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Clearance Approaches in Pharmacology*

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I. Introduction

CLEARANCE was developed by renal physiologists in the early 1930s as an empiric measure of kidney function (231, 313). The pharmacokinetic basis of the term was defined at about the same time with the recognition that the concept could be more generally applied to other organs and elimination pathways (reviewed in ref. 323). Over the subsequent years, clearance approaches have been applied to a wide variety of in vivo and in vitro systems involving both endogenous and exogenous compounds. Pharmacology in particular has recently provided new emphasis and additional insights into so-called clearance concepts that extend beyond the simple estimation of functional parameters. This review will describe some aspects of the current understanding and application of clearance as it broadly relates to the disposition of xenobiotics, especially their metabolism in humans.

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Because of its multidisciplinary usage and application to a wide variety of situations, "clearance" has been used in several different contexts with slightly different meanings. The number of different approaches used to estimate clearance potentially adds further confusion. The most general definition of clearance (CL) is that it is a proportionality constant describing the relationship (equation 1) between a substance's rate of transfer, in amount per unit time, and its concentration (C), in an appropriate reference fluid (238). Clearance, therefore, has the unit of volume rate (e.g., ml/min), and this is often expressed by the concept of a virtual volume of fluid from which the substance is completely removed per unit time. The true nature of clearance is better illustrated, however, by considering it as a rate of substance transfer "normalized" to a concentration (C). This definition has the advantage that reversible transfer, as occurs, for example, with xenobiotic distribution between plasma and tissues, may be considered (180) as well as the more customary processes of irreversible elimination.

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However, unless explicitly stated, clearance usually refers to elimination rather than intercompartmental transfer. Clearance may be expressed in terms of the concentration of unbound (CL^u) or total drug (CL^{tot}). Also, depending on the time period over which either the rate of transfer or concentration is determined, clearance can reflect an instantaneous process or a time-averaged value. In the latter case, significant alterations in instantaneous clearance due to a variety of factors may be dampened, and possibly obscured.

$$CL = \frac{\text{rate of transfer}}{C} \quad \text{equation 1}$$

Elimination may arise as a result of processes occurring in the kidney, the liver, the lung, and a number of other organs. Total clearance (CL_{TOT}) is equal to the sum of all of these individual and simultaneously occurring *organ clearances*. That is, it is an additive term in the same way that no single milliliter of reference fluid has all of its drug removed during one transit through an eliminating organ(s); rather a fraction is cleared from each of the many milliliters perfusing the organ(s). This amount is summed and expressed as if it were derived by completely clearing a smaller volume of perfusate of all of its contained drug. Generally, a xenobiotic is eliminated by a combination of excretory and biotransformation pathways; often the processes involved in the latter are collectively termed *metabolic clearance*. It is also possible to "partition" such overall elimination pathways into their composite *fractional clearances* reflecting a specific route of elimination, e.g., conversion to an individual metabolite. Finally, *intrinsic clearance* (CL_{int}) is becoming increasingly used as a measure of intracellular drug removal. For example, metabolism by an organ such as the liver can be additively expressed according to the Michaelis-Menten kinetic parameters of each individual *i*th enzymatic pathway (equation 2).

$$CL_{int} = \sum_{i=1}^{n} \frac{V_{max,i}}{K_{m,i} + C} \quad \text{equation 2}$$

The large majority of drugs exhibit linear (dose/concentration-dependent) elimination kinetics over the range of interest, because the K_m for overall metabolism, or its analog when active transport is involved, e.g., biliary, renal tubular secretion, is substantially greater than C. In this situation, intrinsic clearance is approximated by the summed ratio of V_{max} to K_m, and clearance is a constant. For drugs that have nonlinear (dose/concentration-dependent) kinetics, the K_m for one or more routes of elimination may not be sufficiently greater than C, and clearance will then vary depending on the drug concentration.

II. Estimation of Clearance

A. Total Clearance

Total clearance is probably the most commonly determined clearance term, not only because it reflects the contribution of all elimination pathways in the whole system under study, but because of its practical value in predicting the steady-state concentration (C_{ss}), especially in clinical situations (equation 3).

$$C_{ss} = \frac{\text{drug delivery rate}}{\text{total clearance}} \quad \text{equation 3}$$

The usual technique for estimating the time-averaged CL_{TOT} under linear pharmacokinetic conditions consists of administering a single dose of the xenobiotic of interest and calculating the ratio between the available dose and the area under the circulating concentration/time curve (AUC) measured from time zero to infinity

$$CL_{TOT} = \frac{F\ \text{dose}}{{}_0^{\infty}|\,\text{AUC}} \quad \text{equation 4}$$

where F is the fraction of the administered dose that reaches the sampling site in the circulation, often termed availability. Unless metabolism occurs within the vasculature, F is unequivocally known to be unity only after intraarterial administration (vide infra). Nevertheless, total clearance is generally estimated after intravenous dosing with an implicit assumption that $F = 1$ by this route. When availability is unknown, as for example after oral or intramuscular injection, then the administered dose/AUC ratio provides an *apparent clearance* value that requires qualification regarding the route of administration, e.g., apparent oral clearance (CL_{oral}). AUC may be measured directly using the linear trapezoidal and/or the log trapezoidal rules with appropriate correction for the "missing" area from the time of the last experimentally determined concentration value to infinity (85, 518). Alternatively, AUC may be estimated by integrating the mathematical equation describing the concentration/time curve. Frequently, this is a multiexponential function and, therefore, the total area is given by the sum of the ratios of the coefficients and exponents (467). In the case where the dose of drug is administered rapidly as a "bolus" dose, it is conventionally assumed that distribution is instantaneous and homogeneous throughout the central pool from which sampling occurs. This allows extrapolation of concentrations at times earlier than the first experimentally determined values, which potentially represent a significance fraction of the total area. Often, however, it is practially difficult to accurately measure and describe the very rapidly declining concentrations that are present initially after a bolus dose. Moreover, the venous concentration is initially zero rather than the value obtained by back-extrapolation to the time of administration. Thus, back-extrapolation of the curve based on data collected at a later time may result in an incorrect estimation of the actual concentrations. Also, mixing, recirculation, and other hemodynamic factors probably produce a much more complicated concentration/time profile immediately after rapid intravascular drug administration than generally considered (86).

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Thus, the early AUC after bolus administration may be poorly estimated (89). Because of this, it is often more prudent to estimate total clearance, especially in vivo, following short term intravascular infusion of the xenobiotic rather the bolus injection. A further means of estimating AUC is by use of continuous sampling of the blood at a constant rate through a nonthrombogenic catheter (265–267, 465). This approach provides a single concentration representing the integrated value over the period of withdrawal. Extrapolation of the concentration to infinite time is possible if the sampling is discontinued prior to the actual blood level reaching zero (465). Continuous sampling for as long as 24 h has been achieved (267), and the approach has the advantage that far fewer concentration determinations are required compared to the more conventional multiple sampling designed experiment. The technique has also proven useful in obtaining accurate AUC determinations in the first few minutes after rapid intravenous drug administration (217). Nevertheless, the approach has not been as widely applied as might be expected.

It is also possible to determine total clearance by means of equation 3, i.e., continuous drug administration and the measurement of the resulting steady-state concentration. Again, administration must be intravascular in order to obtain an absolute clearance term, otherwise the estimate is only an apparent value. At steady-state the AUC during a dosing interval following repetitive, multiple dosing is equal to the total AUC following a single dose, providing that linear pharmacokinetics are present (470). Accordingly, total clearance may also be estimated using this type of dosing regimen. Such steady-state estimates are critically dependent on the actual attainment of steady-state, since total clearance will be overestimated if this is not the case. Accordingly, evidence of such a condition must be present before the estimate can be accepted. Moreover, the possibility of nonlinear elimination is more likely following multiple dose administration that results in drug accumulation and, therefore, the clearance estimate may not necessarily be valid at lower drug concentrations. Similarly, time-dependent changes in clearance may occur during prolonged drug administration that may perturb the system under study, e.g., autoinduction and inhibition of drug metabolism.

Ideally, total clearance should be based on the AUC determined from arterial concentrations, but in practice venous drug levels are invariably used. Provided that elimination does not occur between the arterial side of the circulation and the venous sampling site, then theoretically the two AUCs will be equivalent, and no error will occur in estimating clearance (88, 453). Few studies, however, validate this assumption. Similarly, little consideration is usually given to the possible difference between total clearance estimated after giving the drug intravenously rather than the more appropriate central-arterial route of administration. All of the venous blood must circulate through the lungs prior to reaching the arterial side of the circulation, and pulmonary elimination by excretion and/or metabolism is possible with many drugs. Accordingly, a first-pass effect (vide infra) may occur after intravenous dosing such that only a fraction of the administered dose reaches the aorta. Thus, application of equation 4 with the assumption that F equals unity after intravenous administration leads to an overestimation of CL_{TOT} (86, 99). Viewed somewhat differently, CL_{TOT} estimated after intravenous dosing always reflects any initial pulmonary clearance in addition to the summed contributions of the other individual eliminating organs, including the lung.

B. Organ Clearance

Based on steady-state, mass balance considerations, the instantaneous rate of organ elimination is equal to the difference between the rate of drug delivery to the organ in the arterial inflow and its rate of exit in the venous outflow. This is equal to the product of the organ's perfusion rate (Q) and the arteriovenous concentration difference ($C_{art} - C_{ven}$). Accordingly, organ clearance (CL_{org}) may be defined by equation 5.

$$CL_{org} = \frac{Q(C_{art} - C_{ven})}{C_{art}} = QE \qquad \text{equation 5}$$

Since the arteriovenous difference "normalized" to the inflow concentration is equal to the fraction of the xenobiotic entering the organ which is removed during transit, i.e., the extraction ratio (E), organ clearance is equivalent to the product of perfusion rate and extraction ratio.

It is possible to estimate CL_{org} by direct determination of the parameters of equation 5. However, the practical problems involved in applying this approach usually preclude its use, especially for in vivo studies. First, an accurate estimation of organ perfusion rate is extremely difficult to obtain unless it is mechanically controlled as, for example, in an isolated perfused organ preparation or a hemodialysis system. Moreover, total flow may not necessarily be constant over the study period or reflect "functional" flow because of the presence of intraorgan shunts. Also, the analytical methodology for measuring the drug concentrations may not be adequate to determine either the low venous levels associated with a high extraction ratio or alternatively the small arteriovenous difference present when extraction is low. Finally, an arteriovenous difference obtained under non-steady-state conditions will not be the same as that at steady-state (522), even though distribution equilibrium is present (406).

When a single organ is solely responsible for the complete elimination of all of a xenobiotic, then a time-averaged organ clearance can be measured by application of either equation 3 under steady-state conditions or equation 4, since organ and total clearance are synony-

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mous. For a drug completely eliminated by metabolism it is, however, virtually impossible to definitively associate such a process with a single organ, since multiple putative sites frequently exist. Often there may be evidence or a suspicion that one organ plays a predominant, if not exclusive, role, e.g., liver. However, such association is, at best, an inferred one that requires cautious application. In contrast, the excretion of a large number of substances is not only complete but also limited to the kidney. In this particular situation, the measurement of total clearance provides an accurate estimate of renal clearance. However, a more general means exists to determine directly renal clearance (CL_R) because the rate of excretion ($\Delta A_E/\Delta t$) can be assessed from urinary rather than blood/plasma data (equation 6).

$$CL_R = \frac{\Delta A_e/\Delta t}{C_{mid}} \qquad \text{equation 6a}$$

where Δ indicates a finite increment of change, and C_{mid} is the blood or plasma drug concentration at the midpoint of the urine collection interval (455). Renal physiologists usually write equation 6a in the form:

$$CL_R = \frac{Q_{urine} C_{urine}}{C_{mid}} \qquad \text{equation 6b}$$

where Q_{urine} is urine flow rate, and C_{urine} is the drug concentration in urine. Provided that renal clearance is neither concentration or time dependent, then CL_R may be obtained by averaging several estimates based on equation 6. Alternatively, renal clearance can be estimated from the slope of the curve of $\Delta Ae/\Delta t$ versus C_{mid}. The latter approach is particularly useful in detecting nonlinearities which are not unusual if the drug is administered as a rapid intravenous bolus. Such deviations may reflect an actual biological phenomenon, for example, saturation of an active secretory and/or reabsorption process, but often they are artifactual. Ideally, C_{mid} should be measured in the arterial circulation, but frequently the peripheral venous concentration is used instead. After rapid intravenous administration, such venous levels may be considerably lower than the renal artery concentration (72), especially if little cutaneous dilatation is present at the sampling site (264). As a result, time-dependent renal clearance appears to be present (90, 274, 278). In contrast, underestimation of renal clearance may occur because the observed rate of excretion lags behind the blood/plasma drug concentrations. This may reflect the time necessary for urine to pass through the dead space of the kidney and ureter, which is normally about 5 min in man (455). Alternatively, if renal tubular secretion contributes significantly to the net clearance, then slow equilibration between drug in the blood and that in the interstitial fluid may also lead to nonlinearity, especially when the concentrations are rapidly changing (102).

Equation 6 provides the time-averaged estimate of CL_R rather than an instantaneous value. The accuracy of the determination, therefore, depends on the length of the urine collection interval. Providing the Δt is not longer than the half-life of the drug, then the error appears to be less than about 2% under first-order conditions of elimination (294). Unless bladder catheterization is used, a practical lower limit for Δt in man is about 0.25 to 0.5 h. Hence, the greatest errors are again likely to occur using data collected during the initial period after intravenous bolus administration when distribution equilibrium is being established. Water-induced diuresis may be used to facilitate short urine collections, and this has the added benefit of reducing the volume error due to incomplete bladder emptying (455). It is also possible to use the logarithmic mean $[(C_1 - C_2)/\ln(C_1/C_2)]$ of blood or plasma concentration during the urine collection interval to reduce errors when the levels are rapidly changing. However, providing that Δt is reasonably small, the error in assuming $\Delta Ae/\Delta t$ is the instantaneous rate of excretion is probably less than normal experimental error from other factors. One exception where this may not be true is when appreciable drug reabsorption occurs in the bladder (511). For example, the plasma clearance of saccharin in the rat is faster if urine is removed from the bladder at 5-min intervals compared to 60-min collections periods (92). Mathematical modeling suggests that a similar situation occurs with N-hydroxyarylamines; the longer the period prior to micturition, the smaller the recovery of this type of metabolite in the voided urine and, most importantly, the greater the underestimation of the exposure of the bladder epithelium to such ultimate carcinogens (519). However, this is not a particularly well-studied aspect of renal elimination. Many of the sampling and collection problems associated with equation 6 can be avoided if renal clearance is measured under steady-state conditions during constant rate intravenous infusion of the drug, and this is the customary approach.

An alternative approach to estimating renal clearance is based on the integrated form of equation 6a:

$$CL_R = \frac{{}_{t_1}^{t_2}\sum Ae}{{}_{t_1}^{t_2}|\,AUC} \qquad \text{equation 7}$$

where $\sum Ae$ is the cumulative amount of drug unchanged in the urine in the time interval t_1 to t_2, and AUC is the area under the blood or plasma concentration/time curve during the same period. Generally, t_1 is the time at which the drug was administered, i.e., zero time. Also, t_2 may be set to the limit so that CL_R is given by the ratio of the total amount of drug excreted unchanged in the urine to the AUC extrapolated to infinity. If the drug is known to be entirely eliminated by the kidney, then the numerator may be equated with the administered intravascular dose. In general, however, this step must be taken with great caution. Again, a time-averaged estimate of renal clearance is obtained with equation 7, but over a longer

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time period than equation 6 so that the value is less sensitive to time-dependent changes in renal clearance. The method is also critically dependent on complete urine collection during the defined interval. However, there is the advantage that precise timing of urine collection is not required, except in the final instance, nor is there any problem with incomplete bladder emptying.

C. Blood versus Plasma Clearance

Xenobiotic present in blood is distributed not only in the plasma but also to a varying extent in the formed elements. The plasma clearance of many drugs exceeds plasma flow through the eliminating organ(s) indicating that drug present in these elements, such as the erythrocyte, must be available for extraction. Accordingly, clearance from the blood is generally a more appropriate measure of organ function than is plasma clearance. In certain comparative types of investigations, for example, bioavailability studies, the difference is not critical. But, whenever physiological interpretation is placed upon clearance, then drug in the total perfusate must be considered. Exceptions to this generality are limited to the situations where the blood/plasma concentration ratio is unity, e.g., ethanol, antipyrine, where distribution of drug within the blood is limited to the plasma, and where the rate of equilibration of drug between the formed elements and plasma is sufficiently slow that drug removal from the plasma does not lead to significant re-equilibration during organ transit. The latter situation appears to hold with many of the substances used to estimate various renal clearance values. For example, erythrocyte concentrations of both creatinine (459, 490) and *p*-aminohippurate (379) are the same in the renal artery and renal vein despite the fact that significant arteriovenous plasma level differences are present. Accordingly, the measured clearance of these compounds reflects plasma clearance and plasma flow rate. Studies using the multiple indicator dilution technique also suggest that, depending on the drug's permeability, the erythrocyte membrane can serve as a complete or partial diffusion barrier with respect to hepatic uptake (190). For example, the mean transit time of thiourea through the isolated perfused liver is different after preequilibration with erythrocytes compared to direct injection into the perfusate. In the latter situation there is little opportunity for the thiourea to enter the red cells during its single passage through the liver. The effect, however, is much smaller with urea and chloride, which exchange more rapidly between plasma and erythrocytes. Generally, however, it is assumed that the plasma/erythrocyte diffusion equilibrium is sufficiently rapid that it does not limit the exchange of drug between the erythrocyte and organs (404).

Drug distribution into and out of the erythrocyte, and probably to other formed elements, appears to be according to classical, non-ionic diffusion (416, 417). Accordingly, the rate of translocation across the erythrocyte membrane is determined by the lipid solubility of the transported moiety, i.e., the unionized form of a weak electrolyte, or a neutral nonelectrolyte. This may be at a rate too rapid to experimentally determine for compounds with very high partition coefficients, but equilibrium may not be achieved for several hours with more polar compounds (416, 417). An often underappreciated consequence of such slow equilibration is that, unless specific steps are taken, the blood/plasma concentration (B/P) ratio may change during the collection, handling, and storage of the biological sample. That is, drug is extracted only from the plasma in vivo, but diffusion out of the erythrocytes continues to occur in vitro prior to harvesting of the plasma. Rapid centrifugation immediately after drawing the blood is, therefore, important in situations where plasma clearance is to be estimated (379). Other poorly understood blood/plasma distributional and storage phenomena affecting plasma clearance determination may also be minimized by immediate centrifugation (84, 279, 280).

Additional precautions may also be necessary to ensure that redistribution of drug does not occur during sample processing because of other factors. For example, the erythrocyte/plasma concentration ratio of aldosterone changes by about 3-fold over the temperature range of 4°–37°C (83). A similar temperature-dependent redistribution occurs with cyclosporin; plasma separated at room temperature has up to 50% lower cyclosporin levels than samples separated at 37°C. This process is reversible, since reequilibration occurs within 2 h when the separated blood is incubated at body temperature (385). Whether this type of phenomenon occurs with other drugs is largely unknown, but plasma is almost routinely harvested at room rather than body temperature. Small volumes of heparin solution are frequently injected into the circulation to facilitate the collection of blood samples, and clinical procedures such as hemodialysis and cardiopulmonary bypass require extensive heparinization. Administration of heparin releases lipoprotein lipase from the capillary endothelium and hepatic lipase into the blood. This leads to the hydrolysis of triglycerides and an increase in the circulating concentration of nonesterified fatty acids which can then act as competitive inhibitors of drug binding to albumin. As little as 100 units of intravenous heparin doubled the total free fatty acid plasma level within 5 to 10 min, and the dose-related effect was greater after a meal than in the fasting state (135). A 5-fold increase was observed after 800 units (512). Significant relationships between such heparin-induced changes and a decrease in the in vitro binding of several drugs have been reported (135, 249, 322, 331, 401, 508, 512). In contrast, with warfarin an increase in binding occurs (322, 331, 400). The effect is, to some extent, dependent on the source and particular lot of heparin (322). It is likely, however, that such perturbations in binding are, to a large extent, artifactual

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and related to the continued in vitro formation of free fatty acids by the in vivo liberated lipases subsequent to withdrawal of the blood sample. Thus, when in vivo heparinized plasma was rapidly incubated at 0°C to reduce lipase activity (176), or the enzymes were inactivated with an inhibitor such as paraoxon (71, 174) and protamine (71), the increase in free fatty acids and changes in binding were minimal. Since the B/P concentration ratio is frequently dependent on the unbound fraction of drug in the plasma (equation 8b), the plasma concentration may alter during processing of a blood sample prior to harvesting unless precautions are taken to minimize this type of "heparin effect." Artifacts in the binding of basic drugs to α_1-acid glycoprotein can also occur as a consequence of the collection system used to obtain the blood sample, and this can result in the measured plasma concentration being different from that in vivo. In particular, the tube into which the blood is placed after withdrawal is critical for these types of drugs. Many studies have documented that the "rubber" stoppers of certain commercial collection tubes, Vacutainer in particular, contain a binding inhibitor(s) which may leach out when in contact with blood (380). It is suspected that the plasticizer, tris(2-butoxyethyl)phosphate, is responsible in large part for the phenomenon (45). A similar binding displacement interaction may also occur if the blood is collected through certain types of cannulae (112).

