2}$$

where

$$K = \frac{kk_{1e}}{k_{e0} k_{10} \tau} \tag{A6.3}$$

The respective Laplace transforms of these equations are (see Appendix A)

$$s\bar{C}_s - C_s^\circ = (k_s - KX_0 - k_{sr})\bar{C}_s + k_{rs}\bar{C}_r \tag{A6.4}$$

and

$$s\bar{C}_r - C_r^\circ = k_{sr}\bar{C}_s - (k_{rs} + k_r)\bar{C}_r \tag{A6.5}$$

where C_s° and C_r° are the concentrations or numbers of sensitive and insensitive cells at time zero. Collecting common terms in these two equations yields the following:

$$(s + KX_0 + k_{sr} - k_s)\bar{C}_s = k_{rs}\bar{C}_r + C_s^\circ \tag{A6.6}$$

$$(s + k_{rs} + k_r)\bar{C}_r = k_{sr}\bar{C}_s + C_r^\circ \tag{A6.7}$$

Multiplying Eq. (A6.6) by $(s + k_{rs} + k_r)$ and (A6.7) by k_{rs}, adding the resulting expressions, and solving for $\bar{C}_s$ yields

$$\bar{C}_s = \frac{(s + k_{rs} + k_r)C_s^\circ + k_{rs}C_r^\circ}{s^2 + s(KX_0 + k_{sr} + k_{rs} + k_r - k_s) + (k_{rs} + k_r)(KX_0 + k_{sr} - k_s) - k_{rs}k_{sr}} \tag{A6.8}$$

If we consider the identity

$$s^2 + s(KX_0 + k_{sr} + k_{rs} + k_r - k_s) + (k_{rs} + k_r)(KX_0 + k_{sr} - k_s) - k_{rs}k_{sr} = (s + \alpha_1)(s + \alpha_2) \tag{A6.9}$$

Eq. (A6.8) can be rewritten as follows:

$$\bar{C}_s = \frac{(s + k_{rs} + k_r)C_s^\circ + k_{rs}C_r^\circ}{(s + \alpha_1)(s + \alpha_2)} \tag{A6.10}$$

where

$$\alpha_1 + \alpha_2 = KX_0 + k_{sr} + k_{rs} + k_r - k_s \tag{A6.11}$$

and

$$\alpha_1\alpha_2 = (k_{rs} + k_r)(KX_0 + k_{sr} - k_s) - k_{rs}k_{sr} \tag{A6.12}$$

Solving (A6.10) for C_s using a table of Laplace transforms (Appendix A) gives

$$C_s = \frac{(k_{rs} + k_r - \alpha_1)C_s^\circ + k_{rs}C_r^\circ}{\alpha_2 - \alpha_1} e^{-\alpha_1 t} + \frac{(k_{rs} + k_r - \alpha_2)C_s^\circ + k_{rs}C_r^\circ}{\alpha_1 - \alpha_2} e^{-\alpha_2 t} \tag{A6.13}$$

C_r can be solved for in a similar manner. Multiplying (A6.6) by k_{sr} and (A6.7) by $s + KX_0 + k_{sr} - k_s$, adding the resulting expressions, solving for $\bar{C}_r$, and considering the identity given by (A6.9) yields

$$\bar{C}_r = \frac{(s + KX_0 + k_{sr} - k_s)C_r^\circ + k_{sr}C_s^\circ}{(s + \alpha_1)(s + \alpha_2)} \tag{A6.14}$$

The following equation for C_r as a function of time can be determined using a table of Laplace transforms (Appendix A):

$$C_r = \frac{(KX_0 + k_{sr} - k_s - \alpha_1)C_r^\circ + k_{sr}C_s^\circ}{\alpha_2 - \alpha_1} e^{-\alpha_1 t} + \frac{(KX_0 + k_{sr} - k_s - \alpha_2)C_r^\circ + k_{sr}C_s^\circ}{\alpha_1 - \alpha_2} e^{-\alpha_2 t} \tag{A6.15}$$

An expression for the total number of cells in the system, C_T, can be obtained by adding (A6.13) and (A6.15). Addition followed by simplification yields

$$C_T = C_s + C_r = A_1 e^{-\alpha_1 t} + A_2 e^{-\alpha_2 t} \tag{A6.16}$$

where

$$A_1 = \frac{C_s^\circ(k_{rs} + k_r + k_{sr} - \alpha_1) + C_r^\circ(KX_0 + k_{sr} - k_s + k_{rs} - \alpha_1)}{\alpha_2 - \alpha_1} \tag{A6.17}$$

and

$$A_2 = \frac{C_s^\circ(k_{rs} + k_r + k_{sr} - \alpha_2) + C_r^\circ(KX_0 + k_{sr} - k_s + K_{rs} - \alpha_2)}{\alpha_1 - \alpha_2} \tag{A6.18}$$

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