Ideally, if blood clearance is to be determined, then drug concentration in the blood should be directly determined. However, analytical considerations and other factors may preclude this approach, and plasma levels may have to be measured and then "corrected" to the equivalent blood values from knowledge (equation 8) of the B/P concentration ratio. Mass balance consideration indicates that this ratio is related to the hematocrit (H) and the drug concentration in the blood cells (C_{BC}) and plasma (C_P) by equation 8a (453)

$$\frac{B}{P} = (1 - H) + H\frac{C_{BC}}{C_P} \qquad \text{equation 8a}$$

Since partitioning of drug from plasma into the blood cells is usually limited to drug that is not bound to plasma proteins, then equation 8a can be modified to reflect the partition coefficient of drug concentration in the blood cell to that unbound in the plasma (K_P) as reflected by the unbound fraction in plasma ($f_P{}^u$), providing that equilibrium distribution is achieved.

$$\frac{B}{P} = (1 - H) + HK_P f_P{}^u \qquad \text{equation 8b}$$

Thus, the B/P concentration ratio varies between the limits of an infinitely large value, when the drug has an affinity for blood cells greatly exceeding that for plasma, to a value of $(1 - H)$, when the drug is highly bound to plasma proteins or partitions poorly into the formed elements. As previously noted, the measured clearance in the latter situation reflects plasma clearance and plasma flow through the organ (404). Because of the dependence of the plasma drug level on the hematocrit, it is possible for plasma clearance to change without necessarily reflecting alteration in the eliminating efficiency. This appears to be the case with propranolol in renal failure where the reduced hematocrit in such patients results in an increase in the B/P concentration ratio, but the clearance of propranolol from the blood is similar to that in healthy control subjects (509). This confounding factor is infrequently considered in situations where the hematocrit is significantly different from normal.

In many studies, the B/P concentration ratio is determined in vitro; i.e., drug is added to freshly drawn blood and, after allowing sufficient time for equilibrium to be achieved, the concentration in the blood and a harvested plasma sample is determined. Provided that evidence is obtained that distribution equilibrium is actually attained and that hemolysis does not occur during the incubation procedure, then this approach probably provides a valid estimate of the B/P concentration ratio. However, extrapolation to the in vivo situation requires caution, since the in vitro conditions may not accurately reflect those in vivo (258). Moreover, the B/P concentration may not be a constant value, so that the plasma and blood concentration/time curves may not parallel each other. For example, erythrocyte distribution may involve slowly reversible and saturable binding rather than partitioning. This occurs with certain carbonic anhydrase inhibitors, where the dissociation from the enzyme present in erythrocytes is very slow (292). Accordingly, the erythrocyte functions as a peripheral tissue binding site rather than a readily available intravascular source of drug for elimination. Plasma elimination is faster than that from the blood, and urine clearance, for example, reflects plasma not blood flow to the kidney (153, 154, 293). It is far preferable, therefore, to estimate the B/P concentration ratio by direct measurement of the two concentrations following drug administration, and ideally on several occasions during the study period. This approach also reveals time-dependency in the B/P concentration ratio due to factors such as altered plasma binding, the accumulation of metabolites, etc.

In general, serum drug concentrations are considered to be the same as plasma levels, and the two clearance values are similar. Limited data suggest that this might not always be correct. For example, the concentration of chloroquine and its metabolite, desethylchloroquine, was about 2 and 4 times greater, respectively, in human serum compared to plasma (39). These differences result from extensive distribution of the compounds into granulocytes and other white blood cells, as well as platelets, and their release from the latter during the coagulation process. An additional complication of such distribution

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into the formed elements is that the duration and force of centrifugation used for separation affect the concentration in the harvested plasma (399). Heparin per se, and possibly other anticoagulants, may also affect drug binding leading to an alteration in distribution within the blood. For example, the serum binding of warfarin, salicylic acid, and phenytoin in the rat is smaller than that is plasma, while the reverse applied for bilirubin (493). Such poorly studied phenomena may, however, be species as well as drug specific since the difference is not seen in human samples or with all drugs (492, 493).

D. Absolute versus Normalized Clearance

Experimental estimates of clearance always have the units of volume rate (e.g., ml/min); however, attempts are frequently made to normalize the measured value with an anthropomorphic parameter related to size. The rationale for this appears to be an attempt to take into account differences in clearance which simply reflect organ size rather than inherent eliminating ability. While there is merit for and validation of allometric scaling for interspecies comparisons (vide infra), the application of this type of approach within a species is mostly intuitive with little experimental support. With the exception of organ weight, which is only routinely and easily available in isolated perfused organ systems and to a very limited extent in humans (213, 381, 396), the difficulty is the selection of the most appropriate normalizing factor. Unfortunately, there is no firm basis to choose one over another.

Normalization of renal function has become customary to account for the developmental changes that occur from birth to adulthood. Generally, a factor of 1.73 m^2 body surface area is used (296). A recent attempt to confirm the original finding upon which this procedure is based, however, failed, and it was concluded that the definition of a unique normal clearance range for all ages was not realistic based on either body surface area or lean body mass (204).

An increasing number of studies have investigated the effects of obesity on drug disposition with an implicit hope that some normalization factor would emerge that could be useful in determining appropriate drug regimens in such individuals (4). However, a confusing picture has emerged. For drugs that are oxidatively metabolized and have a low hepatic extraction, absolute clearance is minimally altered in obesity with the exception of diazepam (5), ibuprofen (3), prednisolone (309), and thiopental (237). For the latter three drugs, the increase in clearance is highly correlated with total body weight, but the reason for this is unclear. Unknown mechanisms are also involved in the enhanced clearance by glucuronidation of drugs such as lorazepam (6), oxazepam (6), and acetaminophen (1, 6) in obese individuals. In view of the known secondary effects of obesity on cardiac output and organ blood flow (12), it is surprising (vide infra) that the clearance of drugs with high hepatic extraction ratios such as lidocaine (2) and verapamil (7) is similar in obese and normal weight individuals. Finally, it appears that glomerular filtration rate (136) and the renal clearance of drugs are generally increased by about 50% in obese patients, and this is approximately proportional to the change in total body weight.

Undoubtedly, anthropomorphic normalization of clearance values will continue to be used, especially in comparative studies where size may be a factor. In certain instances, this may result in decreased interindividual variability in clearance values. However, the interpretation of the normalized clearance value should be made cautiously, and in certain instances the conclusions drawn from normalized data may be different from those based on the absolute values. There appears to be no substantiated inherent value of normalized versus absolute clearance, or vice-versa. Interindividual variability in all of the determinants of various clearance processes appears to be the rule, and there is no reason to expect that a simple anthropomorphic value such as body size will uniformly and universally take into account such variability.

III. Clearance and Rate of Elimination

Following the termination of any absorption/distribution phase, drug levels of any system decline, and in many instances a large proportion of this latter phase may be described by a monoexponential relationship. This type of concentration/time profile led to the use of a half-life ($t½$), often described further by the term "elimination" or "biological," and a corresponding first-order rate constant ($k = 0.693/t½$). For many years this parameter alone was extensively used to characterize the elimination process, even though its dependence (equation 9) on the drug's volume of distribution (Vd) had been well established at an earlier time (75).

$$t½ = \frac{0.693\ \text{Vd}}{\text{CL}_{TOT}} \qquad \text{equation 9}$$

Subsequently, it was recognized that, if appropriate samples were taken and a sufficiently sensitive assay was available, the concentration/time profile usually declined in a multiphasic fashion, frequently described by a polyexponential relationship. Accordingly, several effective half-lives could be present, depending on the time period under consideration. In many instances the terminal half-life is considered to be more relevant than values at earlier times. However, this choice is highly dependent on the particular pharmacokinetics of the drug and the purpose for which the half-life is being used (34).

Half-life is, therefore, best conceived as a derived expression of the relationship between volume of distribution and total clearance. These are determined by different physiological factors, and the two parameters are independent of each other. The existence of several

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half-lives can be accounted for by time-dependency in the attainment of the final pseudo-equilibrium distribution volume (325). Accordingly, half-life, even in the terminal phase, has little value as an indicator of intrinsic drug elimination. Appreciation of this fact is particularly important in comparative studies such as investigation into the effects of disease states on drug disposition or drug interactions. Many examples exist where distribution and total clearance are both affected in such situations, and often with offsetting results with respect to the half-life. Accordingly, a half-life is best used as an indicator of the time required to attain or decline from a steady-state situation after beginning or stopping a particular rate of drug administration, and as a determinant of peak to trough fluctuations after repetitive dosing at a particular dosing interval.

Another way of appreciating the relationship between total clearance, volume of distribution, and elimination is to express equation 9 in terms of the equivalent first order rate constant (equation 10).

$$k = \frac{CL_{TOT}}{Vd} = \frac{QE}{Vd} \qquad \text{equation 10}$$

This relationship emphasizes that k is a derived constant reflecting the fraction of the volume of distribution which flows to the organ(s) of elimination and is then extracted. Rearrangement of equation 10 provides an expression for total clearance.

$$CL_{TOT} = k\ Vd \qquad \text{equation 11}$$

Equation 11, or the equivalent form of equation 9, therefore, provides a means of estimating CL_{TOT}. However, estimation of the Vd term often requires procedures that are implicit in the more standard approaches (equations 3 and 4) and, therefore, these are more generally used. The relationship does, however, provide a useful link between different multicompartmental models of concentration/time data. Importantly, equation 11 does *not* indicate that total clearance is dependent on a drug's volume of distribution. These two parameters are biologically independent of each other, so that factors that affect Vd should not have any effect on total clearance unless a common determinant is involved, such as the unbound fraction in the plasma. Alternatively, independent changes in the different determinants may occur as, for example, in obesity where alterations in organ perfusion arise along with the increase in body/organ mass.

IV. Clearance and the First-Pass Effect

Xeniobiotic elimination may occur in many different organs and tissues that are anatomically arranged in both parallel and series. Additionally, administration of the xenobiotic can be by a variety of routes relative to the site(s) of elimination. Likewise, the sampling site for determining the concentration term necessary for estimating clearance may be spatially different with respect to both of these factors. Therefore, with the exception of intraarterial administration and sampling, the potential exists that an estimated total clearance (equations 3 and 4) will be an apparent value dependent upon the relative locations of the above. This complicating factor is exemplified in fig. 1 where, for simplicity only, a single organ of elimination is considered. In this system, blood perfuses an organ and then recirculates through a reservoir representing the remainder of the body and the sampling site. In both the blood and the organ, drug exists bound (C^b) to macromolecules and also in an unbound (C^u) form. If drug is administered at site II, i.e., distal to the organ of elimination, and sampling occurs from the reservoir, then the previously classic concept of total clearance is valid (equations 3 and 4). On the other hand, if drug administration is immediately proximal to the organ of elimination (site III), then a fraction of the dose, equivalent to the extraction ratio (E), will be eliminated during the initial transit through the organ. Therefore, only the fraction $(1 - E)$ of the administered dose will be delivered to the sampling site and reservoir (404). Accordingly, total clearance will be overestimated when based on the administered dose, by a factor reflecting the organ's "availability" (F_{organ}), which is equal to $(1 - E)$ or C_{ven}/C_{art} for that organ. This phenomenon is frequently termed "first-pass" or "presystemic" elimination (172, 382, 402).

Dependent upon the sites of administration and sampling, several organs capable of first-pass may be arranged in a series. For example, a drug must be available for absorption (ABS) after oral administration and then may be eliminated by a number of organs arranged in series, e.g., gastrointestinal lumen (GL), gastrointestinal mucosa (GM), liver (L), lung (LU), and blood (B) prior to sampling. In such instances, the oral availability measured at the peripheral sampling site (F_{oral}) may be viewed as the continuous mathematical product of the fractions of drug that escape loss in each successive tissue (80, 187, 382).

$$F_{oral} = F_{ABS} \cdot F_{GL} \cdot F_{GM} \cdot F_{L} \cdot F_{LU} \cdot F_{B} \qquad \text{equation 12}$$

If sequential elimination occurs by two or more organs, then such first-pass effects result in total clearance being less than the sum of the actual individual organ clearances (186). Two simple and alternative approaches have been developed to indicate the potential quantitative significance of such a difference (186). The "partitioned blood flow method" is based on distributing the cardiac output according to the arterial flow rate through individual organs that consistute the sampled, central compartment. Simple mass balance equations can be developed based on the rates of drug delivery and elimination according to the physiological arrangement of the various organs. A somewhat simpler and more versatile approach is based on "poly input" organ clearances. According to this method, the apparent clearance of a particular organ

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($CL_{pin\,organ}$) is given by the product of its extraction ratio (E_{organ}) and its blood flow (Q_i) modified by the continuous product ($\prod$) of the individual availabilities of the organs through which the delivered blood passes before reaching the organ of interest, i.e., $F_{preorgan}$, where $F_{preorgan}$ is the F_{organ} of a given preorgan (equation 13). In both approaches, total clearance is obtained from the sum of the individual partitioned blood flow or polyorgan input clearances.

$$CL_{pin\,organ} = (\sum Q_i \prod F_{preorgan})E_{organ} \qquad \text{equation 13}$$

These types of considerations indicate a number of important relationships (187), some of which are non-intuitive.

1. The apparent total clearance of a drug estimated from either equations 3 or 4 is dependent on the route of administration (equation 14). It is highest after oral administration; second highest when given intraperitoneally with absorption through the intestinal wall; third highest after intraperitoneal administration followed by absorption by the mesentery; fourth highest when given intramuscularly, subcutaneously, and intravenously; and lowest after intraarterial administration.

$$CL_{TOT}^{apparent} = CL_{TOT}/F_{overall} \qquad \text{equation 14}$$

where $F_{overall}$ is the overall ability equivalent to equation 12, by the particular route of administration.

2. Providing that no diffusional barriers exist between the blood and metabolizing enzymes in the lungs and all the administered dose reaches the pulmonary mucosa, the apparent total clearance after inhalation and intravenous administration of the drug will be identical.

3. After oral administration of a drug that is rapidly cleared by several sequential tissues, the apparent total clearance will be greater than the individual organ clearances because only a fraction of the administered dose reaches the arterial side of the circulation and the sampling site. Therefore, alterations or differences in the activity of the metabolizing enzymes (intrinsic clearance) in the first-pass organ(s) may cause a disproportionately greater effect on apparent total clearance than the perturbation in intrinsic clearance would suggest. For example, a 2% decrease in hepatic clearance from 99 to 97% of hepatic blood flow results in a bioavailability of $(1 - E)$ increase of 200% (from 0.01 to 0.03).

4. Regardless of the route of administration, the apparent clearances by the lungs and kidneys are additive, and the first-pass effects of the intestinal lumen, mucosa, and liver will affect both apparent clearances equally.

5. The apparent clearance by the kidney can never exceed its organ blood flow, regardless of the route of administration. Results are similar for any other eliminating organ which has the same relationship between the site of administration and the sampling site. Thus, when clearance by the lungs is absent, apparent total clearance estimated after intravascular administration cannot exceed cardiac output. On the other hand, drug delivery to the lungs is always by way of site III (fig. 1), and apparent total clearance is given by equation 15. Therefore, whenever the pulmonary extraction ratio (E_{Lu}) is greater than 50%, apparent total clearance following intravenous administration will exceed the cardiac output (Q_{co}). This situation may also arise if elimination takes place within the vasculature as occurs with drugs metabolized or degraded within the blood and/or by enzymes located in the vascular endothelium, e.g., nitroglycerin (301).

$$CL_{TOT}^{apparent} = \frac{CL_{TOT}}{F_{Lu}} = \frac{Q_{co}E_{Lu}}{(1 - E_{Lu})} \qquad \text{equation 15}$$

Since CL_{TOT} is considered to be the same regardless of the route of administration, equations 4 and 14 may be combined following equal doses of drug at two sites separated by a first-pass organ(s), so that an estimate of differential or relative availability may be obtained (equation 16).

$$\frac{F_{proximal}}{F_{distal}} = \frac{AUC_{proximal}}{AUC_{distal}} \qquad \text{equation 16}$$

where AUC is the total area under the blood or plasma concentration/time curve after giving drug at a site proximal and then distal to the first-pass organ. Providing linear pharmacokinetics are present, the AUCs may be

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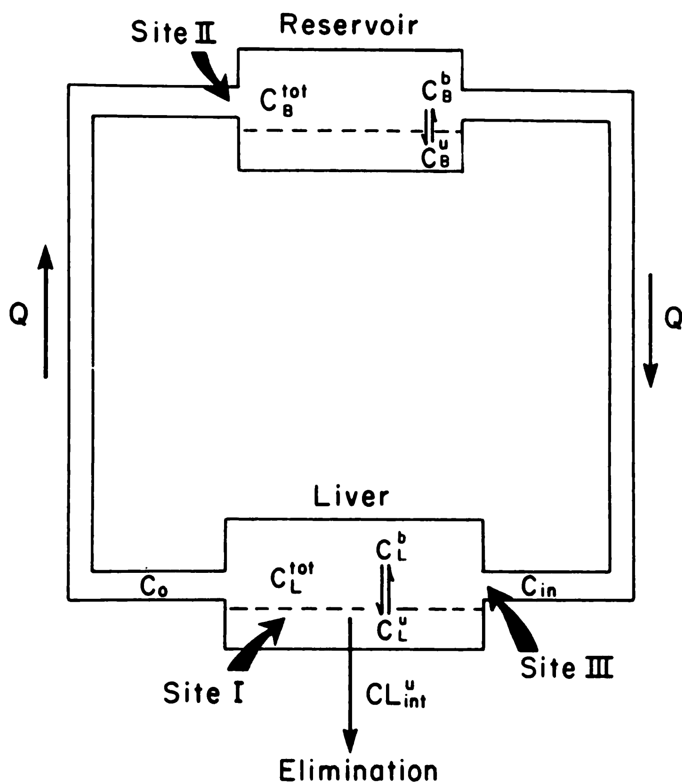

FIG. 1. A simple physiologically based model of hepatic elimination illustrating the importance of the site of drug administration relative to the organ and sampling site. Q, blood flow through the organ; CL_{int}^u, free intrinsic clearance of drug within the organ; and C^{tot}, C^u, and C^b, the concentrations of total unbound and bound drug in the blood (B) and liver (L).

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proportionally adjusted to take into account different doses at the two sites. Frequently, the intravenous route is used for distal administration, in which case the availability estimate is considered to be absolute, since in this case all of the dose reaches the vascular system, and it is assumed that F_{distal} is unity. However, when a pulmonary first-pass effect is present, this is not correct and drug administration into the pulmonary vein or aorta is required to provide an absolute measure of availability (187). It is also possible to use equation 16 to determine relative bioavailability of two different drug preparations administered by the same route.

By far the most extensive application of equation 16 has been in the evaluation of drug bioavailability following oral administration. A voluminous literature exists on the relative availability of two or more formulations of a drug or a drug product's absolute availability. Since such studies are generally directed towards the regulatory aspects of drug product development, the focus is on the overall availability rather than on an assessment of the relative contributions of the individual sequential first-pass effects (equation 12). Consideration of the latter often lead to complex theoretical interrelationships between the various elimination processes (93, 97, 187, 256, 350). Nevertheless, a number of studies have successfully used drug administration at different anatomical sites and other experimental approaches (169) to separate the first-pass effects of individual organs in animals. For example, comparison of the plasma AUCs following oral, intraportal, and intravenous administration of acetylsalicylic acid in the dog indicated that 20 to 30% of an oral dose is metabolized in the gastrointestinal lumen or mucosa during absorption. An additional 22 to 41% of the dose is subsequently removed during the initial passage through the liver, so that the overall oral availability is only 37 to 52% of the administered dose (206). More recently, it has been shown that the very low availability (3%) of an orally administered dose of phenol in the rat is due primarily to gastrointestinal enzymes that extract about 92% of the dose during absorption (80). The liver's contribution to first-pass elimination is unexpectedly small, since its extraction ratio is only about 6% (F_L = 94%), but the lung has a pronounced metabolic function (E_{Lu} = 62%). Subsequent studies demonstrated the dose-dependency of each of the organs' extraction ratios (81) and extended the approach to the hepatic and extrahepatic conjugation of naphthol (310). The low oral bioavailability of isotretinoin in the dog was also shown to be largely due to loss of drug prior to reaching the portal circulation; i.e., degradation occurred in the gastrointestinal tract (101). Similar studies with buprenorphine showed that the mean availabilities relative to the intra-arterial route were 98% for the intravenous route; 54%, intrarectal; 49%, intrahepatoportal; 13%, sublingual; and 9.7%, intraduodenal (68).

The hepatic first-pass effect has also been assessed in vivo by surgically constructing a portacaval shunt so that the venous return from the stomach, small intestine, and colon is delivered into the vena cava, thus bypassing the liver. This model was able to show that, of the 78% first-pass extraction of salicylamide when administered orally in the dog, 36% is due to hepatic elimination, whereas the remaining 42% is accounted for by metabolism in the intestinal wall (197). Similarly, the pre-hepatic and hepatic first-pass effects were about equal following oral administration of pentazocine in this model (175). The analogous situation in patients with various types of extrahepatic shunts has not, however, been extensively exploited except for the finding that propranolol's oral availability was complete in a patient with an end-to-side portacaval anastomosis compared to less than 30% in normal subjects (428). An alternative animal model for investigating the sequential first-pass effects after oral administration involves surgical end-to-end transposition of the portal vein and inferior vena cava in the dog (289). With this preparation, an oral dose passes through the intestinal wall and is delivered to the central vena cava, thus bypassing the liver. Administration into the hind limb is equivalent to giving the drug intraportally, whereas forelimb administration provides the usual intravenous situation. Studies with propranolol (139, 290) confirm the suggestion in man (428) that intestinal metabolism is absent, and the liver is the sole contributor to the overall first-pass effect. Unfortunately, all of these models cause physiological and metabolic changes that affect hepatic function, including drug elimination. Accordingly, extrapolation of the findings to the normal situation may not be simple, even if the problems of interspecies extrapolation are absent.

Because of the potentially large first-pass effect after oral administration, even though all of the drug is absorbed, there has been increased interest in drug delivery by other routes, particularly for drugs whose clinical use is precluded because of this factor. In this regard, there has been renewed interest in the rectal route of administration since the lower hemorrhoidal veins drain directly into the vena cava, bypassing the liver. A number of studies in both animals and man have demonstrated that for drugs with a high hepatic clearance the rectal route of administration can potentially lead to avoidance of the hepatic first-pass effect (128). For example, in the rat the availability of lidocaine was 80 to 100% after rectal administration compared to about 7% following oral dosing (126), and similar findings were obtained with propranolol (127). In man, less impressive findings have been obtained (125, 134) probably related to intrinsically poor absorption from the small surface area of the rectum and the fact that the superior rectal vein drains into the portal system and the hepatic first-pass effect is still present.

Transdermal drug delivery has also received increased attention in part because of the avoidance of hepatic

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first-pass metabolism. The skin, however, possesses a drug metabolizing ability that can be quite high (488) and, therefore, a potential first-pass effect is still present at this site. For example, with topically applied nitroglycerin in the rhesus monkey, this percutaneous first-pass effect was about 20% (489), but additional experimental data on this phenomenon are limited.

The amount and concentration of drug during its initial presentation to a first-pass organ may be considerably higher than when the same dose is given at another site with the opportunity for subsequent extravascular distribution. The ratio of the initial concentrations by the two routes is a function of the rate of drug delivery (absorption), the drug's volume of distribution, and the blood flow rate to the organ (382). After oral administration, for example, the initial concentration entering the liver may be many times greater than after an equivalent intravenous dose if the volume of distribution is large and the rate of absorption is rapid. This may result in saturation of one or more of the individual clearance processes, and the first-pass effect becomes nonlinear with availability being a function of the administered dose and its rate of absorption (382). A number of drugs in man exhibit "hockey-stick" shaped curves when overall oral availability is plotted against administered dose, and it is generally considered that this reflects saturable metabolism during a first-pass effect. An additional factor that may also be involved is that the higher initial blood concentration may decrease the binding of drug to plasma proteins resulting in increased first-pass organ uptake and elimination. This possibility has not, however, been experimentally investigated. A similar situation exists with respect to the potential effects of slow distribution of drug from the plasma into the formed elements of the blood. Following absorption, only a few to several seconds are available for equilibration before the blood reaches the first-pass organ(s). If distribution is still incomplete after this period, the first-pass effect will be greater than expected based on data obtained after equilibration or the measurement of blood clearance after intravascular administration (87).

Because of these types of factors, and also the potential for large intrasubject variability in drug elimination, it is increasingly recognized that the optimal application of equation 16 for the assessment of availability requires simultaneous drug administration by the two routes under consideration. Such concurrent administration ensures that each dose will be identically handled regardless of the kinetics of the clearance processes. An exception to this appears to be in relative oral availability studies, where one drug preparation is administered in a far more rapidly absorbed form, e.g., solution, than the other drug product. If a nonlinear first-pass effect is present, then the initial availability associated mainly with the more rapidly absorbed drug will be lower than at later times when drug from the second preparation passes through the involved organs (419). Obviously the concurrent administration approach requires labelled drug so that the contributions of each dose to the overall blood/plasma concentration/time profile can be differentially assessed. Both radiolabelled (263, 474) and stable-isotope labelled (140, 210, 321) compounds have been successfully used for this purpose.

It is generally assumed that the organ extraction ratio operating on a drug undergoing a first-pass effect is the same as that for systemically delivered drug. While this appears to be valid for the liver and many other organs, it does not necessarily apply to gastrointestinal drug elimination. First-pass metabolism within the lumen would seem unlikely to reoccur once the drug has been absorbed or after administration by other routes. Similarly, there is no a priori reason that mucosal metabolism after luminal exposure should occur to the same extent as when drug is delivered to the intestine by the mesenteric blood supply, of which only 20% is distributed to the mucosa (40). In both of these situations, the fraction of the dose presystemically eliminated is greater than would be predicted based on the systemically determined organ extraction ratio (402). Experimental determination and quantification of such "true" first-pass effects are difficult, but a number of examples support the possibility of the phenomenon. For example, the availability of methyldigoxin in man is about 80%, which is significantly less than that predicted from a calculated splanchnic extraction rate of 8% (212). Similarly, levodopa, which is well absorbed from the gastrointestinal tract, is not eliminated to any extent by the liver, yet it undergoes significant presystemic elimination in man (8) and the dog (113), and evidence exists for metabolism in the intestinal lumen and mucosa (395). Quantitative changes in metabolite patterns may also indicate a "true" first-pass effect; for example, with terbutaline the urinary excretion ratio of the glucuronide metabolite to unchanged drug in the rat was 1:1 after subcutaneous administration, 2:1 after intraperitoneal or intraportal dosing, but 13:1 following oral administration (109, 429). A similar finding was observed with salbutamol in man where the major metabolite constituted 61% of the dose after oral administration compared to the intravenous value of 27% (146). Isoproterenol's metabolism has also been extensively studied for the presence of "true" presystemic elimination, since the pathways of metabolism differ between the gastrointestinal tract, which forms sulfate conjugates, and the liver, which O-methylates the drug. In the dog (108), the fraction of conjugates was greater (50%) after oral than after intravenous or intraportal administration (<10%). Similarly, in man only unchanged isoproterenol, 3-O-methylisoproterenol, and its conjugates were excreted in the urine after intravenous administration, but isoproterenol's sulfate conjugate appeared after oral dosing (105). Direct evidence that this sulfation pathway is used largely after direct

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mucosal exposure and not on systemic recycling of the drug also has been obtained in the canine, isolated perfused gut preparation (170). Pentazocine also undergoes extensive first-pass elimination after oral administration with the production of a glucuronide conjugate. However, no such metabolite was observed following mesenteric infusion of drug in the in situ rabbit jejunum preparation (227).

It is also probable that the pulmonary extraction after inhalation may also be greater than that affecting drug already present in the pulmonary vascular bed. For example, when isoproterenol was introduced into the "vascular" system of the isolated dog lungs, the plasma concentration of unchanged drug, particularly early after administration, was high and little metabolite was formed (69). In contrast, when the drug was introduced intrabronchially, the 3-O-methyl metabolite was the predominant plasma moiety, and its concentration always exceeded that of isoproterenol. However, quantification of this phenomenon has not been reported with any other drug.

V. Clearance Models of the Liver

Estimation of a clearance value provides a measure of the efficiency of the involved removal process(es) and as such has predictive utility, but only for a particular xenobiotic and under conditions of the original determination. Thus, it is possible under linear conditions to estimate steady-state blood concentrations for any given dosage regimen and, along with knowledge of the half-life, the blood concentration/time profile. However, clearance per se cannot predict the quantitative changes in these concentrations when a determining factor such as the activity of the drug metabolizing system is perturbed as, for example, by enzyme induction or inhibition. This is because the clearance estimate is simply a descriptor whose value is determined by the biology of the system; it does not provide in itself any insight into this "black box." Such knowledge requires an understanding of the physiological determinants of the process and, most importantly, how these interrelate with each other in a quantitative fashion, i.e., a model of organ elimination.

The liver has been the focus of much of this modeling in an attempt to develop a unified and general system that would account for the different and apparently contradictory eliminating characteristics of this organ. Subsequently, similar approaches have been applied in a more limited fashion to other eliminating tissues such as the kidney. The critical modeling issue has been the mathematical relationship between the a priori biological determinants of organ uptake and removal, namely drug delivery to the organ as controlled by blood flow rate, reversible binding of drug to blood constituents like albumin and α_1-acid glycoprotein, and the inherent ability of the eliminating process such as the activity of drug metabolizing enzymes. Several different models have been successfully developed which have certain similarities in their general ability to describe and predict broad phenomena, but differ at a finer level of resolution.

A. The Well-stirred or Venous Equilibration Model

In the late 1960s–early 1970s, Bischoff and Dedrick (reviewed in refs. 173 and 291) made a major contribution to pharmacokinetics by developing physiological modeling based on an understanding of actual anatomical and physiological considerations that determine drug disposition, e.g., blood flow, tissue and organ size, membrane transport, clearance rates, etc. Rowland et al. (406) applied this approach to a consideration of hepatic clearance, and their analysis was subsequently refined and extended (498) into what is now commonly referred to as the well-stirred or venous equilibration model of hepatic elimination (357, 498). In this model, the liver is conceived to be a single well-stirred compartment with intimate mixing between portal and hepatic arterial blood in the sinusoids. Also, it is considered that only unbound drug can translocate into the hepatocyte, and the subsequent rate of drug elimination is a function of the concentration of this moiety. The degree of ionization of drugs that are weak electrolytes and the possibility of intratissue pH gradients are rarely considered, although it is theoretically possible to incorporate these factors (41). Accordingly, at steady-state, hepatic clearance may be defined by equation 17 (184, 187).

$$CL_H = \frac{Q f_B{}^u CL_{int}^u CL_{dif}}{CL_{int}^u (f_B{}^u CL_{dif} + Q) + Q CL_{dif}} \qquad \text{equation 17}$$

where Q is liver blood flow, CL_{int}^u is the free intrinsic clearance of unbound drug from liver water, CL_{dif} is the diffusional clearance of total drug between blood and liver tissue, and $f_B{}^u$ is the fraction of unbound drug in the blood. The latter is related to the more commonly determined fraction in plasma, $f_P{}^u$, by the relationship $f_B{}^u = f_P{}^u \div (B/P)$, where B/P is the concentration ratio of blood to plasma (equation 8). Thus, the rate-limiting step in the overall process may either be the rate of diffusion of drug out of the blood into the tissue ($CL_{dif} \ll f_B{}^u CL_{int}^u$) or, if this step is sufficiently rapid, the rate of delivery of drug to the tissue ($CL_{dif} \gg f_B{}^u CL_{int}^u$). Rarely is experimental evidence available to determine which of these alternatives is appropriate. Instead, a particular mechanism is assumed, which in the case of many xenobiotics is the perfusion-limited case. It should be noted, however, that subsequent interpretation may depend upon the correctness of this assumption for any given drug (133, 409). In the case where diffusion is not limiting, the concentration of unbound drug in the emergent blood is assumed to be in equilibrium with that in the liver tissue, and the concentration profile across the organ is constant (fig. 2). Accordingly, equation 17 degenerates into the relationship (equation 18)

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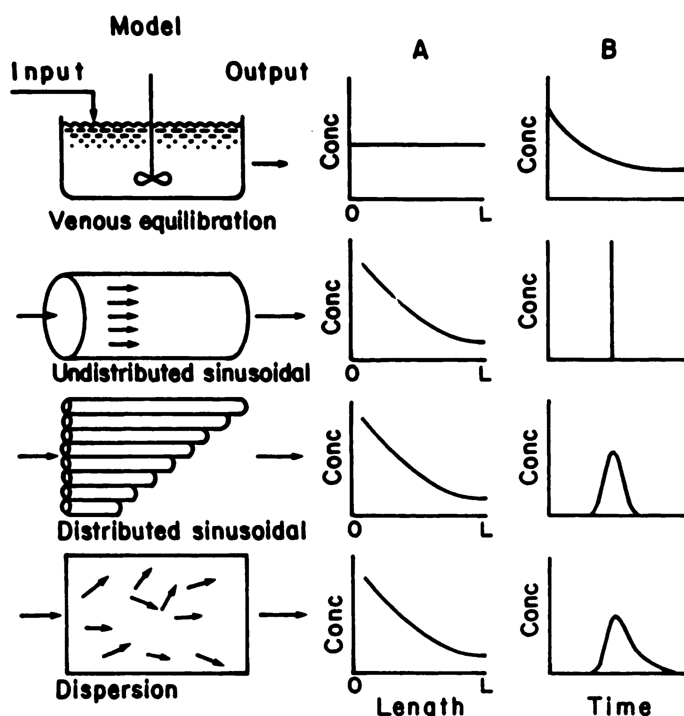

FIG. 2. Schematic representations of various models of hepatic elimination; column *A* shows the concentration/length profiles along the hepatic sinusoid, and column *B* is the output concentration/time profile. Modified with permission from Roberts and Rowland (397).

$$CL_H = Q\left[\frac{f_B{}^u CL_{int}^u}{Q + f_B{}^u CL_{int}^u}\right] \quad \text{equation 18}$$

where the parenthetical term is equivalent to the steady-state hepatic extraction ratio.

The important contribution of equation 18 was the development of the concept of intrinsic clearance, a measure of the liver's inherent ability to eliminate a drug, i.e., administration at site I (fig. 1). Originally, this was conceived in terms of total drug (CL_{int}^{tot}) and indicated the maximal eliminating ability in the absence of flow limitations (406, 498). Subsequently, it was recognized that the free intrinsic clearance (CL_{int}^u) of a drug whose elimination was rate limited by an intracellularly located process, such as biotransformation, could be conceptualized as the clearance rate from liver water, i.e., irreversible removal of unbound drug subsequent to dissociation from binding sites in the blood, transport into the hepatocyte, and equilibration with intracellular binding sites. When rate-limiting steps other than drug metabolism or biliary excretion are present, for example, active transport across membranes, then free intrinsic clearance is less readily visualized, but it still corresponds to the liver's intrinsic clearance of total drug corrected for the degree of binding in the blood ($CL_{int}^{tot} = f_B{}^u CL_{int}^u$ = rate of elimination/$C_L{}^u$, where $C_L{}^u$ is the unbound drug concentration in liver water).

From a biochemical standpoint, free intrinsic clearance is related to the kinetic constants of the overall eliminating process, which in the case of biotransformation (equation 19) are the maximal rate of metabolism (V_{max}) and the concentration at half-maximal velocity (K_m).

$$CL_{int}^u = \sum_{i=1}^{n} \frac{V_{max,i}}{K_{m,i} + C_L{}^u} \quad \text{equation 19}$$

where i different individual enzymes contribute to the overall elimination, and $C_L{}^u$ is assumed to be equal to the unbound level in the emergent blood (357).

In many instances, the driving concentration for metabolism ($C_L{}^u$) is far less than the K_m of the enzyme system, and the kinetics become independent of the drug concentration. Under such linear or first-order conditions, the free intrinsic clearance reaches a constant maximum value equal to the summed ratios of V_{max} to K_m (equation 20) (181).

$$CL_{int}^u = \sum_{i=1}^{n} \frac{V_{max,i}}{K_{m,i}} \quad \text{equation 20}$$

Rearrangement of equation 18 under the assumption of first-order provides an empirical definition of total intrinsic clearance after oral administration of a completely absorbed drug (equation 21).

$$CL_{int}^{tot} = f_B{}^u CL_{int}^u = \frac{CL_H}{1 - E} = \frac{(1 - f_R - f_{EH})\ \text{dose}}{AUC_0} \quad \text{equation 21}$$

where f_R and f_{EH} are the fractions of an intravenous dose which are eliminated unchanged and by metabolism at extrahepatic sites, respectively. Drug excretion is frequently limited to the renal route and, therefore, f_R is readily estimated. Furthermore, if there is no extrahepatic metabolism, then the drug's total intrinsic clearance by the liver is equal to the ratio of the fraction of the orally absorbed dose not excreted to the total area under the blood concentration/time curve. This simplifies even further to dose/AUC_0 for a drug which is totally eliminated by the liver (375, 498). If extrahepatic metabolism and/or extrarenal excretion unknowingly occurs, then the determined CL_{int}^{tot} will be an overestimate of the actual value. Such considerations apply regardless of the absolute value of CL_{int}^{tot}; thus, the approach is valid for all drugs, providing absorption from the gastrointestinal trace is complete. If the latter is not true, then the calculated value will again be an overestimate.

B. The Undistributed Sinusoidal Perfusion or Parallel-Tube Model

At the same time that the venous equilibration model of hepatic elimination was being developed by investigators with a pharmacological interest, gastroenterologists were also attempting to model gross hepatic function from their viewpoint. Starting in 1973, Winkler and coworkers published a number of analyses based on an earlier approach (66, 491) on what has become known as the undistributed sinusoidal perfusion or parallel-tube model (26, 243, 244, 503–505).

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In this model, the liver is conceptualized as a large number of identical cylindrical tubes, representing the sinusoids, that are arranged in parallel and with the hepatocytes, each having the same drug eliminating activity surrounding the cylinder. Drug uptake may be limited by diffusion from the unidirectionally flowing blood into the cell, but there is currently no adequate mathematical description of this that is useful for the practical analysis of bulk concentration changes across the organ (191). Accordingly, diffusion is considered to be rapid, and equilibrium exists between drug within the cylinder and at the eliminating site (metabolizing enzymes). For similar mathematical reasons, the unbound drug concentration at the eliminating site is often considered to be far less than the K_m for the process, so that first-order conditions apply. This is not, however, a prerequisite (26, 243–246, 503–505). Finally, the unbound fraction of drug within the sinusoidal cylinder ($f_B{}^u$) is assumed to be the same as that in the emergent blood and at other sites within the body. Under these conditions and assumptions, a concentration gradient exists across the liver (fig. 2), and hepatic clearance may be defined by equation 22.

$$CL_H = Q(1 - e^{-f_B{}^u CL_{int}^u/Q}) \quad \text{equation 22}$$

Free intrinsic clearance is conceptually the same as in the venous equilibration model, i.e., rate of hepatic removal/$C_L{}^u$; however, its absolute value is different. This is because the drug concentration within the sinusoids decreases from an initial level upon entry into the liver to the final emergent value. Accordingly, the "driving force" for elimination in the sinusoidal perfusion model is considered to be the logarithmic mean of the inlet (C_i) and outlet (C_o) concentration ($\hat{C}$) rather than the level in the emergent blood (26, 243, 244, 503–505), where $\hat{C} = (C_i - C_o)/\ln(C_i/C_o)$. Thus, for any given hepatic clearance value, the free intrinsic clearance has to have a lower value in the sinusoidal perfusion model than in the venous equilibration model or, viewed another way, for any value of free intrinsic clearance, hepatic extraction and clearance will be higher in the case of the sinusoidal perfusion model.

An estimate of intrinsic clearance for the sinusoidal model (29) can only be obtained after giving the drug both orally and intravenously (equation 23); *cf.* equation 21 for the well-stirred model.

$$CL_{int}^{tot} = f_B{}^u CL_{int}^u = \frac{D(1 - f_R - f_{EH})\ln \dfrac{AUC_{iv}}{AUC_0}}{AUC_{iv} - AUC_0} \quad \text{equation 23}$$

The distinction between the model-independent *concept* of free intrinsic clearance as a rate of drug removal from liver water and the model-dependent means of its *estimation* from experimental data has unfortunately caused some confusion (243, 469, 471). But in many experimental sitautions, a precise value of intrinsic clearance or model-dependent differences between estimated values are not particularly important. Nevertheless, this model-dependent characteristic of the estimated value must be recognized.

C. The Distributed Sinusoidal Perfusion Model

An attraction of the sinusoidal perfusion model over the venous equilibration system is its closer resemblance to the known physiology of the liver, particularly with respect to the intrahepatic concentration gradient profile. However, it is still oversimplified and deviates from known hepatic characteristics. This is especially true with regard to the assumption that all of the sinusoids are functionally identical. It is well established, for example, that the capillary transit times of labelled erythrocytes and other markers are quite heterogeneous (189, 192). Similarly, heterogeneous distribution of drug metabolizing enzymes within the liver acinus is well established (20, 107, 200, 389, 457, 475). In order to overcome such ideality and improve model predictions, the simple undistributed sinusoidal perfusion model has been theoretically extended to include a distribution of blood flow and enzyme activity within the liver (fig. 2). Analyses have been presented for the general case of the Michaelis-Menten type elimination (24, 28) and also the limiting case of first-order removal (22, 415) when blood flow and intrinsic clearance are assumed to be normally distributed. Differences in prediction of the undistributed and distributed models are determined by the coefficient of variation of this distribution. An alternative approach (155) utilizes a skewed distribution with the potential to utilize other forms. Attempts have also been described to develop an approach that would permit determination of the density function necessary to generate a known hepatic removal profile from a given input function (57). In general, these distributed models involve complex mathematics and are focused on describing intrahepatic events rather than the more global aspects of hepatic clearance following delivery of a drug to the liver. Because of these factors, their application to analyzing the latter type of experimental data has been limited.

D. The Dispersion Model

A new unifying model of hepatic elimination has recently been developed which is not only consistent with hepatic physiology (fig. 2), but simplifies under limiting conditions to all of the already existing models. This has been termed the dispersion model because of its analogy to non-ideal flow in a packed-bed chemical reactor (397a, 397b). The model is characterized by two main parameters: the efficiency number (R_N) which describes the efficiency of drug removal by the liver and is equivalent under first-order conditions to $f_B{}^u CL_{int}^u/Q$; and an axial dispersion number D_N. The latter is a measure of the dispersion or spread in residence times of drug molecules moving through the liver; the higher the value of D_N, the greater the degree of axial dispersion. The mathematical

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solution for hepatic clearance in the dispersion model is quite complex (equation 24)

$$CL_H = Q\left[1 - \frac{4a}{(1+a)^2\exp[(a-1)/2D_N] - (1-a)^2\exp[-(a+1)/2D_N]}\right] \quad \text{equation 24}$$

where $a = (1 + 4R_N D_N)^{1/2}$. Interestingly, when $D_N \rightarrow \infty$, i.e., when there is extensive axial dispersion, equation 24 devolves to equation 25 which is identical in form to the expression for the venous equilibration model (equation 18).

$$CL_H = \frac{R_N}{1 + R_N} \quad \text{equation 25}$$

Similarly, if $D_N \rightarrow 0$, i.e., axial dispersion is negligible, equation 24 reduces to equation 26, which describes the undistributed sinusoidal perfusion model (equation 22)

$$CL_H = Q(1 - e^{-R_N}) \quad \text{equation 26}$$

Moreover, when D_N is small, the dispersion approximates to a normal distribution, and equation 24 simplifies to

$$CL_H = Q[1 - e^{-(R_N + R_N^2 \cdot D_N)}] \quad \text{equation 27}$$

This equation is equivalent to the form of the distributed model of Bass et al. (28).

Development of the dispersion model addresses some of the difficulties caused by the existence of two different and sometimes contradictory models of hepatic elimination. However, its application to experimental data is limited (398), and its advantages/disadvantages need to be further defined (25).

E. Model Predictions of Hepatic Clearance

The importance of the development of physiologically based models of hepatic elimination was that it provided an opportunity to predict the effects of perturbations in the biological determinants of elimination on clearance and blood concentration/time profiles. Because the interrelationships between these factors are different for the various models, the predictions differ. It is, however, important to recognize the levels at which such discrepancies occur. In global terms, all of the models provide similar predictions with respect to the overall effects based on the relative values of the determinants and perturbations in these. Thus, a change in free intrinsic clearance, or liver blood flow, or binding in the blood has the same general predictive effect regardless of which model is used. This has permitted the definition of broad and useful characteristics of pharmacokinetic behavior. On the other hand, intermodel differences exist in the precise value of any prediction. However, such differences only become significant and experimentally determinable when considering drugs which are very efficiently cleared by the liver, i.e., high total intrinsic clearance.

1. Intrinsic clearance relationships. Intrinsic clearance is a measure of the inherent ability of the hepatocytes to irreversibly remove a drug in terms of either unbound or total concentrations. Importantly, its relationship to the liver's eliminating capacity is nonlinear, and the contribution to the organ's overall function is dependent upon its value relative to that of liver blood flow (fig. 3). Accordingly, two extreme characteristics exist. When total intrinsic clearance is small relative to liver blood flow, then hepatic extraction and clearance are low and primarily reflect the removal process, for example, drug metabolizing activity. Thus, a change in intrinsic clearance caused by enzyme induction/inhibition or a difference related to interindividual variability is expressed as an almost proportional change in organ elimination. On the other hand, if the drug metabolizing activity is high so that $CL_{int}^{tot} \gg Q$, then hepatic extraction and clearance are also high and relatively insensitive to changes in intrinsic clearance. This is because drug delivery to the hepatocytes by liver blood flow, rather than the eliminating activity of the hepatocytes, is essentially the rate-limiting factor for the overall removal process. Thus, drugs may be classified by whether their hepatic clearance is "enzyme-limited" ($E < 0.3$) or "flow-limited" ($E > 0.7$), with an intermediate class where both factors are involved (26, 498, 504). Since availability is inversely related to the extraction ratio, it follows that the first-pass effect is also a reflection of total intrinsic clearance. All drugs will exhibit some first-pass elimination, but this will only be significant and important for those with high total intrinsic clearance values.

Differences in blood concentration/time profiles after intravenous and oral administration as well as at different values of total intrinsic clearance can, therefore, be examined. Importantly, such differences manifest themselves in characteristic fashions depending on whether the drug has a low or high total intrinsic clearance relative to liver blood flow (fig. 4). For example, when total intrinsic clearance equivalent to a hepatic extraction ratio of 0.1 is increased by 2-fold, as might occur

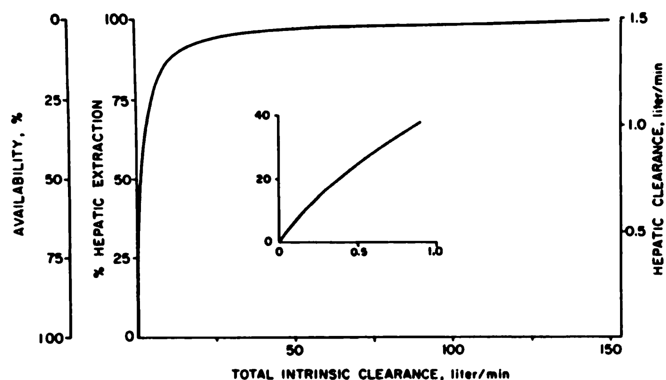

FIG. 3. The relationship between total intrinsic clearance and hepatic clearance, extraction, and availability according to the venous equilibration model, assuming a liver blood flow of 1.5 liters/min. The *inset* indicates on an expanded scale the relationship at low values of CL_{int}^{tot}. Modified with permission from Wilkinson and Shand (498).

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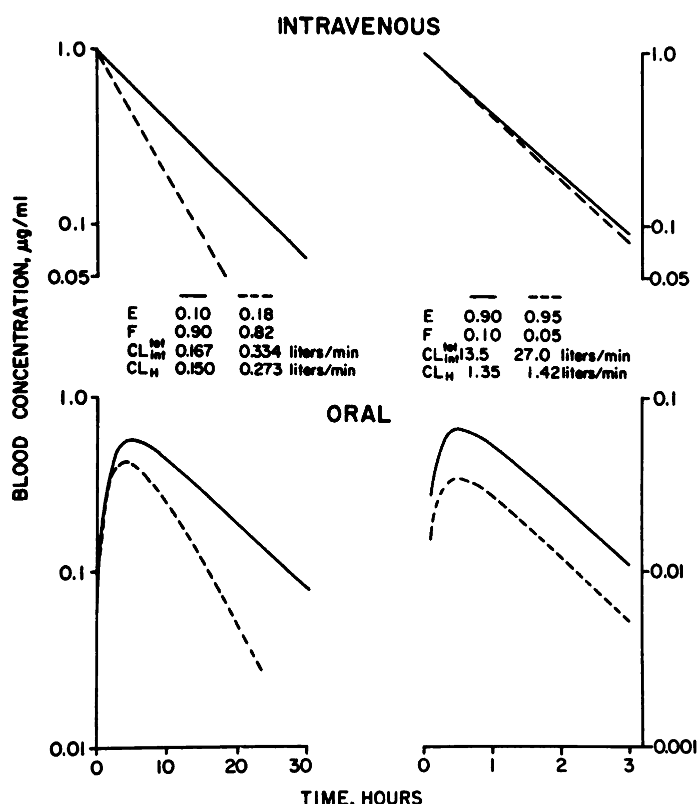

FIG. 4. The effects according to the venous equilibration model of increasing hepatic total intrinsic clearance (CL_{int}^{tot}) on the total blood concentration/time curves after intravenous (*top*) and oral (*bottom*) administration of equal doses of two totally metabolized drugs. The *left panels* refer to a drug with an initial CL_{int}^{tot} equivalent to an extraction ratio of 0.1 at a liver blood flow of 1.5 liters/min, and the *right panels* to one with an initial extraction of 0.9. Essentially similar profiles would be predicted by the other models of hepatic elimination. Modified with permission from Wilkinson and Shand (498).

during enzyme induction, then the major effect is an increase in the efficiency of hepatic extraction by a similar order of magnitude ($E = 0.18$). Systemic clearance is, therefore, altered, and the elimination half-life is approximately halved (fig. 4, *left*). Although the change in extraction is large, the relative effect on oral bioavailability ($1 - E$) is small and, therefore, doubling CL_{int}^{tot} only decreases the systemic availability after oral administration from 90% to 82%. Accordingly, the reduction in AUC_0 is predominantly due to the shortening of the elimination half-life. On the other hand, when CL_{int}^{tot} is such that the initial extraction ratio is 0.9, completely different alterations in pharmacokinetics are elicited by a doubling of CL_{int}^{tot} (fig. 4, *right*). The extraction is increased by only a small factor ($E = 0.95$); consequently, there is minimal alteration in clearance or half-life. However, this change increases even further the already pronounced presystemic elimination after oral administration, and systemic availability falls by one-half (10.0% to 5%) as indicated by the large decrease in peak blood concentration. Accordingly, for a highly extracted drug, the reduction in AUC_0 is mainly caused by a similar reduction in the fraction of the dose of drug reaching systemic circulation.

The pharmacokinetic characteristics typical of a low extraction compound would appear to be applicable to a large number of xenobiotics. In fact, such behavior was once the common dogma, hence the widespread, but incorrect, use of elimination half-life as an indicator of eliminating capacity. This situation arose because few high extraction drugs had been developed or their pharmacokinetics fully investigated prior to the 1970s. There are, therefore, many reports of high oral bioavailability and, when absorption is rapid, almost identical concentration curves after both intravenous and oral dosing, for example, antipyrine, warfarin, and tolbutamide (17). With such compounds metabolic drug interactions, interindividual differences in metabolism, and the effects of disease states such as liver dysfunction are all reflected by changes in elimination half-life (103, 460, 461, 500). In the last 10 yr, however, the total clearance of an increasing number of drugs which are only eliminated by the liver has been shown to approach hepatic blood flow. Accordingly, the oral bioavailability is low even when gastrointestinal absorption is complete, and AUC_0 exhibits considerable intersubject variability reflective of differences in CL_{int}^{tot} (382). There is also now reasonable documentation of the lack of effect of enzyme induction or inhibition on the elimination half-life for this type of drug as contrasted to the profound changes in AUC_0. For example, stimulation of drug metabolizing activity by chronic phenytoin treatment substantially decreased the peak plasma levels and AUC_0 of metyrapone given orally to patients, but had no effect on systemic clearance or elimination half-life after intravenous infusion (304). Similar effects of daily pentobarbital administration on the blood concentration/time profile of alprenolol (13) and chronic antiepileptic therapy on lidocaine disposition (376) in man have also been reported. The inhibition of 6-mercaptopurine metabolism by allopurinol in both man and monkey was characterized by analogous changes, i.e., 300 to 500% increases in AUC_0, but no effect on the pharmacokinetics after intravenous administration (524). Likewise, the effects of chlorpromazine pretreatment of the disposition of propranolol were much more pronounced on AUC_0 than elimination half-life (462).

Because intrinsic clearance differences are always manifest after oral administration, whereas this is not the case after intravenous dosing (fig. 4), the former route is now often used to quantify such changes caused by factors such as drug-drug interactions or disease states. However, the potential pitfalls of this approach are not always appreciated. First, AUC_0 not only reflects hepatic elimination, but also that by any other first-pass organ such as the gastrointestinal tract, both lumen and epithelium, and lung (equation 12). Unless the contributions of these other organs to the first-pass effect are

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negligible, the relationship between AUC_0 and hepatic intrinsic clearance is not unequivocal. Thus, the plasma concentration/time profile of phenacetin is profoundly affected by pretreatment with 3-methylcholanthrene in rats (485). While enhanced hepatic metabolism is undoubtedly contributory, induction also occurs with enzymes of the gut flora, the intestinal epithelium, and possibly the lung (93, 255). In fact, using different routes of administration and applying equation 16, it was shown that 3-methylcholanthrene pretreatment doubled the hepatic extraction ratio from 0.13 to 0.28, but increased the intestinal extraction ratio from essentially zero to 0.54 (255). A similar situation probably occurs in man as well following pretreatment with charcoal-broiled beef (104) and cruciferous vegetables (365). Not only do such data emphasize the need to account for all sites of presystemic elimination when interpreting AUC_0, but they also indicate that the relative contribution of such processes may not be the same in control and experimental studies.

Interpretation of AUC_0 estimates is often limited to total drug concentrations and, therefore, CL_{int}^{tot} so that any effects of $f_B{}^u$ are implicitly included. Thus, when CL_{int}^{u} is unchanged, a perturbation in plasma binding leads to an alteration in the AUC_0 of total drug. Hence, in renal failure patients, the plasma concentrations of propranolol tend to be lower than in control subjects because of reduced binding, but the drug metabolizing ability of both groups (CL_{int}^{u}) is similar (509). In this case, disposition is further complicated by the effect of a decreased hematocrit in the patients which, combined with the binding change, alters the blood/plasma concentration ratio, and blood concentrations of propranolol are the same in both groups. In the same fashion, the almost 2-fold higher plasma concentrations, but similar elimination half-life, of diphenhydramine in Orientals compared to Caucasians can be explained by a difference in plasma binding of similar magnitude. The metabolism of diphenhydramine as estimated by its free intrinsic clearance is the same in both racial groups, as is the distribution of unbound drug (434).

It is also important to recognize that AUC_0 may also be altered by a change in liver blood flow if the drug's hepatic elimination is according to the undistributed sinusoidal perfusion model (equation 23). This is in contradistinction to the situation with the venous equilibration model (equation 21) which predicts that AUC_0 and CL_{int}^{tot} are independent of this determinant (357). Examples of such discrepancies have not, however, been reported.

Finally, it is essential in interpreting AUC_0 to have knowledge of the fraction of the administered oral dose that is actually absorbed from the gastrointestinal tract. Such information is not always available, and assumption of a particular value and/or its constancy between experimental protocols often limits the findings.

2. Blood flow relationships. With drugs having a small total intrinsic clearance relative to liver blood flow, the effects of the latter on hepatic extraction/clearance and the blood concentration/time profile are negligible regardless of the route of administration (fig. 5). However, when $CL_{int}^{u} \gg Q$, then the limiting step in the removal process is the rate of delivery of drug to the hepatocyte, and hepatic elimination and half-life become dependent on liver blood flow (fig. 5). Between these extremes, partial dependency is present dependent upon the actual extraction ratio. In the case of an orally administered drug, the venous equilibration model predicts that the change in the rate of elimination of a high clearance drug is offset by that in its bioavailability, so that AUC_0 is independent of liver blood flow (357, 498). On the other hand, if elimination follows the undistributed sinusoidal perfusion model, AUC_0 increases when liver blood flow falls relative to its normal value of 1 to 2 ml/min/g liver (194) and decreases with enhanced flow (357). This model discrepancy is most pronounced when $E > 0.9$ and manifests itself as a difference in peak blood levels.

Flow-dependent clearance of highly extracted xenobiotics, such as dyes like sulfobromophthalein, rose ben-

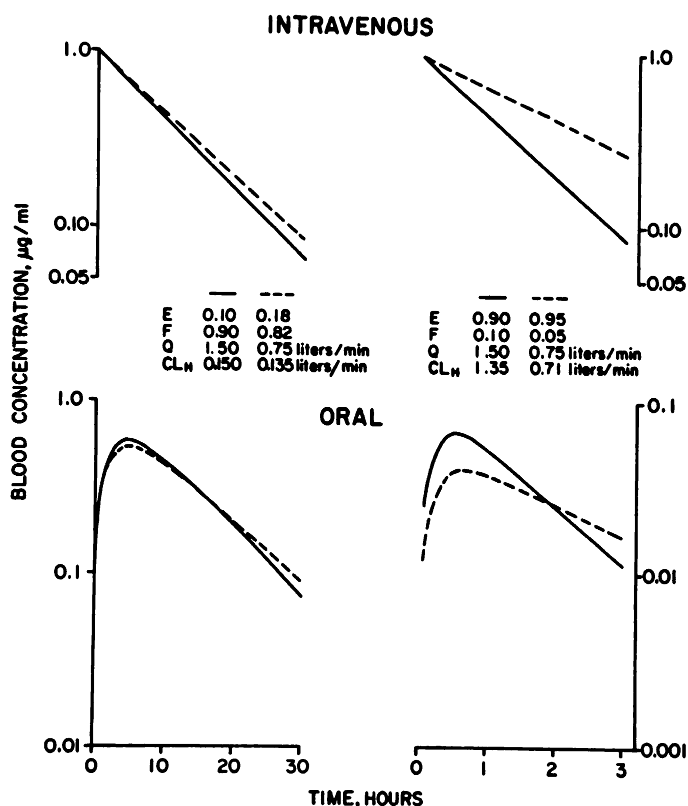

FIG. 5. The effects according to the venous equilibration model of decreasing liver blood flow on the total blood concentration/time curves after intravenous (*upper panels*) and oral administration (*lower panels*) of equal doses of two totally metabolized drugs. The *left panels* show a drug with a total intrinsic clearance equivalent to an extraction ratio of 0.1 when blood flow equals 1.5 liters/min, and the *right panels* to a drug with a CL_{int}^{tot} value equivalent to an extraction ratio of 0.9. Essentially similar profiles would be predicted by the other models of hepatic elimination. Reproduced with permission from Wilkinson and Shand (498).

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gal, and indocyanine green, and of certain colloids has long been recognized and provides the basis for their use as an indirect measurement of liver blood flow in man and other intact animals (168, 337). However, an appreciation that this factor could play an important role in the disposition of drugs did not become apparent until the early 1970s (329, 496). While resting liver blood flow is about 25 to 33% of cardiac output, and 75 to 80% is portal in origin; a number of physiological and pathological conditions as well as drugs and hormones can alter these values (392, 393). In addition to such reactivity to a variety of stimuli, the splanchnic circulation is also one of the major vascular beds used to meet the demands of other parts of the body. Thus, total liver blood flow is very variable within about a 4-fold range, and this is often amplified by disease states.

A change in posture from supine to upright decreases cardiac output and increases total peripheral resistance so that liver blood flow is reduced by 30 to 40% (115, 122). Surprisingly few studies have, however, investigated the possible effects of such a change on hepatic clearance and drug disposition despite its obvious relevance to bed rest versus ambulation by subjects or patients under study (284). In one such investigation (46), a 2-fold difference existed in the systemic clearance of aldosterone between upright and supine postures, and adaptation between these positions took considerable time. Also, smaller interindividual variability in the clearance estimate was obtained in the upright posture relative to an overnight supine state. The maximum plasma concentration of nitroglycerin after sublingual administration was 3 to 4 times higher in subjects who were lying down compared to sitting (119). On the other hand, prolonged recumbency for 7 days had no effect on the systemic clearance of lidocaine (242). As would be predicted from its low hepatic extraction ratio, bed rest produced only very modest changes in the total clearance of antipyrine (143). Additional attention probably needs to be addressed to this area, particularly with respect to drugs with high hepatic clearances.

Rather more information is available on the effects of acute exercise and thermal stress on hepatic elimination. Both factors may produce large increases in cardiac output, but redistribution of blood leads to a significant reduction in liver blood flow. For example, both stresses led to a 40 to 60% reduction in the clearance of indocyanine green in man, along with a doubling of its elimination half-life (122, 403, 445). Not surprisingly, the steady-state plasma concentrations of lidocaine, a drug with a high hepatic extraction, were increased by strenuous exercise (446). On the other hand, and as expected for a drug with a low hepatic extraction, the clearance of antipyrine was unaffected by either exercise or normal stress (445). Similarly, the clearance of diazepam (260) and amobarbital (19) was not altered by acute exercise. In contrast, chronic exercise appears to induce hepatic metabolism as assessed by the clearance of aminopyrine (44, 137), antipyrine (44, 137, 165), and spironolactone (165); effects on the disposition of high clearance drugs are presently unknown.

Ingestion of food is known to affect oral drug availability (305, 486). In many cases, this arises because of gastrointestinal factors such as altered stomach emptying and/or a direct interaction between drug and food constituents resulting in a change in absorption. However, there is considerable evidence that presystemic elimination by the liver of high intrinsic clearance drugs may be affected by food. For example, concomitant ingestion of food results in a 40 to 50% increase in mean AUC_0 of hydralazine, labetalol, metoprolol, and propranolol (306). Since these drugs are completely absorbed in the fasting state, the cause of the alteration is probably subsequent to this step. Interestingly, the food effect is not observed following administration of slow release preparations of these drugs (306). Studies on the putative mechanisms of such increased oral bioavailability have largely focused on a possible role of the well-established increase in splanchnic blood flow after a meal, which is sufficient to affect the systemic clearance of highly extracted drugs such as lidocaine (144). Computer simulations suggested that a transient increase in liver blood flow during the drug absorption phase which returns toward normal within a few hours could account for the food effect (298). The fact that the vasodilator, hydralazine, which is known to enhance splanchnic blood flow, also enhances propranolol oral bioavailability (299, 421) is consistent with this hypothesis. However, subsequent studies have demonstrated that, although certain types of food can lead to a variable and transitory increase in liver blood flow, this is not of sufficient magnitude to account for the observed change in propranolol's oral bioavailability (441–443). Other factors related to hepatic uptake and elimination appear to be involved, and a similar situation also appears to occur in the interaction with vasodilators (111, 441).

Whenever cardiac output is pathologically decreased, liver blood flow is reduced to a similar to slightly greater extent. In such situations, the systemic clearance of drugs with high hepatic extractions is likely to be impaired (37, 501). For example, liver blood flow and cardiac index in patients with cardiac failure were directly correlated with one another, and each was inversely related to steady-state arterial blood concentrations of lidocaine (437). Subsequent studies confirmed that lidocaine's systemic clearance is reduced by about 40 to 60% in congestive heart failure (437, 450, 451, 525), and this is the basis of lidocaine's toxicity when usual dosages are administered to such patients. Interestingly, lidocaine's distribution is reduced to a similar degree in this disease state, and consequently, no significant change is observed in the drug's elimination half-life. Because of the dependency of lidocaine's systemic clearance on liver blood flow, it

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was suggested that its value in individual patients with congestive heart failure could be readily predicted by determining indocyanine green clearance (525). However, this potentially valuable approach has not been confirmed (32). A similar effect of heart failure on aldosterone clearance has also been reported (79). While altered hemodynamics undoubtedly contributes directly to the impaired systemic clearance of drugs with a high hepatic extraction, it is also possible that a reduction in intrinsic clearance is also involved secondary to hepatic ischemia. This might be a factor in the altered plasma concentration/time profiles of certain drugs administered orally to patients with congestive heart failure (31, 501). Unfortunately, studies of this possibility are limited. A similar situation exists with the effects of myocardial infarction in the absence of cardiac failure on hepatic clearance (501). However, studies with indocyanine green and lidocaine would suggest that liver blood flow and clearance are not dissimilar from those in normal subjects (32, 525).

Circulatory collapse with shock is another situation where liver blood flow is compromised, and this can affect the hepatic elimination of high intrinsic clearance drugs. For example, the elimination half-life of indocyanine green was prolonged 2- to 6-fold in patients with shock of varying etiology (394). It has also been noted that, in patients with idiopathic orthostatic hypotension, the reduction in lidocaine's systemic clearance is related to the decrease in liver blood flow as estimated by indocyanine clearance, and both fall in proportion to the degree of hypotension (148). Generally, however, it is difficult to attribute any reduced clearance to altered perfusion per se rather than the reduced oxygen supply to the liver, which would lead to an impaired CL_{int}^{tot}. The latter was suggested to explain the effect of hemorrhage on the rate of hexobarbital metabolism in the dog (118), and the decrease in lidocaine's systemic clearance in the rhesus monkey following 30% hemorrhage was greater than could be explained by the fall in liver blood flow alone (36).

Many drugs can either reduce or increase liver blood flow, but not until the mid-1970s was it recognized that this could lead to a hemodynamic interaction when a second drug with a high hepatic extraction ratio was present (328). For example, when *dl*-propranolol was administered simultaneously with lidocaine, the systemic clearance of the latter in the dog was reduced to about the same extent as the 20 to 25% fall in liver blood flow (64). In contrast, the *dl*-propranolol-induced change in the systemic clearance of oxyphenbutazone was much less as would be expected from the hepatic extraction ratio of 0.1 to 0.2 (62). Importantly, *d*-propranolol, which is essentially without β-adrenergic blocking activity (326), failed to alter the elimination of either lidocaine or oxyphenbutazone. Similar studies with norepinephrine in the rhesus monkey also supported the role of decreased drug delivery rate in the impaired clearance of lidocaine when both drugs are administered together (36). Subsequently, a similar hemodynamic interaction between lidocaine and *dl*-propranolol and other β-adrenergic blockers was shown to occur in man (106, 335, 440). A somewhat novel example of a hemodynamic interaction occurs with propranolol itself. Both enantiomers of this drug have similar high clearances in the isolated perfused rat liver when perfusate flow is kept constant (60). However, in vivo only the *l*-enantiomer affects cardiac output and liver blood flow (326); accordingly, the pharmacological effect of the *l*-isomer affects its own clearance and also that of the *d*-enantiomer. Thus, the systemic clearance of *dl*-propranolol in the monkey is about 25% less than that of *d*-propranolol (327). This interaction probably also accounts in part for the shorter half-life (171) and larger clearance (343) of the *d*-enantiomer compared to that of racemic drug in man. A similar self-induced hemodynamic effect on drug disposition through alterations in liver blood flow also occurs with certain of the calcium-channel antagonists such as nifedipine and verapamil. Increasing the steady-state plasma concentration of these drugs in the dog progressively leads to a reduction in cardiac output and liver plasma flow which results in an up to 50% decrease in their systemic clearance (205). A similar situation may occur in man in that the elimination half-life of verapamil after chronic administration is significantly longer than after a single dose (423, 426), a change that is associated with a reduction in liver blood flow (308). However, these are not consistent findings (142, 422), and the situation is compounded by pronounced stereoselectivity of this drug's disposition (141, 464) as well as the possibility of nonlinear intrinsic clearance (468). The dose-dependent, nonlinear disposition of 4-aminoantipyrine in rabbits has also been explained by reductions in renal and hepatic blood flows caused by the drug itself (311).

All commonly used inhalational and other general anesthetics depress cardiac function, and this may result in a significant dose-related decrease in liver blood flow (30, 324). This possibility has long been qualitatively recognized as a putative mechanism, along with perturbations in drug metabolism and/or distribution, to explain the altered disposition of high clearance drugs in anesthetized patients. For example, halothane markedly reduces the systemic clearance of lidocaine in the dog compared to nitrous oxide (73) and pentobarbital (56) treated animals, which alter liver blood flow to a lesser extent. This relative effect does not, however, preclude a halothane-induced inhibition of lidocaine's metabolism. A similar impairment of lidocaine clearance by halothane is also observed in man (38). The relative contributions of altered liver blood flow and intrinsic clearance have not, however, been extensively investigated except for a halothane-propranolol interaction in the dog (390). Hal-

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othane anesthesia produced a 40% decrease in the systemic clearance of propranolol along with a 26% fall in apparent liver blood flow measured pharmacokinetically, i.e., $\hat{Q}$ (equation 28). The latter was not statistically significant, and its contribution to the reduced hepatic extraction was far outweighed by a 60% reduction in total intrinsic clearance. The perioperative period involves a myriad of often rapidly changing physiological effects and responses, of which anesthesia is only one factor. Nevertheless, additional studies of anesthesia-induced changes in drug disposition and effects, especially the involved mechanisms, including hemodynamic changes, would appear warranted. Of particular interest would be elucidation of any dose-response relationship in the changes, the comparative behavior of different anesthetic regimens, and the differential sensitivity of different types of drugs based on pharmacokinetic and biotransformation characteristics.

A limited number of drugs are capable of increasing liver blood flow and, therefore, enhancing the clearance of another drug with high hepatic extraction ratio. For example, glucagon causes a dose-related increase in splanchnic blood flow in the monkey and increases the systemic clearance of *d*-propranolol in proportion to this change (63). Likewise, isoproterenol has been shown to reduce steady-state plasma concentrations and enhance lidocaine's systemic clearance (36). Chronic phenobarbital pretreatment induces the activity of many drug metabolizing enzymes in the liver, but it also increases liver blood flow in proportion to the increase in hepatic volume in the rat (63, 330, 338, 339) and rhesus monkey (65), but not in the guinea pig (517) and probably not in man (396). Enhanced elimination by phenobarbital of a drug with a high hepatic extraction ratio may, therefore, involve two mechanisms. This possibility was elegantly demonstrated by the phenobarbital-indocyanine green interaction in the rat, which also illustrated the importance of the total intrinsic clearance/liver blood flow relationship (295). After administration of a high dose (50 mg/kg) of indocyanine green, its hepatic extraction was small, and the 40% increase in systemic clearance following phenobarbital pretreatment was almost completely due to an increase in total intrinsic clearance. A similar degree of enhanced elimination was also seen after giving a smaller dose of dye (1 mg/kg) when hepatic extraction was close to 50%, but in this case the phenobarbital-induced increased total intrinsic clearance and liver blood flow contributed almost equally. In the case of a *d*-propranolol-phenobarbital interaction in the monkey, only 43% of the increase in systemic clearance of the β-adrenergic blocker was accountable for by increased drug metabolizing enzyme activity, while 57% of the change resulted from an increase in liver blood flow (65). Again, essentially no hemodynamic contribution was present in the increased elimination of a poorly extracted drug, in this case, antipyrine.

Both the venous equilibration (498) and the undistributed sinusoidal perfusion (29) models indicate that, for a drug which is completely absorbed and only metabolized by the liver, an estimate of liver blood flow ($\hat{Q}$) may be obtained after administering the drug by both the intravenous and oral routes (equation 28).

$$\hat{Q} = \frac{(1 - f_R - f_{EH})}{\dfrac{\mathrm{AUC_{iv}}}{D_{iv}} - \dfrac{\mathrm{AUC_o}}{D_o}} \qquad \text{equation 28}$$

So that identical physiological conditions are present after both routes of administration, it is best that the intravenous and oral doses be given simultaneously, although a sequential design has been utilized to a more limited extent. Such concomitant administration requires differentially labelled forms of the drug so that the separate blood concentration/time profile from each route can be followed. Both radiolabelled and stable-labelled compounds have been used, and such use presumes that no isotope effect be present in the various processes of disposition. In addition to requiring that all of the oral dose be absorbed, or in the case of intraperitoneal injection that absorption does not occur through the abdominal wall directly into the systemic circulation, equation 28 also requires that metabolism in the intestinal mucosa be absent (349). It has also been noted that the error in the estimation of $\hat{Q}$ increases as the hepatic extraction decreases, and therefore, equation 28 is best applied with drugs having high hepatic clearances (436).

The validity of this model-independent and relatively noninvasive approach to estimating liver blood flow to the functioning hepatocytes was first established in the isolated perfused rat liver system where flow could be controlled (427). The approach's feasibility was then evaluated in normal subjects (263), and subsequently it has been applied to evaluate the putative effects of various factors on liver blood flow in man, including chronic dosing with propranolol (506), aging (210, 463), chronic hepatitis (222), renal failure (509), thyrotoxicosis (487), and various drug interactions (149, 390, 462). The drugs used in these studies, predominantly propranolol but also lidocaine and meperidine, appear to possess the necessary disposition characteristics so that equation 28 is valid, and they are essentially metabolized completely so that the fraction of the drug eliminated by the nonhepatic routes ($f_R + f_{EH}$) can be ignored. In general, the values of liver blood flow obtained by the pharmacokinetic approach are consistent with those determined by independent procedures using, for example, indocyanine green. However, formal comparisons between the techniques have been extremely limited. In this regard, it is important to recognize that estimation of apparent liver blood flow by equation 28 provides a net or time-averaged value for the period over which blood samples are collected. Furthermore, it reflects the flow rate as affected by the drug used in the measurement, which may not be

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devoid of hemodynamic effects, e.g., propranolol. This is in contrast with other classical means of estimating liver blood flow (168, 337), which essentially determine the instantaneous flow rate since the measurement period requires only a few minutes. Given this difference, it would not be surprising if the pharmacokinetic approach provides a somewhat different estimate than other techniques depending upon the conditions under which the determinations are made.

Application of equation 28 gives an estimate of liver blood flow to functioning hepatocytes which should correspond to total liver blood flow (Q_H) providing that the hepatic vasculature is normal. If, however, hepatic shunts are present, as occurs in cirrhosis, then $\hat{Q}$ is a biased estimate since only a fraction (f_H) of the orally administered dose is available to the functioning cells of the liver (equation 29).

$$\hat{Q} = \frac{Q_H}{f_H} = \frac{Q_H}{(1 - f_{ES})} \qquad \text{equation 29}$$

It has, therefore, been suggested (424) that the fractional extrahepatic shunting (f_{ES}), exclusive of any splenic contribution, could be determined by combining the physiological approach with a more conventional technique to measure Q_H based on hepatic venous catheterization (168, 337). However, studies to evaluate this approach have yet to be reported.

Considerably more attention has been directed towards intrahepatic shunts. This has arisen because of the observation in patients with chronic liver disease that the systemic clearances of drugs which have high total intrinsic clearance values in normal subjects, such as propranolol (507), indocyanine green (59), galactose (16), lidocaine (164), and lorcainide (261), are positively correlated with that of antipyrine, which has a small total intrinsic clearance, despite the relative preservation of total liver blood flow (61). Such correlations are unexpected since the rate-limiting determinants of systemic clearance in normal subjects are different for the two classes of drug. In theory, it is possible that these observations could arise because of an association between liver blood flow and total intrinsic clearance, so that cirrhosis produces a proportional decrement in both. In this case the hepatic extraction ratio should be the same in normal subjects and patients with cirrhosis, but numerous studies with a variety of xenobiotics have demonstrated that this is not so. The assumption of the presence of functional intrahepatic shunts, which have been anatomically demonstrated (383), provides an operational model, termed the "intact hepatocyte hypothesis," to account for these conflicting findings (61, 510).

The actual hepatic clearance of the cirrhotic liver in the presence of intrahepatic shunts is given by equation 30:

$$Q_H E_{(actual)} = Q_H f_M E_{(true)} \qquad \text{equation 30}$$

where $E_{(actual)}$ is the measured hepatic extraction ratio, $E_{(true)}$ is the extraction ratio of functional tissue, and f_M is the fraction of blood flowing around it. Unfortunately, neither $E_{(true)}$ or f_M can be directly measured. The intact hepatocyte hypothesis assumes, however, that even in cirrhosis $E_{(true)}$ is normal, so that the reduced extraction ratio is a result of intrahepatic shunts. That is, the cirrhotic liver is visualized has having a reduced mass of normally functioning and perfused tissue. This approach has been applied in two different fashions to data obtained with propranolol. In the first instance, Q_H was directly measured via hepatic vein catheterization, and propranolol's hepatic extraction in a group of patients with hepatic fibrosis was assumed to be equivalent to that in normal subjects, i.e., $E_{(true)}$ (377). This led to the interpretation that the impaired clearance of propranolol in cirrhotics was primarily due to an almost 80% reduction in total intrinsic clearance along with an almost 40% decrease in total liver blood flow, of which only 60% flowed to functioning hepatocytes, i.e., a 40% intrahepatic shunt (58). In an alternative approach the need for hepatic vein catheterization was obviated by assuming that the change in total intrinsic clearance of a low clearance drug, such as antipyrine, was proportional to the change in liver blood flow to functioning hepatocytes, thus providing a measure of f_M (58). Using the data of Wood et al. (507), for example, it was concluded that liver blood flow in cirrhotics was reduced by 37% and that 13% was through intrahepatic shunts. This latter approach is similar to that of McLean et al. (297) except that these investigators suggested the use of indocyanine green clearance as a measure of liver blood flow rather than that estimated from the pharmacokinetic technique. It must be noted, however, that it was erroneously concluded that this latter method is able to estimate extrahepatic shunting. It has also been suggested that the administration of a precursor that is metabolized in the liver and measurement of unchanged drug and metabolite can also be used to estimate liver blood flow and intrahepatic shunting (188), but this approach has not been experimentally validated.

3. Protein binding relationships. The reversible binding of drugs to plasma proteins has long been recognized to be an important determinant of drug disposition. Based on studies of renal function, it is appreciated that only unbound drug is cleared by glomerular filtration, but total drug is potentially available for active secretion in the proximal tubule, since this process may be sufficiently efficient to "strip" the bound drug from the protein. However, extension of these concepts to other organs of elimination like the liver was limited and, more importantly, an integrated and quantitative understanding of any binding effect was unavailable regardless of the involved organ. Development of physiologically based models of elimination, especially the venous equilibration model, has permitted description of the binding relation-

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ships in hepatic removal (357, 498). In these models, binding is usually referenced to blood since it is generally assumed that drug in the various formed elements is in rapid equilibrium with that in plasma, and, therefore, is readily available for extraction. On the other hand, the major macromolecules involved in binding are in the plasma, and experimentally either this fluid or serum is used to determine the extent of binding. Interconversion between the unbound fraction in blood ($f_B{}^u$) and plasma ($f_p{}^u$) is possible by knowledge of the blood/plasma concentration ratio (equation 8) which itself is dependent on plasma binding ($f_B{}^u = f_p{}^u \div B/P$).

The effect of altered binding in the blood on hepatic extraction is highly dependent on the free intrinsic clearance of the drug (fig. 6). When CL^u_{int}/Q is small, so that the extraction ratio is low ($E < 0.25$ when binding is absent), then $f_B{}^u$ is a limiting factor to clearance across the whole binding range, and the two parameters are almost proportionally related (equation 31).

$$CL_H^{tot} \sim f_B{}^u CL^u_{int} \quad \text{equation 31}$$

Such "restrictive" elimination, i.e., extraction less than the unbound fraction in the delivered blood, describes the conventional view of the effect of binding on drug metabolism by the liver. It has been shown to be valid in vivo and in the isolated perfused liver for a number of drugs, including warfarin and other anticoagulants (273, 454, 513, 515), diazepam (259), and tolbutamide (418, 502). The clearance of disopyramide (303) and prednisolone (302) in man shows a similar characteristic that is complicated by their concentration-dependent plasma binding, which also results in the clearance of total drug varying with the plasma concentration. In contrast, if the liver is very efficient at drug removal ($CL^u_{int} \gg Q$), elimination is less affected by the extent of binding, with this lack of sensitivity increasing with the value of CL^u_{int} (fig. 6). Also, changes in binding produce a less than proportional change in extraction and total drug clearance relative to the alteration in $f_B{}^u$. Nevertheless, a linear relationship may be approximated when only a limited range of binding is considered. Such behavior has been termed "nonrestrictive" elimination, indicating that the extraction ratio is greater than the unbound fraction in the blood entering the liver (498). It has been conceptualized that this occurs because the unbound drug is so rapidly removed from blood by the intrinsic clearance process that binding equilibrium leads to spontaneous dissociation of the ligand-macromolecule complex and generation of further unbound drug, which is then extracted during further transit through the liver. The in vivo clearances of a large number of extensively bound drugs with high hepatic extraction ratios in the species studied have been shown to be either unaffected or relatively insensitive to limited alterations in binding, e.g., propranolol (145), quinidine (195), cortisol (374), and S-disopyramide (220). Moreover, studies in the isolated perfused rat liver across a wide range of binding have demonstrated a nonlinear relationship between clearance of total drug and $f_B{}^u$ when CL^u_{int}/Q is high (408, 425).

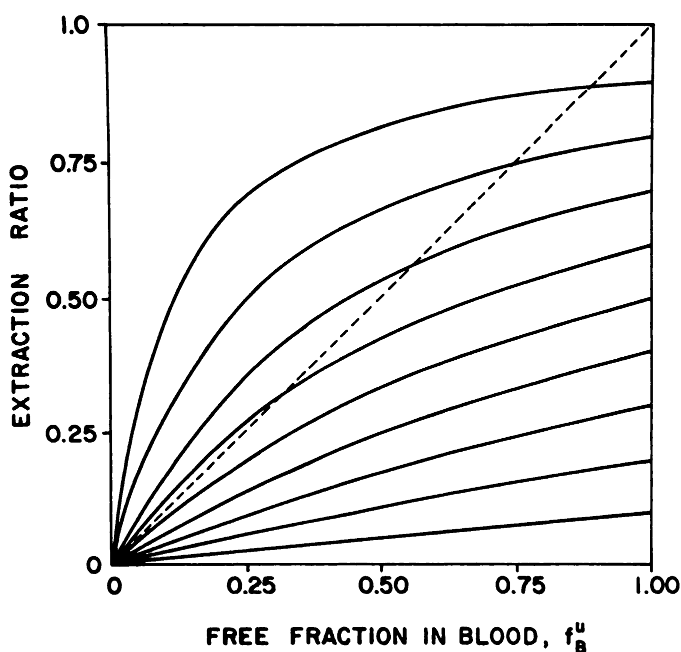

FIG. 6. The relationship between hepatic extraction (E) and unbound fraction of drug in the blood ($f_B{}^u$). The *dashed line* indicates when $E = f_B{}^u$; below this line extraction is less than the unbound moiety delivered to the organ, whereas above the line nonrestrictive extraction occurs. The individual *curves* represent different values of CL^u_{int}/Q corresponding to 10% stepwise changes in extraction when $f_B{}^u = 1$. Reproduced with permission from Wilkinson and Shand (498).

Extension of the consequences of drug binding in the blood on hepatic clearance to its effect on the elimination half-life is complicated, because $f_B{}^u$ also determines the drug's distribution volume (equation 32).

$$Vd = V_B + \sum_{i=1}^{n} \frac{f_B{}^u}{f^u_{T,i}} V_{T,i} \quad \text{equation 32}$$

where V_B is the blood volume, $V_{T,i}$ is the water volume of other individual body tissues, and $f_B{}^u$ and $f^u_{T,i}$ are the fractions of unbound drug in the plasma and individual tissue, respectively (181, 498). The possibility that the binding macromolecule, e.g., albumin, may be located in the interstitial fluid as well as the vasculature has also been considered (147, 342). Thus, the volume of distribution increases as binding is reduced ($f_B{}^u$ is increased) from a limiting value to an infinitely large value determined by the ratio of the unbound fractions in the blood and tissue (181, 498).

When a drug is eliminated in a "restrictive" fashion (i.e., low CL^u_{int} and/or $f_B{}^u$), reducing the unbound fraction in blood decreases both total clearance and the volume of distribution. The overall result depends on the magnitude of these changes. For example, if the unbound fraction in the tissues is large so that Vd is relatively small, the change in clearance predominates and half-

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life is prolonged. Thus, total drug concentrations are higher, whereas the unbound, and presumably pharmacologically active levels are lower, and both moieties decline more slowly (178, 497). This represents the conventional and well-recognized situation that applies to many drugs, including warfarin (286). However, when distribution is more extensive ($f_T{}^u \rightarrow 0$), then the elimination half-life is increasingly determined by the degree of tissue binding (179), and perturbations in binding in the blood have minimal effect on the rate of drug removal from the body. At the other extreme, when $CL^u_{int} \gg Q$, an increase in the unbound fraction has essentially no effect on clearance until it becomes very small (fig. 6), but distribution is still affected. Accordingly, peak concentrations of total drug are higher as $f_B{}^u$ becomes smaller and the elimination half-life shortens as, for example, with propranolol (145). Significantly, the initial blood concentrations of unbound drug after oral administration increase as the unbound fraction decreases, an effect opposite to that observed with drugs exhibiting "restrictive" elimination (497). For drugs which are not so effectively eliminated, i.e., intermediate extraction ratio, a biphasic relationship exists such that increased binding in the blood can shorten or prolong the elimination half-life, depending on the relative degrees of plasma and tissue binding (498). A nomogram has been described that permits ready estimation of these predicted effects of altered binding on the direction and change in the elimination half-life (187).

Consideration has also been made of the effects of altered blood binding on steady-state drug concentrations (198, 357). Again, predicted differences exist between drugs that are "restrictively" or "nonrestrictively" eliminated. When free intrinsic clearance is small relative to liver blood flow, then the average steady-state blood level of unbound drug is independent of binding in the blood regardless of the route of administration, and total concentrations become smaller as $f_B{}^u$ increases. One of the most familiar examples of such behavior is that of phenytoin in renal failure (198). On the other hand, for a drug with a high free intrinsic clearance, steady-state drug concentrations after intravenous administration are minimally affected by binding, except when this is very extensive, but unbound levels increase as $f_B{}^u$ increases. With oral dosing, however, the situation is similar to that for a restrictively eliminated drug; i.e., steady-state total drug levels are reduced as the unbound fraction increases. However, the magnitude of the predicted change is model dependent, and this difference is even more apparent in the blood concentration of unbound drug. According to the venous equilibration model, the unbound level would be expected to be unaffected by changes in binding, whereas a decrease in the unbound fraction would be predicted to result in an increase in the unbound concentration if the undistributed sinusoidal perfusion model was operative (320). Unfortunately, few experimental studies have been reported to confirm these theoretical effects of plasma binding on blood concentration/time profiles of drugs with high free intrinsic clearances, especially with respect to different routes of administration and duration of dosing.

The plasma binding of certain drugs is concentration dependent within the range of levels that are experimentally or clinically encountered. Accordingly, clearance and volume of distribution of total drug are constantly and independently changing according to the blood level. Not unexpectedly, the effect of this on the blood concentration/time profile is complex. Initial simulations were based on the simplifying assumptions that clearance was either proportional to the unbound drug or independent of drug binding (300). Later a more realistic analysis incorporated the venous equilibration model of hepatic elimination (341). It was found that, when CL^u_{int}/Q and Vd are both small, then the amount of drug in the body, the total plasma concentration, and the unbound drug level all declined in a concave fashion when plasma binding is nonlinear. In contrast, when CL^u_{int}/Q is high, the effects of saturable binding are quite different; the amount of drug in the body and the total concentration profiles exhibit convexity, while the unbound levels decline in a sigmoidal fashion. If, however, the drug has a large volume of distribution, the slope of the amount of drug in the body and the total plasma level are essentially unchanged with time, while the unbound concentration shows convex curvature, provided that CL^u_{int}/Q is small. On the other hand, with a high intrinsic clearance drug, the decline of all three variables is convex. The possibility of saturable tissue binding in the presence of both linear and nonlinear binding in the plasma was also examined, and even more complex concentration/time relationships were predicted (341). However, few experimental studies have substantiated these predictions, although they were based on validated concepts.

The problem of nonlinear binding in blood and of hepatic elimination has also been theoretically explored from the perspective that removal of the unbound fraction within the sinusoid may lead to a lower unbound fraction within the liver than that in blood entering the organ (219); this possibility was not incorporated into earlier simulations (300). The expected result of this phenomenon would be that the hepatic clearance and extraction ratio would be smaller than expected based on linear binding considerations at any given value of $f_B{}^u$ in the entering blood. Not surprisingly, the higher the drug's free intrinsic clearance, the greater the effect of the intrahepatic change in $f_B{}^u$, which results in a reduction in the curvature of the extraction ratio/$f_B{}^u$ relationship (fig. 6) toward linearity dependent upon the ratio of the unbound drug concentration and the equilibrium dissociation constant for the binding interaction. Importantly, under certain conditions of saturable binding, drugs with a low extraction ratio could be very sensitive

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to hepatic blood flow changes, and furthermore, high extraction ratio compounds could be sensitive to binding changes within the blood, both of which are contrary to the more familiar situation when linear binding is present. Again, no experimental studies are available to substantiate these theoretical predictions.

A central dogma of pharmacology is that only unbound drug is capable of translocation across biological membranes, the ligand-protein complex being too polar and large. Thus, hepatic uptake is assumed to be solely determined by the unbound concentration of the diffusible moiety at the surface of the liver cell. A further critical assumption of all conventional models of hepatic elimination is that binding equilibrium exists within the sinusoid so that spontaneous dissociation of the ligand-protein complex leads to immediate replacement of unbound drug as it is removed from the blood; i.e., the rate constant of dissociation is extremely rapid relative to the transit time through the liver. However, an increasing number of experimental observations with xenobiotics that are normally very extensively bound to plasma proteins (>99%) appear to be inconsistent with these assumptions. This suggests that bound drug is in some fashion intimately involved in the hepatic uptake process beyond its role as a passive store for replenishing the unbound moiety.

Early evidence of the involvement of bound drug in hepatic uptake was obtained from studies in the isolated perfused rat liver with oleate, which is essentially completely bound by albumin (480). Increasing the fatty acid concentration at a constant albumin level resulted in a proportional increase in the hepatic removal rate despite the fact that the unbound fraction varied over 10-fold and in a nonlinear fashion; i.e., the essentially constant bound fraction appeared to be rate determining. In contrast, maintaining the oleate and albumin concentrations at a fixed molar ratio so that the unbound fraction was virtually constant resulted in apparent saturation kinetics with increasing concentration. This suggested that the uptake mechanism for bound drug was saturable, and it was the albumin portion of the albumin-ligand complex that was responsible. Moreover, the apparent saturation did not appear to reflect any limitation in intrinsic clearance, since it occurred at rates well below those attained in the studies in which linear uptake was observed with a constant albumin level. Similar findings were also observed for other organic anions, including bilirubin and sulfobromophthalein (479). A direct involvement of albumin was also independently implicated from the steady-state uptake of taurocholate by the perfused rat liver, where a 10-fold increase in albumin concentration, producing a 5-fold reduction in unbound taurocholate, only changed the extraction ratio by 50% (156). Similar findings were also obtained with rose bengal when bound to albumin (157, 163) but not to gamma globulin (162). The non-steady-state, first-pass removal of thyroid (370, 371) and steroid (369) hormones bound to certain, but not all, plasma proteins was also found to be greater than expected based on the conventional assumption that only unbound ligand was transported into the rat liver. Uptake into isolated hepatocytes in the presence of albumin of iopanoic acid (74), rose bengal (152), sulfobromophthalein (312, 334), and oleate (334), and into cultured hepatocyte monolayers of palmitate (151) has also been observed to be greater than predicted from the unbound drug concentration.

To explain these observations, it has been suggested that a limited number of receptors for albumin are present on the surface of hepatocytes (156, 163, 479, 480). The ligand-albumin complex transiently interacts with these receptors in a saturable fashion which results in enhanced dissociation of the complex followed by normal uptake of the released unbound drug. The mechanism of the albumin-catalyzed dissociation is not known, but it has been speculated to involve a conformational change in the albumin which alters the ligand-albumin binding affinity (367, 478). Thus, when binding is low, hepatic uptake is limited in the conventional way by the unbound fraction, but for highly bound drugs, uptake from the bound fraction predominates (336, 481).

Support for the albumin receptor model was obtained by demonstration of saturable binding sites for ^{125}I-albumin on the cell surface of hepatocytes. Binding was found to be rapid, reversible, and of relatively low affinity (480). Moreover, the predicted number (10^7 per cell) and affinity ($K_d = 10^{-5}$ to 10^{-6} M) of surface receptor sites necessary to account for the uptake of rose bengal were found to be similar to the values obtained independently using equilibrium binding (157). Studies have also shown that the surface receptor is unable to distinguish between free albumin and the ligand-albumin complex (152). On the other hand, it has been observed that binding to albumin is not a prerequisite for the hepatic uptake of bilirubin (296) and sulfobromophthalein (228) in analbuminemic rats, or for bilirubin in the perfused rat liver (438). However, these findings are not contradictory to the albumin receptor hypothesis, since they were obtained under conditions of relatively low binding where the conventional uptake of unbound drug could account for the efficient elimination. Similarly, the inability to demonstrate the presence of albumin receptors by a variety of means based on techniques applicable to high affinity ligand-receptor interactions (439) is not necessarily contrary evidence, since it is postulated that the cell surface interaction is transitory and of low affinity. More difficult to explain is the suggestion that surface-mediated dissociation is not specific to ligand-albumin complexes. For example, similar uptake kinetics, consistent with a protein-surface interaction, were observed with rat hepatocytes when sulfobromophthalein or oleate was bound to either albumin or β-lactoglobulin (334). It has also been shown that propranolol is efficiently ex-

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tracted (>90%) regardless of whether it is bound to albumin or α_1-acid glycoprotein over a range of binding (232). Unfortunately, the extent of binding in these studies in the isolated perfused rat liver did not exceed 75 to 80%, and it is, therefore, likely that uptake was determined by the unbound drug according to the conventional concept (477). However, there are other indications that the nature of the binding macromolecule is just as important a determinant of uptake/elimination as is the unbound fraction (162, 369–371).

An alternative mechanism that has been suggested to account for the more efficient hepatic removal of highly bound drugs than predicted solely on the basis of unbound drug is an albumin-mediated increase in diffusibility of the drug across the unstirred boundary layer in the space of Disse (74). Mathematical simulations, however, have indicated that such diffusional resistance is much too small to be a determinant of rose bengal uptake (159). More direct evidence against this mechanism is the finding of surface-mediated dissociation of palmitate in a vigorously stirred suspension of hepatocytes (151).

A further possible explanation of hepatic uptake above that consistent with the equilibrium unbound drug concentration questions the assumption that binding equilibrium is maintained between the ligand and albumin within the sinusoid. Such dissociation-limited uptake has been theoretically considered for both the venous-equilibration and undistributed sinusoidal perfusion models (230). It was concluded that the rate of dissociation of the binding complex could limit the hepatic elimination of highly bound (>99%) drugs whose free intrinsic clearance was sufficiently high that the extraction ratio was greater than 95% when binding is absent. More recently, it has been further recognized that the characteristics of dissociation-limited binding can result in the type of findings previously attributed to the albumin receptor model (476, 483). The stimulus for considering this possibility was the observation that hepatic removal of sulfobromophthalein by the skate liver exhibited an almost identical pattern with respect to bound drug as that observed previously in the rat (483). Since elasmobranchs lack serum albumin, and by inference an albumin receptor, this suggested that either the cell surface receptor is a nonspecific membrane component that was not specifically evolved to recognize albumin, for example, a hydrophobic binding region, or that an alternative mechanism is operative which does not require interaction of albumin with the cell surface. Theoretical analysis confirmed that, with either the venous equilibration or the undistributed sinusoidal perfusion models, binding equilibrium cannot exist within the sinusoid when a sufficiently rapid rate of removal of unbound drug is present (476, 483). That is, uptake removes the unbound moiety faster than it can be replenished by spontaneous dissociation from albumin. In this situation, uptake is rate limited by dissociation and becomes proportional to the concentration of bound drug. Information on the relative rates of dissociation and uptake/elimination rates is extremely sparse. For the bilirubin-albumin complex, the half-life of dissociation is about 22 to 78 s, while for long chain fatty acids, it is in the range of 14 to 230 s (478). These values compare to the less than the 5-s value needed to account for the observed rate of removal of bilirubin and oleate by the perfused rat liver (336, 480). Accordingly, dissociation-limited binding could be responsible for the experimental observations that uptake is determined by the bound drug rather than unbound concentration. Additional simulations (476, 483) also showed that the removal process in general may be determined by the rate of plasma flow, dissociation from albumin, uptake into the hepatocyte, free intrinsic clearance, or any combination of these factors. Importantly, binding equilibrium was found to exist within the sinusoid only for albumin concentrations above the minimum value, equivalent to the ratio of the uptake and binding rate constants; at lower albumin concentrations, removal of bound drug was dissociation limited. Thus, the apparent situation seen on increasing the concentration of ligand-albumin complex and the competitive inhibition of uptake by added albumin results from a shift in the rate-limiting step from dissociation to either uptake or free intrinsic clearance at higher albumin concentrations. That is, at low albumin levels, rebinding of dissociated unbound drug is slow compared to uptake, and essentially each dissociation event leads to drug removal, i.e., dissociation-limited uptake. However, with increasing albumin, rebinding is able to compete with hepatic uptake, and at sufficiently high levels the rate of dissociation is effectively equal to the rate of rebinding; equilibrium is established, and a subsequent step in the removal process becomes rate limiting. Since the albumin level at which binding equilibrium is established varies according to the binding characteristics of a particular drug as well as the uptake rate, the rate-limiting step under each experimental or physiological condition needs to be individually established.

The finding, that the hepatic uptake/elimination of very highly bound drugs is inconsistent with the conventional hypothesis of the driving force being the unbound drug concentration generated by spontaneous dissociation of the bound complex, is extremely provocative. The involved mechanism(s) is not well understood, although two distinctly different possibilities have been suggested. The validity of such hypotheses needs to be further examined with particular emphasis on discrimination between alternative models. This will be experimentally challenging (161, 318, 477), but may well provide new and fundamental insights into drug uptake and elimination of application not only to the liver, but to other organs. For example, albumin-mediated uptake has also been observed to occur with steroids and drugs across

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the blood-brain barrier (236, 366–368) and also with fatty acids into heart (223, 224).

F. Model Comparisons and Discrimination

Comparison of the various alternative models of hepatic elimination reveals similarities and differences in their predictions. For example, at the two extremes of behavior, that is, for drugs with either very high or very low extraction ratios, there is essentially no distinction between the models based on measurements of extraction ratio or clearance as affected by changes in either hepatic blood flow, binding, or free intrinsic clearance. When free intrinsic clearance greatly exceeds hepatic blood flow, the extraction ratio approaches unity; all drug in blood, whether bound or unbound, is completely extracted, and clearance approaches the limiting value of hepatic blood flow. At the other extreme ($CL^{u}_{int} \lll Q$), the extraction ratio approaches $f_B{}^{u}CL^{u}_{int}/Q$ and changes proportionally with the unbound fraction in the blood and inversely with hepatic blood flow, while clearance is insensitive to changes in flow. There are, however, certain conditions under which the models provide different predictions of behavior which theoretically provides an opportunity to evaluate the validity of a particular model with respect to experimental data. Attempts to this end have been reported in response to perturbations in either hepatic blood flow or binding in the blood.

There is very little difference in the change of extraction ratio and clearance between the venous-equilibration and undistributed sinusoidal perfusion models when hepatic blood flow is altered (357). At the maximum, the difference is only about 30%, and occurs for drugs with extraction ratios between 0.7 and 0.8. Thus, both models equally well describe the changes in the hepatic extraction ratio of oxyphenbutazone and radiocolloidal chromic phosphate when perfusion rate was altered over 4- to 10-fold ranges, respectively (358). In contrast, the predicted change in availability differs greatly between the two models, especially for drugs with a high hepatic extraction ratio. For example, a 1000-fold discrepancy exists between the predicted availabilities for a drug with an extraction ratio greater than 0.99 (357). Moreover, the venous equilibration model indicates that the hepatic venous concentration and related values such as AUC_0 and the steady-state blood concentration after oral dosing should be insensitive to changes in hepatic blood flow, whereas these parameters increase in value with increased perfusion according to the undistributed sinusoidal perfusion model (357). This distinction has been used in discrimination studies. Thus, the lack of effect of altered perfusion rate in the isolated rat liver preparation on the steady-state venous concentration following constant rate infusions of lidocaine (10, 358, 427), propranolol (427), and meperidine (10) has been interpreted as supportive of the validity of the venous equilibration model. On the other hand, advocates of the undistributed sinusoidal perfusion model have reported similar studies with galactose (245), ethanol (247), and propranolol (248) which are more consistent with this particular model. Reanalysis of the galactose study suggests that the observations are even better described by the distributed sinusoidal perfusion model (23, 27). However, concern has been expressed over the appropriateness of the experimental data base in this study and suggests that these findings are, therefore, inconclusive (317).

Differences between the predictions of the two models for the extraction ratio and clearance as determined by the unbound fraction in the blood are also small for drugs with either very high or very low extraction ratios. Even for an intermediate extraction ratio, the differences are modest: 2.5-fold change with a 10-fold alteration in $f_B{}^{u}$ (357). This probably accounts for the inability to discriminate between the venous equilibration and undistributed sinusoidal perfusion models using data obtained with quinidine (195) and S-disopyramide (218) in rabbits with altered levels of plasma proteins and phenytoin (76) in the isolated rat liver. The greatest difference between the models' predictions with changes in binding is found in the hepatic vein concentration and its dependent parameters such as availability, AUC_0, and the steady-state blood concentration after oral administration. This is especially so with high values of the extraction ratio when these parameters all vary in inverse proportion to $f_B{}^{u}$ in the venous equilibration model and exponentially in the undistributed sinusoidal perfusion model (357). Based on such an approach, it was concluded that the effect of altering the unbound fraction of diazepam over a 20-fold range on its availability in the isolated perfused rat liver was more consistent with the undistributed sinusoidal perfusion model than the venous equilibration model (408). Additional analysis also supported this conclusion (76). By contrast, the effects of altered binding of propranolol in vivo on its availability and AUC_0 in the rat were found to be more closely described by the venous equilibration model (138). Measurement of unbound drug concentrations after oral administration provides even better discrimination between these two common models than total drug; unbound levels are independent of the unbound fraction according to the venous equilibration model, but fall with increasing $f_B{}^{u}$ in the undistributed sinusoidal perfusion model (320). Alteration of the unbound fraction over a 6-fold range produced no significant effect on the steady-state perfusate concentration when propranolol was infused into the portal vein of the isolated rat liver preparation, indicating that the venous equilibration model was more consistent with the experimental data (233). On the other hand, studies in vivo resulted in the AUC_0 for unbound propranolol increasing as the unbound fraction decreased (516), which is not compatible with this model.

The findings, that some experimental data are more consistent with one model of hepatic elimination com-

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pared to another and the reverse for other observations, have generated considerable debate as to which is the "right" model (21, 23, 94, 96, 158, 160, 283, 319, 378, 499). Since a major role of mathematical modeling is to polarize thinking and to pose sharp questions leading to experimentation, such a situation is not unexpected or undesirable. Thus, the evolution of a valid model depends on a continual cyclic process of abstraction, prediction, verification by experiments, refinement of imagery, then again abstraction, and so on through the cycle (332, 333). It must also be recognized that all models have discrepancies, and need not be "right" in order to perform useful functions; in fact, model validity is best evaluated within the context of the particular application for which the model is being used.

Simplifying and sometimes unrealistic assumptions are critical in the modeling of biological systems, and this accounts for the dictum that "all models are wrong, but some are more useful than others." Certainly the liver is more complex than depicted for any of the available elimination models. The hepatic architecture and microcirculation are such that considerable turbulence and mixing of portal and hepatic arterial blood occurs within the sinusoid (194). This may be the reason why some experimental data are operationally consistent with the well-stirred or venous equilibration model, even though it is physiologically unrealistic because concentration gradients have indeed been demonstrated along the sinusoidal flow path (201). The undistributed sinusoidal perfusion model overcomes the latter criticism, but assumptions regarding uniform distribution of drug metabolizing enzymes in either model and ideal bulk blood flow along the sinusoid are clearly oversimplifications of reality. A variety of studies indicate that the activity of many different drug metabolizing enzymes is heterogenously distributed within the hepatic acinus (19, 107, 200, 389, 457, 475). Similarly, the multiple-indicator dilution technique has clearly demonstrated that sinusoidal transit times vary considerably (189, 192). These considerations suggest that, for certain purposes, models incorporating such distributions (22, 28, 155, 415) might be more appropriate despite their additional complexity. It is also possible that these heterogeneities may result in the elimination of one drug being best described by one model and that of another by alternative model.

Aside from modeling assumptions, interpretation of discriminative studies based on alterations in either liver blood flow or binding in the blood implicitly assumes that the experimental perturbations have no effect on hepatic function aside from that predicted by the model. This may not be the case. For example, as portal blood flow increases, the degree of mixing with blood from the hepatic artery may decrease, shifting the liver from a venous equilibration system towards that described by the sinusoidal perfusion model. In addition to such alterations in intrahepatic perfusion, altered liver blood flow may also affect sinusoidal oxygen tension, which is known to be important in drug metabolism (70, 118, 234, 235). Altering intravascular binding may also change liver function in a complex way. For example, in the absence of binding, thyroxine (482) and sulfobromophthalein (199) uptakes exhibit distinct concentration gradients across the acinus, but the addition of albumin abolishes this, and a more homogeneous distribution occurs, i.e., a shift from a sinusoidal perfusion type of model towards a venous equilibration type model. Moreover, albumin and α_1-acid glycoprotein in addition to reversibly binding drugs have been unexpectedly found to affect the drug metabolism process per se by an unknown mechanism. Thus, in the isolated perfused rat liver, albumin enhanced the clearance of antipyrine even though this drug is not bound to this protein, and a similar phenomenon was observed with prazosin (340). On the other hand, α_1-acid glycoprotein decreased the unbound clearance of prazosin (340). Furthermore, changing the albumin concentration may alter the rate-limiting step in the removal process (476). Also, extrapolation of data obtained in the perfused liver, where only portal blood is present, to the in vivo situation, in which the hepatic artery contributes significantly to overall perfusion, must be made cautiously. The availability of lidocaine and meperidine was found to be 18 and 3 times greater, respectively, when infused through the hepatic artery compared to portal vein administration (11). When both routes of drug delivery were used, hepatic extraction was dependent on the relative contributions of the two flow rates. Finally, it should be recognized that the isolated perfused liver is a fairly variable preparation so that one liver may provide data supportive of one model, another may be more consistent with an alternative model, and a third may support neither.

Because of these types of considerations and the lack of complete understanding of the precise biological processes involved in hepatic elimination, overzealous dogmatism for any currently available model would appear misplaced and premature. Many more data on many compounds whose elimination is determined by different mechanisms and processes are needed before a clear and possibly unified picture of hepatic elimination emerges. Also, future discrimination studies should ensure that the choice of drug and the experimental design are optimal to provide maximal differences between alternative models.

VI. Clearance Models of Organs Other than the Liver

Despite the long-standing use of clearance concepts to quantify kidney function, models to describe renal excretion based on physiological determinants are surprisingly limited. This reflects the additional complexity of the process compared to, for example, hepatic elimination. The renal clearance of drugs usually involves three processes: glomerular filtration; proximal tubular secretion;

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and reabsorption from the distal tubule and collecting duct. In addition, metabolism may also occur. Glomerular filtration is a passive process which is considered to be a function of the unbound drug concentration in plasma (202, 452). On the other hand, tubular secretion is characterized by active transport which has the potential to strip bound drug from vascular proteins, and it may, therefore, be a function of total drug concentration. Reabsorption is also passive in nature and is often complicated for weak electrolytes by the varying urinary pH that alters the concentration of reabsorbable un-ionized drug. Finally, water reabsorption takes place along the whole of the nephron which affects the concentration gradients between tubular fluid and the blood. Currently no unified model of renal function exists which incorporates all of these physiological aspects. A number of studies have, however, attempted to model certain aspects of the renal excretion process.

Early models were limited to theoretical considerations based on functional descriptions of the involved processes; i.e., the individual components of renal clearance were characterized by intuitive mathematical functions which were then summated to yield an operational model (167, 269, 466). Thus, the effect of plasma binding on glomerular filtration was incorporated, and active secretion was presumed to follow Michaelis-Menten kinetics based on total drug concentration in plasma. Some success was achieved with such models in describing the excretion of certain sulfonamides (214, 239), but data with high extraction compounds such as *p*-aminohippurate (251) and iodopyracet (208) could not be accounted for. These deviations were considered to reflect the almost complete extraction of the compounds at their site of secretion, so that the driving concentration decreased along the tubule; i.e., equilibrium did not exist between peripheral plasma and that in the peritubular capillaries. Extended forms of Michaelis-Menten kinetics were, however, developed to successfully describe this situation (208, 251).

Attempts have also been made to apply the venous equilibration model approach of hepatic elimination to renal secretion. The purpose of these theoretical analyses (110, 285) was to demonstrate the differences in clearance profiles when active secretion is small relative to renal plasma flow and is a function of unbound rather than total drug concentration in the plasma. Data from studies in the rat with furosemide (203) and salicylate (285), neither of which is reabsorbed, were consistent with the former situation, whereas it was concluded that the renal secretion of sulfisoxazole was determined by plasma level of total drug (514). Water reabsorption and the effect of urine flow rate on drug excretion have also been successfully modeled, but only for drugs which undergo glomerular filtration and passive reabsorption (202, 268, 447).

The uptake of compounds into noneliminating tissues and organs has also been investigated. Physiologists have long been interested in this area from the standpoint of capillary permeability, the exchange of gases and endogenous substrates, and measurement of organ blood flow (193, 282, 522, 523). In many instances, the approaches are analogous to those incorporated into the sinusoidal perfusion type models of hepatic elimination. For example, the Kety-Crone-Renkin equation (114, 250, 391), which is widely used to estimate transcapillary clearance and membrane permeability in single vessels and organs, is mathematically identical to equation 22 describing the undistributed sinusoidal model of the liver. The only difference between the two equations is the numerator of the exponent, which in the former instance is a permeability-surface area product rather than total intrinsic clearance. Clearances between compartments in conventional linear, multicompartmental pharmacokinetic models have also been estimated by this approach (47, 209, 435). On the other hand, physiologically based modeling of exogenous drug uptake has generally assumed that tissues are well-stirred and have incorporated the venous equilibration model (173, 291). Comparison of these two approaches has been made assuming linear plasma and tissue binding with the conclusion that, although both models predict similar organ uptake under a variety of conditions, significant differences can exist when the extraction ratio and/or perfusion rates are high (448). However, examination of distribution data with a number of drugs with widely different characteristics was unable to reveal that one model was more appropriate than the other under pseudoequilibrium conditions.

VII. Clearance of Metabolites

Clearance concepts were primarily developed for and applied to unchanged drug; however, with the increased recognition of the potential pharmacological and toxicological significance of active and reactive metabolites, they have been extended to consider the disposition of metabolites. This aspect is still in its formative stages, it is generally limited to metabolites that are sufficiently stable to escape from the organ in which they are formed under linear conditions, and quantitative experimental data are sparse. Nevertheless, the principles and approaches that have been described provide a sound basis upon which to interpret the formation and elimination of metabolites.

A. Metabolite Concentration Profiles

Early theoretical studies (116, 117) were based on simple compartmental models to describe metabolite plasma concentration/time profiles. Subsequent refinement led to the classifications of "formation rate-limited" and "elimination rate-limited" disposition (117, 215). In the former and more common situation, the metabolite is eliminated almost as fast as it is formed, and the terminal phase of the plasma concentration/time profile parallels that of parent drug. By contrast, in elimination

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rate-limited disposition, the terminal half-life of metabolite exceeds that for unchanged drug and reflects the true elimination of the metabolite. Simulations also reveal the potential for modest and continuous curvature of the logarithmic concentration/time profile over a considerable portion of the disappearance curve and the likelihood that this would not be recognized when typically "noisy" experimental data were available. As a result, the estimated terminal half-life of metabolite tends to be overestimated, and this error increases as the value of the rate constant for metabolite formation approaches that for elimination of parent drug (117, 215, 352). Several practical methods of establishing the relative and absolute values of the formation and elimination rate constants for a metabolite produced and removed solely by the liver have been described (82, 346, 352). The influence of the route of drug administration, intravenous versus oral, on the shape of the metabolite plasma concentration/time curve has also been studied (95, 216). In many instances, the metabolite profile appears to be biexponential regardless of route, when the oral absorption of parent drug is rapid and clearance by the liver is moderate to high ($CL_H > 25$ liters/h). However, if metabolite distribution is rapid, a triphasic curve may be observed after oral administration, even though the profile following intravenous dosing is biphasic, and the peak plasma levels are lower. This occurs because metabolite formed during the first-pass effect behaves in a fashion analogous to that when it is given intravenously; i.e., a distribution phase is present prior to establishment of pseudoequilibrium conditions. Such behavior probably accounts for the observation that 4-hydroxypropranolol plasma concentrations were observed only after oral administration of propranolol, and they appeared to decline faster than those of parent drug (373). The use of analytical methodology with appropriate sensitivity, however, revealed that this metabolite was indeed formed after intravenous dosing and had a slower terminal phase subsequent to the initial rapid decline (473). An analogous situation probably occurs with alprenolol (100), chlorpromazine (121), and methotrimeprazine (120). The rate of absorption of parent drug may also markedly affect the metabolite plasma concentration/time curve (216). It has also been speculated that the dependency of the metabolite profile on the route of administration is probably less marked for secondary than primary metabolites (216).

The pharmacokinetics of a metabolite after administration of parent drug are complex because metabolite formation, sequential elimination, distribution, and further elimination of the metabolite by excretion or conversion to a secondary metabolite all occur concurrently. As a result, data interpretation has shifted towards the use of area under the curve (AUC) measurements, and such simple analysis often provides useful information. For example, if the liver is the only site of linear metabolite formation and elimination of parent drug, then the AUC for the ith metabolite (AUC_{m_i}) is the same regardless of route of administration. Thus, the ratio of metabolite area after intravenous and parenteral administration under this assumption may be used to assess bioavailability providing that drug absorption is complete (344, 346). On the other hand, if parent drug is also eliminated by another organ, for example, the kidney, then AUC_{m_i} will change according to the route of administration of parent drug. Because of metabolite formation during the first-pass effect, the area under the curve will be greater after oral administration than after intravenous dosing by a fraction which equals CL_R/Q. Accordingly, AUC_{m_i} after different routes of administration provides an indication of the presence or absence of extrahepatic clearance. Similar route-dependent differences also occur in the fraction of the administered dose excreted in the urine as unchanged drug (177). Additional complexity occurs when organs other than the liver (gastrointestinal tract, lung and kidney) contribute to the formation of the metabolite, and sequential first-pass metabolism occurs (257, 346). The metabolite area is then dependent not only on the site of drug administration but also the sites of metabolite formation and elimination. Such theoretical analyses emphasize the difficulty of accurately interpreting differences between areas under the curve for metabolites without precise knowledge of the organs involved in formation and elimination, data that are often unknown.

B. Fraction of Drug Converted to Metabolite

The term "fraction metabolized" is an attractive concept that has been extensively used as an indicator of the extent of drug metabolism. Unfortunately, this term is relatively imprecise, since its definition depends on the experimental approach used for estimation. Attempts to clarify the situation have noted that distinctions can be made at several different levels (346, 356). Thus, the fraction metabolized may be defined in reference to the dose or the clearance of drug, in terms of the amount of metabolite formed or available to the systemic circulation, with respect to specific metabolite or all metabolites collectively, with or without specifying the organ(s) of metabolism or excretion, and combinations of any or all of these.

In considering metabolite formation, there is obvious merit in relating the fraction metabolized to a clearance term, since such a value is independent of the route of administration as well as the magnitude of the administered dose, so long as linear conditions are present. The fraction of total clearance that is attributable to overall metabolism (f_m), in contrast to other routes of elimination, is the simplest fractional estimate and may be experimentally determined from the ratio of the nonrenal clearance of unchanged drug to its total clearance after intravenous administration. Since it is assumed that the nonrenal pathway is entirely accounted for by metabo-

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lism, the presence of any other pathways of elimination, e.g., enterohepatic recycling and fecal loss, pulmonary clearance, etc., results in an overestimate of this fraction. Because of the ease of determination, f_m is a frequently estimated parameter, but it provides no information concerning a specific metabolic pathway. In order to obtain information on this aspect, it is necessary to measure the area under the metabolite plasma concentration/time curve after administration of both parent drug and the individual metabolite per se. The latter takes into account the quantitative fate of the metabolite subsequent to its formation. The most common experimental approach is to administer both parent drug and metabolite by the intravenous route, ideally at the same time using differently labelled moieties. Comparison of the relative areas (equation 33) then provides an estimate of the fraction of total body clearance (f_{m_i}) that furnishes a specific metabolite, m_i, to the systemic circulation (240, 346, 407)

$$f_{m_i} = \frac{\mathrm{AUC}_{m_i}^{D^{iv}}/D^{iv}}{\mathrm{AUC}_{m_i}^{M_i^{iv}}/M_i^{iv}} \qquad \text{equation 33}$$

where AUC_{m_i} is the total area under the metabolite plasma concentration/time curve after intravenous doses of parent drug (D^{iv}) or metabolite (M_i^{iv}). This fractional clearance is independent of where the metabolite is formed or the routes of elimination of parent drug. The formation of salicylic acid from acetylsalicylic acid has been studied in this fashion (407), as has that of a number of metabolites from N_4-ethoxyacetylsulfamethoxazole (240); the generation of an S-methyl metabolite from diethyldithiocarbamate (91); carbamazepine's metabolism to its 10,11-epoxide (372); N-demethylation of chlordiazepoxide and the subsequent formation of a lactam (241); and the formation of various primary and secondary metabolites from isoniazid (54).

It has been pointed out, however, that a distinction may exist between formation of a metabolite and its appearance in the systemic circulation as reflected by f_{m_i} (344, 351, 362). This arises because of the possibility of sequential first-pass metabolism within the liver or other metabolizing organs. That is, the metabolite is further eliminated by the liver prior to leaving the organ. Such a situation is analogous to the concept of organ availability for unchanged drug. Thus, for a metabolite which has a significant sequential first-pass effect, f_{m_i} provides an underestimate of the actual formation clearance by a factor $[F_{H(m_i)}]$ which corresponds to the fraction of preformed metabolite that survives a single passage through the eliminating organ. This fraction may be experimentally determined by application of equation 16 following administration of the metabolite per se by appropriate routes, e.g., in the case of the liver by intravenous and portal venous routes. However, in practice this is not necessary, since the fraction of total clearance of the parent drug which forms the metabolite, g_{m_i}, may be simply estimated by measuring the total area under the metabolite plasma concentration/time curve (AUC_{m_i}) after intravenous administration of parent drug (D^{iv}) and metabolite per se (M_i^{pv}) by the portal venous route, or orally if gastrointestinal metabolism is absent (equation 34).

$$g_{m_i} = \frac{\mathrm{AUC}_{m_i}^{D^{iv}}/D^{iv}}{\mathrm{AUC}_{m_i}^{M_i^{pv}}/M_i^{pv}} \qquad \text{equation 34}$$

This approach may be further refined to estimate the formation clearance as a fraction of hepatic clearance (h_{m_i}) provided that information is available on the fraction of an intravenously administered dose of parent drug which is excreted unchanged (f_R) or eliminated by other routes besides metabolism (f_{other}); i.e., the liver is the only site of metabolite formation (equation 35).

$$h_{m_i} = \frac{g_{m_i}}{(1 - f_R - f_{other})} \qquad \text{equation 35}$$

A more general theoretical analysis has also been described in which metabolite formation can occur in any organ, i.e., hepatic and/or extrahepatic metabolism. This approach requires measurement of the AUCs for parent drug after administration intravenously and immediately proximal to the organ of metabolism as well as giving the metabolite per se by the latter route (33). Although it does not take into account the possibility of sequential metabolism by different organs arranged anatomically in series, the generality of this approach is noteworthy and should be experimentally explored.

The magnitude of the difference between the formation fraction (g_{m_i}) and the fractional availability (f_{m_i}) is clearly determined by the extent of first-pass metabolism of the metabolite. When this is high, then f_{m_i} may provide a marked underestimation of metabolite formation. On the other hand, if little sequential metabolism occurs, then the two estimates will provide comparable values, and either the intravenous or portal/oral routes may be used to administer the metabolite. Experimental study of the error involved is largely limited to investigation of the formation of acetaminophen from phenacetin where an almost 2-fold difference between the two fractional clearances was observed (351, 362). Similarly, the difference between the fractional formation clearance relative to total clearance (g_{m_i}) and that for hepatic clearance (h_{m_i}) depends on the contribution of the liver to the overall elimination of parent drug and the validity of the assumption that the liver is the only organ responsible for generating the metabolite.

Because of the equivalency of AUC and steady-state concentrations per unit of drug or metabolite delivery rate (equations 3 and 4), the fractions of total or hepatic clearance responsible for metabolite formation or availability (equations 33 to 35) may also be defined in terms of steady-state levels after either drug/metabolite infusions or repetitive chronic dosing. In a similar fashion,

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AUC determinations obtained after a single dose of parent drug permit the prediction of steady-state plasma concentrations of metabolite (215, 275) as well as the ratio of metabolite to parent drug (272, 276, 372). It should, however, be noted that, when the parent drug is at steady state, this does not necessarily imply the same conditions for the metabolite. The rates of its formation and elimination determine the time required to achieve steady state for the metabolite and, particularly in the case of elimination rate-limited metabolism, this condition may be attained much more slowly than for the parent drug.

A different and commonly used approach to estimating the fraction of parent drug metabolized is based not on clearance, but on the dose of drug administered and the total amount of metabolite eliminated [$A^{\infty}_{m_i}$]. If d_{m_i} is defined as the fraction of the dose that is metabolized to m_i and this occurs solely in the liver, then a general expression has been derived (346, 356).

$$d_{m_i} = \frac{A^{\infty}_{m_i}}{D} = \frac{\mathrm{AUC}^{\ D}_{m_i}/D}{\mathrm{AUC}^{M_i^{\mathrm{pv}}}_{m_i}/M_i^{\mathrm{pv}}} \qquad \text{equation 36}$$

The actual amount of metabolite formed depends on the route of administration of parent drug which is specified by appropriate superscripts on d_{m_i} and D in equation 36. In the case of intravenous administration, equation 36 is identical to equation 34, indicating that $d^{\mathrm{iv}}_{m_i}$ is the same as g_{m_i}, the fraction of total clearance which forms m_i. For all other routes of parent drug administration, absorption and first-pass metabolism/availability must be taken into consideration. For example, after oral administration of parent drug in which a fraction F_A is absorbed and reaches the liver, then if parent drug elimination includes hepatic biotransformation, renal excretion, and other nonmetabolizing pathways, the recovery of metabolite is given by equation 37. Similar relationships may be defined for other routes and conditions (346, 356).

$$d^{\mathrm{oral}}_{m_i} = h_{m_i} F_A (1 - f_R F_L - f_{\mathrm{other}} F_L) \qquad \text{equation 37}$$

The difficulty in applying equation 36 is the problem of accounting for all of the formed metabolite which is eliminated by all routes. In practice, experimental data are often limited to the quantitative urinary excretion profile of unchanged drug and metabolites. Since many primary metabolites are themselves biotransformed to secondary and tertiary metabolites, and multiple primary metabolites are frequently formed, this mass balance problem is often insurmountable. In theory it is possible to administer a metabolite per se and determine its quantitative urinary profile so that the fractional recovery after parent drug administration may be adjusted for the metabolite's subsequent fate. However, unless the total number of metabolites is small, this approach is not really practicable. An exception to this is when the urinary excretion profile accounts for essentially all of the administered dose as unchanged parent drug and/or metabolites. In this case, the fractional formation clearance of each primary metabolite can simply be obtained by summing all the metabolites derived from this route and relating this amount to the dose of administered parent drug. A noteworthy example of this approach is with antipyrine, whose total clearance has been used extensively as an indicator of hepatic drug metabolizing ability (460). Because different cytochrome P-450 isozymes are probably involved in antipyrine's metabolism to 4-hydroxyantipyrine, 3-hydroxymethylantipyrine, and norantipyrine, which are subsequently conjugated, it has been suggested that fractional formation clearances might provide more valuable information than total clearance (67, 123). Limited studies in both animals and man appear to support this contention. For example, relatively poor correlations were found between the total oral clearances of antipyrine and hexobarbital in the rat, but high correlation coefficients were obtained between the fractional formation clearance of 3-hydroxymethylantipryine and the oral clearance of hexobarbital, as well as the generation of its 3′-oxidative metabolites (458). Similarly, in man the formation clearance of 4-hydroxyantipyrine was far better correlated with the total oral clearance of theophylline and the formation clearances of its individual oxidative metabolites than was antipyrine's total clearance or production of its other oxidative metabolites (449).

Equations 33 to 37 provide a sound theoretical foundation upon which drug elimination may be partitioned into fractions reflecting total metabolism, the formation of an individual metabolite m_i, or its availability to the systemic circulation. They also emphasize the ambiguity of the term fraction metabolized. It must, however, be recognized that application of these approaches may be practically difficult, even if assumptions regarding the site of metabolism are valid. For example, intravenous doses of both parent drug and metabolite are required to estimate f_{m_i}, and while this may be possible in animal experiments, the availability of suitable preparations for use in humans may be a formidable constraint. Portal venous administration is virtually impossible to perform in human studies and must be approximated by oral dosing. This complicates interpretation if incomplete absorption and/or metabolism occurs either in the lumen or mucosa of the gastrointestinal tract. Similar concerns potentially exist when the fraction metabolized is related to the administered dose rather than clearance.

A further problem is the validity of the critical assumption that administration of preformed metabolite leads to the same disposition, especially in the organ of biotransformation, that occurs when the same moiety is generated in situ. Metabolites are usually, but not always, more polar than the parent drug, and distribution within and into an eliminating organ may, therefore, be different when administered per se, than when formed in the organ. Thus, the extent of exogenously administered

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metabolite elimination will be less than that of generated metabolite which enters the organ in the form of a more lipophilic precursor. Moreover, a metabolite generated in close proximity to enzyme systems responsible for its subsequent metabolism is probably eliminated to a greater extent than the preformed moiety. For example, oxazepam glucuronide formation did not occur in the isolated rat liver preparation when oxazepam was continuously infused in a single-pass fashion, but when the precursor, N-methyloxazepam, was similarly administered, high levels of the conjugate were found in the venous outflow (410). The presence of a diffusional barrier to preformed metabolite also appears to account for the 4-fold difference in biliary excretion of the angiotensin converting enzyme inhibitor enalaprilat when formed from a precursor, enalapril, than when given per se (133, 347). Other confounding factors that may require consideration include end-product inhibition (18, 410, 433), time- or concentration-dependent autoinduction (372) or inhibition (281) of metabolism, cosubstrate depletion (166), the presence of triangular metabolic systems (277, 287), and enterohepatic recycling of an aglycone involving gastrointestinal hydrolysis of conjugated metabolite as well as biliary excretion of the parent drug (350).

An additional factor related to the differing disposition of metabolite is the effect of heterogeneous distribution of drug metabolizing enzymes within the hepatic acinus (20, 107, 200, 389, 457, 475). Such heterogeneity has received limited consideration with respect to the parent drug, i.e., a distributed sinusoidal model (21, 24), but its consequence, particularly on sequential metabolism, has been more extensively explored. An initial kinetic approach was based on the concept of "metabolic duration time" within the liver (345, 364). Both phenacetin and acetanilide are converted to acetaminophen in the isolated perfused rat liver, and the metabolite is subsequently sulfated. However, the enzymatic capacities (intrinsic clearances) for the formation of acetaminophen differed markedly between the two precursors, and this was associated with a highly significant difference in the extent of sulfation; the faster the formation of primary metabolite, the greater the extent of secondary metabolite production. These observations were explained by the uneven distribution of the involved enzymes within the acinus such that the median of oxidative activity, expressed as distance along the sinusoidal path or a transit time, was proximal to that for sulfation. Since blood transit time through the liver is finite, the more time required for drug oxidation within the liver, the less likelihood there will be for subsequent biotransformation of the primary metabolite, and conversely. Thus, the extent of sequential metabolism of a generated metabolite is only similar to that for preformed metabolite when conversion from precursor to the primary metabolite is very rapid relative to its subsequent elimination. In other cases, where the intrinsic clearances for formation and further metabolism of the metabolite are comparable or the former is smaller, then quantitative discrepancies in sequential metabolism will occur. These considerations probably account for the inability of either the venous-equilibration or undistributed sinusoidal models to account for the kinetics of acetaminophen following the administration of phenacetin in the isolated perfused rat liver, despite the fact that both models adequately described the disposition of parent drug (348). A more refined approach to examining sequential metabolism has been based on models that incorporate continuous linear or step gradients across the liver for the enzyme activities forming the primary and secondary metabolites (124, 361). In general, these models confirm the importance in sequential metabolism of the relative distribution of the involved enzymes and their degree of overlap, and the absence of any effect of these factors on the disappearance kinetics of the parent drug. In addition, the importance of the absolute and relative values of the respective intrinsic formation clearances has been clarified. Thus, sequential metabolism was found to be least sensitive to enzyme distributions within the liver when both intrinsic clearances are very high or when parent to primary metabolite formation is very rapid. In contrast, high sensitivity occurs when both metabolic activities are low, because the effective activity of the second enzyme depends not only on its intrinsic clearance, but also on the availability of its substrate, the primary metabolite, whose presence depends on the distribution of the two enzyme systems. From a practical standpoint, however, the latter may not be readily detectable because of the small concentrations involved and analytical constraints. Experimental studies have attempted to discriminate between certain of these enzyme-distributed models. For example, the sulfation and glucuronidation of harmol exhibit Michaelis-Menten kinetics in the perfused rat liver, but the K_m value is dependent on the experimental concentration term designated to reflect substrate level at the metabolizing site (354). In addition, the steady-state extraction ratio was found to be higher, and the sulfate/glucuronide ratio was decreased during retrograde perfusion compared to when flow was in the normal physiological direction (355). These findings suggested an uneven distribution of the conjugating enzymes across the liver with sulfotransferase activity in the periportal region and glucuronidation distal to this. Of five models with this type of enzyme distribution, those with an evenly distributed glucuronyltransferase activity and either a continuously linear declining distribution or a step decrease in sulfating ability between the periportal and centrilobular regions were found to be better predictors than alternative models with similar medians of enzyme distribution but in which sulfotransferase activity increased across the liver either continuously or stepwise (124). A similar type of modelling approach has also been used to study the formation of oxidative metabolites

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of lidocaine in the isolated perfused rat liver (363). The hepatic availability of lidocaine after both normal and retrograde perfusion was best predicted when N-deethylation was proximally located relative to hydroxylation, but these activities were not necessarily identically distributed when various primary and secondary metabolites of lidocaine were the substrates. Undoubtedly, such heterogeneous types of models of hepatic elimination that account for metabolite formation and its subsequent biotransformation are oversimplified. For example, the effects of altered perfusion rate on the kinetics of lidocaine and metabolites (363) cannot be accounted for; the simpler venous-equilibration model provides better predictions in response to this perturbation, confirming earlier findings (359). Similar discrepancies in response to altered perfusion rates also arise with harmol (124), and these may be related to the assumptions of ideal flow and its homogenous distribution. Nevertheless, such approaches provide valuable insights into metabolite kinetics which, in turn, may serve as a powerful discriminating function in evaluating the validity of alternative models for hepatic elimination. Certainly, the experimental findings, although limited, raise further doubts concerning the general adequacies of the commonly used venous-equilibration and undistributed sinusoidal models.

C. Chemically Reactive Metabolites

Certain drug metabolites are so unstable because of their chemical reactivity that they do not leave either the enzyme, cell, or organ where they are formed. Instead, they irreversibly interact with cellular constituents, such as proteins or nucleic acids, which may result in toxicity including carcinogenesis, mutagenesis, tissue necrosis, and blood dyscrasias. Longer-lived metabolites which escape from the organ in which they are formed may also undergo covalent interaction at distal sites. This phenomenon of chemically reactive metabolites has received extensive investigation, especially with respect to the involved chemistry, mechanisms, and biological effects (14, 432). However, only limited analysis has been made of kinetic considerations despite the fact that a number of aspects are different from those of stable metabolites that produce their pharmacological effects by reversibly interacting with specific receptors. An important distinction is that the biological response produced by a reactive metabolite is related to the amount of metabolite formed rather than its concentration/time course as determined by the rates/clearances of formation and degradation. In addition, a fraction of this amount as determined by the relative rates of interaction with the target versus other sites or route of elimination is also of importance, along with the rate at which the target molecule is repaired.

Based on conventional linear systems, Gillette (183, 185) showed that the proportion of the dose of parent drug that becomes covalently bound may be regarded as a series of ratios, the size of which depends on the number of sequential metabolic elimination steps between parent drug and generation of the active metabolite(s). The numerator of each ratio is the formation clearance of the metabolic pathway involved in generating the reactive metabolite, or at the final step the covalent interaction, while the denominator is the sum of all of the clearances, including inocuous pathways, at the individual elimination step. Thus, the fraction of the dose converted to a reactive metabolite may be affected by either changing the formation clearance from precursor to metabolite, i.e., the numerator, or the total clearance, i.e., the denominator. The magnitude of the alteration, therefore, depends on the relative importance of the activation reaction and the other pathways that contribute to the elimination process. Hence, for example, inducing or inhibiting the formation of reactive metabolite may not greatly change the extent of covalent interaction if the pretreatment also causes parallel changes in other pathways; i.e., a degree of specificity is required. Consequently, enzyme perturbations may have dramatic effects on parent drug clearance without affecting the ratios of clearances, and no change in parent drug disposition may be associated with a large change in the extent of covalent binding. In the case of the fraction of the generated metabolite which covalently interacts with cellular constituents, it is likely that this is only affected by factors that change the clearance of the reactive metabolite, since the interaction is probably not enzymatically mediated. It is, therefore, difficult to predict changes in the magnitude of covalent binding reactive metabolite generation, toxicity from alterations in the pharmacokinetics of parent drug, or changes in the pattern of urinary metabolites (183, 185). These kinetic considerations do not, however, limit the value of covalent binding as an indicator of a putative role for a reactive metabolite in eliciting a particular toxicity (182).

VIII. In Vitro-In Vivo Prediction and Interspecies Extrapolation

In vitro systems, such as intact cells and various subcellular preparations, are routinely and extensively used to study a wide variety of aspects of drug metabolism. Much valuable knowledge and insight have been obtained in this fashion, but a major difficulty has always existed concerning the quantitative extrapolation of such findings to the intact organ or whole animal. In a similar fashion, it has not been generally possible to extrapolate a xenobiotic's pharmacokinetic characteristics established in one species to those in another. These problems are particularly relevant to the drug discovery and development process. A number of studies based on physiological modelling and allometric approaches have, however, indicated that reasonably good predictions can be made from in vitro data, especially with respect to clearance and elimination.

Under first-order conditions, a drug's free intrinsic clearance is equal to the summed ratio of the maximal rate of metabolism (V_{max}) and the Michaelis-Menten

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constant (K_m) for each individual pathway of metabolism (equation 20). In principle, therefore, this important parameter may be experimentally defined by conventional in vitro enzyme kinetic approaches using, for example, hepatocytes, a 9000 × *g* supernatant, or microsomes. Scale-up of V_{max} to the whole organ level may then be made based on a readily established mass recovery relationship for the particular preparation used. Incorporation of this in vitro determined free intrinsic clearance along with separately determined values of reversible plasma/blood binding ($f_B{}^u$) and blood flow rate (Q) into one of the physiological models of organ elimination (equations 18, 22, and 24) will then provide an estimate of the drug's clearance by the organ of interest. The feasibility of such a predictive approach based entirely on in vitro and/or a priori information was first investigated with 7 drugs having widely disparate extraction ratios (0.1 to >0.9) in the isolated perfused rat liver (388). An excellent agreement ($r = 0.988$) was found between the predicted extraction ratios using in vitro data from 9000 × *g* supernatant or microsomal preparations along with the venous equilibration model and the experimentally determined values. Using the same approach, the clearance of alprenolol in the isolated perfused rat liver (20 ml/min) was predicted (430) with varying success from studies with microsomes (12 ml/min), hepatocytes (15 ml/min), and a 9000 × *g* supernatant (18 ml/min). Diazepam's hepatic clearance in the rat (0.65 ml/min) was also well predicted (226) from studies with microsomes (0.62), as was the hepatic extraction ratio of chlorpheniramine (221) in the rabbit (0.84 versus 0.89). On the other hand, the hepatic extraction ratio of phenacetin in the rat was underestimated by 20 to 40% using kinetic measurements for O-deethylation obtained with hepatocytes (353), and similar differences between observed and predicted clearances were reported with phenytoin in the same species (98). In the latter instance, the use of a 9000 × *g* rather than a 100,000 × *g* supernatant fraction would probably have significantly improved the in vitro/in vivo correlation, since preparation of washed microsomes reduces the V_{max} of phenytoin metabolism by one-half (271). In vitro studies of monoamine oxidase activity in rat liver homogenate also provided a good prediction of 5-hydroxytryptamine's hepatic clearance in vivo (494). Studies of nonoxidative pathways of metabolism have been limited to the glucuronidation of morphine in the rhesus monkey, where the predicted hepatic extraction ratio estimated from liver microsomes significantly underestimated that determined in vivo (387), and the sulfation of acetaminophen by hepatocytes where application of the venous-equilibration, but not the undistributed sinusoidal, model provided an excellent prediction of clearance in the isolated perfused rat liver (353).

The use of in vitro parameters and of the venous equilibration model for elimination has also been applied to pulmonary metabolism. For example, no significant difference was found between the predicted and observed pulmonary clearance of mescaline by the isolated perfused rabbit lung (211), and the extraction ratio of benzo(a)pyrene 4,5-oxide by epoxide hydrolase was well predicted, but not that by glutathione S-transferase in the same preparation (431). Similarly, the agreement between the in vitro predicted and experimentally determined clearance of 5-hydroxytryptamine by the rabbit lung was poor despite the fact that data from the liver showed a good correlation (494). An interesting aspect of these studies (211, 494, 495) was that the overall metabolizing ability of the lung was compared to that of the liver. Because of the differences in intrinsic clearance, organ size, and blood flow, the relative contributions of the two organs to overall elimination from the body varied, as did the sensitivity of their clearances to changes in intrinsic clearance produced by enzyme inducers, or altered perfusion rates. Such conclusions would not have been predicted on the basis of in vitro enzyme activity alone and indicate a limitation of this type of approach compared to the application of clearance concepts. In vitro studies using isolated intestinal mucosal cells have also been used to successfully predict the extent of first-pass metabolism of phenacetin by the gastrointestinal tract in control and 3-methylcholanthrene-pretreated rats (254).

Good in vitro/in vivo correlations of drug metabolism have also been reported for drugs exhibiting nonlinear elimination, e.g., cytosine arabinoside (132) and ethoxybenzamide (288). In both of these case, hepatic clearance and plasma binding are sufficiently low so that the kinetic constants determined in vitro may be directly compared to those in vivo, i.e., no clearance model involving perfusion is required. Potential problems in evaluating Michaelis-Menten constants in vivo have, however, been discussed (360).

Successful in vitro/in vivo predictions require that the conditions of metabolism in vitro be identical to those in vivo. The latter are never known, and this is the crux of the problem. It would appear, however, that clearances by oxidative metabolism in the liver can be reasonably well predicted from in vitro data, although some consideration must be given to the particular preparation used, i.e., microsomes, cell supernatants, hepatocytes. Less success has been obtained in predicting pulmonary clearance, which is probably a reflection of the cellular heterogeneity of this organ. The in vitro underestimation of clearance by glucuronidation (387) is also not unexpected given the known lability of glucuronyltransferase activity; the possibility of using the physiological predictive approach to establish optimal conditions for in vitro studies in such situations has not, however, been explored. It must also be recognized that the success of in vitro/in vivo prediction of drug metabolism is critically dependent on the model of organ elimination selected

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for incorporating the in vitro determined intrinsic clearance. At high intrinsic clearance values, equivalent to an extraction ratio greater than about 75%, the accumulated experimental data for the liver suggest that the venous equilibration model (equation 18) underestimates, whereas the undistributed sinusoidal perfusion model (equation 22) overestimates the measured extraction ratios. The dispersion model (equation 24), on the other hand, provides a much better agreement between prediction and experimental observation (398). Additional comparative studies of the various models for prediction are clearly warranted, especially using drugs with low organ availabilities. It should be noted, however, that certain applications may not require a high degree of accuracy. In many instances, knowledge of an approximate clearance value may be valuable, for example, in determining whether a drug's hepatic extraction will impose "enzyme-limited" or "flow-limited" characteristics on the drug's pharmacokinetics. Because of the general success of the in vitro/in vivo prediction approach based on estimation of free intrinsic clearance and incorporation into a physiological model of elimination, further studies of its value need to be undertaken. Of particular interest, given the increasing availability of human liver microsomes, is the possibility of predicting in man a xenobiotic's in vivo hepatic clearance, or that of any other organ, at an early stage in the drug development process.

A related issue to in vitro/in vivo prediction is that of interspecies extrapolation, i.e., the ability to quantitatively predict a pharmacokinetic parameter or overall disposition of a drug in man, or any other species, based on data derived from one or more other animal species. In the past, such extrapolation has been largely empirical and descriptive despite the fact that the general issue of animal scaling has been studied for many decades (78, 420). One such approach, for example, has been to search for correlations between the same pharmacokinetic parameters for a series of related drugs in a single test species and also the animal of interest, e.g., man. If significant relationships exist, then the pharmacokinetics of another drug in the series could be predicted based on its behavior in the test animal. The comparative disposition of various benzodiazepines in dog and man (50), six β-lactam antibiotics in monkey and man (412), and nine weakly acidic and six weakly basic drugs in rat and man (413) have been investigated in this fashion. Reasonable correlations were obtained, particularly for parameters considered to reflect intrinsic values such as CL_{int}^{u} and $Vd/f_T{}^{u}$ rather than more hybrid values like elimination half-life. However, in spite of predictions for the group of drugs as a whole being quite good, it is probably unrealistic to expect this type of approach to provide precise estimates for any compound in particular. This probably reflects well-established qualitative and quantitative interspecies differences in drug disposition. However, recent studies suggest that useful predictive information concerning pharmacokinetic behavior can indeed be obtained, if appropriate allometric analysis is applied.

Mammals share a remarkable geometric similarity with each other, including a common arrangement of organs and interconnection by the vascular system. However, as animals decrease in size, many of their internal organ sizes, perfusion rates, and metabolic activities increase as a fraction of body weight, and smaller animals, therefore, have a greater opportunity to dispose of xenobiotics in any period of chronological time. If such interspecies differences can be accounted for as, for example, in physiologically based pharmacokinetic models (173, 291, 405), then scale-up becomes a simple matter of adjusting parameter values from the experimental species to those of the animal of interest. Examples of such a priori prediction include: thiopental (rat to human; ref. 42); methotrexate (mouse to rat, dog, human, and the sting-ray; refs. 43, 520, and 521); cytosine arabinoside (a priori/in vitro to human; ref. 132); sulfobromophthalein (rat to human; ref. 314); lidocaine (rhesus monkey to man; ref. 35); digoxin (dog to human; ref. 207); polychlorinated biphenyls (rat to mouse; ref. 456); styrene (rat to human; ref. 386); diazepam (rat to human; ref. 225), and phenobarbital, phenytoin, hexobarbital, quinidine, tolbutamide, valproic acid, and diazepam (all rat to human; ref. 414). Although relatively successful, this type of interspecies prediction is critically dependent on the physiological determinants of disposition remaining constant between species. While binding of xenobiotics to plasma proteins often exhibits interspecies variability, and can be readily determined in vitro, reversible interactions with tissue constituents appear to be quite similar in different animals (129, 150, 270, 411). Thus, steady-state tissue/blood or plasma distribution ratios determined in one species may be applied to other animals with a good likelihood that the drug's overall distribution will be well predicted. The renal clearance of xenobiotics also appears to be predictable between species on the basis of simple allometric considerations (43, 207, 520, 521), probably because of the constancy of function and size of the mammalian nephron (49). On the other hand, drug metabolism (free intrinsic clearance) varies considerably between species with respect to the type of biotransformation pathways involved, their activity, and localization in specific organs. For example, the presence of extrahepatic metabolism of diazepam in the rat (259) probably accounts for the lack of predictability when data in this species are allometrically scaled to man (414). Thus, interspecies predictions of drugs undergoing metabolism require some insight into the characteristics of this process in the involved species. An in vitro/in vivo prediction approach (vide supra) can provide such information, but its application in this fashion has been extremely limited (132). Other success-

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ful examples of physiologically based model predictions have invoked untested assumptions concerning the interspecies relationship between the drug metabolizing parameters; e.g., biotransformation increases allometrically with body weight (414, 456) or basal metabolic rate (386). Alternatively (35, 42, 225), previously obtained in vivo data in the species to be predicted have been utilized in a feedback fashion, which clearly undermines the purpose of the exercise. Qualitative differences in xenobiotic disposition between species also have to be considered in such models; e.g., biliary excretion is often an important elimination pathway in rat but not in humans. Finally, intraspecies differences in disposition must be recognized; for example, in man the interindividual variability in drug metabolizing ability is often 50- to 200-fold. How can interspecies extrapolation be performed or evaluated in such situations? Despite all of these potentially limiting factors, the potential of physiologically based pharmacokinetic models for interspecies prediction of drug disposition, including clearance, suggests that further evaluation and application of the approach are warranted and will likely be valuable and useful.

A practical difficulty of physiologically based models is that conventional pharmacokinetic parameters such as clearance and volume of distribution are not explicitly defined; rather, they are derived from the interaction of various a priori parameters, such as free intrinsic clearance and organ blood flows, etc. Some of these needed data are not routinely obtained and may in fact never be available for the drug of interest. Attempts have, therefore, been made to directly scale commonly estimated pharmacokinetic terms according to allometric considerations based, for example, on body weight (equation 38).

$$Y = aB^x \qquad \text{equation 38}$$

This empirically expresses some physiological or anatomical variable (Y) as a function of body mass (B) raised to a fractional power x, and a is a constant. In practice, a plot of log Y against log B yields a straight line with a slope equal to the allometric exponent which is the only parameter value of interest when considering the relative difference $(Y_1/Y_2 = B_1/B_2)^x$, between species (420, 484). Such an approach is founded on similar analyses for a wide variety of anatomical, physiological and functional parameters across a wide range of species (9, 77, 78, 420).

An increasing number of successful applications for different pharmacokinetic parameters have been reported: for example, the renal clearances of cytosine arabinoside (131), ceftizoxime (315), β-lactam antibiotics (412), and an aminothiadiazole anticancer agent along with its metabolic clearance (252). The total clearances of methotrexate (49, 130), cyclophosphamide (49, 307), a number of β-lactam antibiotics (412, 444), vinyl chloride (15), and tetrachlorobenzofluran (253), have also been examined, as has the relationship of body size to the free intrinsic clearances of antipyrine (48), phenytoin (48), and β-lactam antibiotics (412). In general, the allometric exponents for clearance cluster about a value of 0.75 which is considered to reflect the rate at which oxygen and oxidizable materials are delivered to metabolically active cells (55), although hepatic functions tend to be related to body weight by a slightly larger power ranging from about 0.85 to 0.90 (55, 77, 384, 420). In many of these studies allometric relationships for the volume(s) of distribution of the various drugs have also been examined. In many such cases, the power exponent is close to unity, suggesting that the ratio V_T/f_T^u is approximately proportional to body weight, where V_T is the summed physiological volume of extravascular tissue and f_T^u is the unbound fraction of drug in the tissue (52). Since elimination half-life is dependent on both clearance and distribution (equation 9), and both of these parameters are allometrically related to body weight, it would be expected that $t½$ would be similarly correlated. Data in the above studies as well as from other investigations (49, 316) confirm this expectation as well as indicating that the allometric exponent is approximately 0.25, a value which has been explained on the basis of the turnover time of energy utilization in an organism (49).

In many instances, the linear correlation coefficient associated with the log-log allometric plots is greater than 0.90 and indicates an acceptable level of prediction. In fact, with the β-lactam antibiotics (412), the predicted pharmacokinetic parameters in man based on the relationships developed from five other animal species indicated an average absolute error of between 20 and 70%. Given the simplistic nature of the allometric equations, which only consider interspecies differences in body weight, such predictability, i.e., a value within the range of about one-half and twice the observed data, is laudable and extremely encouraging for future applications, especially with investigational drugs prior to their administration to human subjects.

Interspecies scaling, according to a power function of body weight, is entirely empirical and arbitrary. Other scaling factors are possible, and a seminal contribution of Dedrick and coworkers was the recognition that the independent variable of pharmacokinetics, i.e., time, could serve such a purpose. A remarkable finding from their disposition studies with methotrexate in mouse, rat, dog, monkey, man, and the sting-ray was that the plasma concentration/time data from all of these species after intravenous or intraperitoneal administration were superimposable when the dose normalized plasma level was plotted against chronological time divided by $B^{0.25}$ (130, 521). This transformation converted chronological time into dimensionless time equivalents, subsequently termed pharmacokinetic time (49), and was an intuitive attempt to take into account the consequences of allo-

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metry. Namely, that the smaller the animal the more rapidly events occur with respect to chronological time; however, relative to an internal clock that is correlated with body weight, the rate of process tends to be species invariant (one unit of pharmacokinetic time is equivalent to B^{1-x} units of chronological time). Thus, for methotrexate, 1 min in a 22-g mouse is equivalent to about 7.5 min in a 70-kg man, but in both cases, these transform to an identical pharmacokinetic time of 260 units (52). The allometric and pharmacokinetic basis for this so-called elementary Dedrick plot was subsequently considered in detail and shown to be of general applicability providing that a drug's volume of distribution is directly proportional to body weight, i.e., its allometric exponent is unity (49, 52, 55). The biexponential plasma disappearance of antipyrine after rapid intravenous injection in the dog and man was found, for example, to be described by such a plot (52, 55). On the other hand, similar data for chlordiazepoxide elimination in these two species were not superimposable, although the areas under the curves were similar, thus confirming species invariance of clearance relative to pharmacokinetic time. However, by taking into account the smaller body weight-adjusted volume of distribution of chlordiazepoxide in man relative to the dog, i.e., a complex Dedrick plot, data from both species could be described by a single disposition curve (52, 55).

Boxenbaum has further extended the concept of pharmacokinetic time as well as considering some metaphysical aspects of drug disposition (51, 52, 55). He has speculated that, at least for phase I metabolism, each species has an equivalent amount of "pharmacokinetic stuff" for detoxifying naturally occurring xenobiotics, and although short-lived species metabolize quickly and long-lived species metabolize slowly, at the termination of their maximum life spans, each species will have cleared the same volume of these substances per kilogram of body weight. Accordingly, it has been suggested that a scaling factor involving the maximum life span potential (MLP) should be incorporated into certain types of interspecies extrapolations. Empirical support for this approach comes from the finding that hepatic microsomal activity by mixed-function oxidation is intrinsically lower in humans than in other mammalian species (53, 472). For example, the free intrinsic clearance of antipyrine in man deviates by approximately one-seventh from the allometric body weight relationship established in ten other species (48). However, a much improved prediction is obtained when CL^{u}_{int}/MLP is related to body weight, and similarly for phenytoin and clonazepam (53). This concept involving MLP has also been applied in a limited fashion to the Dedrick plot approach of interspecies scaling, but mainly to demonstrate its feasibility rather than any practical application (52). Clearly the ability for interspecies prediction of plasma concentration/time profiles for unchanged drug based on scaling according to pharmacokinetic rather than chronological time is a potentially valuable and useful tool that warrants additional consideration and application.

Allometric relationships appear to provide a general basis for interspecies scaling of pharmacokinetic parameters, such as clearance, as well as plasma concentration/time curves. Application of various empirical relationships, although somewhat limited, has demonstrated the feasibility of the approach. Hopefully, further studies, especially in the area of preclinical investigation during the new drug development process, will be forthcoming and improve the quantitative aspects of such critical predictions.

IX. Future Perspectives

Over the past 25 yr, pharmacokinetics has evolved from a somewhat esoteric aspect of pharmacology to a major tool of widespread application to the understanding and quantification of drug action. Clearance concepts have played a major and critical role in this development. At the functional level, knowledge of a drug's total and major fractional clearance values and of factors that determine them is now recognized as essential for the rational use of a drug. For example, considerable time, effort, and financial expenditure are committed to the determination of such parameters in various species and populations during the development of a drug. Clearance, in contrast to other elimination measurements, provides a unifying means of evaluating such comparative studies. Similarly, therapeutic success in a patient is frequently dependent on recognition of a particular individual's clearance of a drug and how this may differ from that in other patients. Such routine information is frequently required by regulatory agencies, and very large numbers of studies of this type will continue to be performed. Investigators should always be mindful, however, of the assumptions and limitations that are implicit in even the simplest application of certain clearance approaches. As in all science, uncritical and inappropriate use of a particular technique may yield erroneous and invalid conclusions.

More importantly, perhaps, the application of clearance concepts has shifted attention away from simple descriptive models towards more biologically based systems that permit mechanistic interpretation. Despite the fact that currently available clearance models are obviously oversimplifications of often complex events and interrelationships, they provide an integrated basis for determining and understanding how various factors affect the clearance process. At the same time, their deficiencies provide a stimulus for further experimentation and understanding. This will undoubtedly lead to improved clarification of the involved biological phenomena. The finer aspects of hepatic function will be of particular interest in future studies concerned with the formation and subsequent elimination of metabolites, as well as the uptake and removal of highly bound sub-

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stances. Current models may also require modification and improvement as more information becomes available on the prediction of organ clearance on the basis of in vitro data. It is also likely that clearance relationships in eliminating organs other than the liver, for example, the lung, kidney, and peripheral tissues, will need to receive additional study, since there is no a priori reason why a single model should apply equally well to all organs, or for that matter to all drugs. Such investigations will, at times, be challenging, but they undoubtedly will provide new and fundamental insights into the quantitative relationships involved in the elimination of drugs and other xenobiotics.

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