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PRESYSTEMIC DRUG ELIMINATION

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Presystemic elimination occurs when orally administered drugs are metabolized during their passage from the gut lumen to the systemic circulation. The organs that may be potentially involved are the intestine, the liver, and the lung, though the latter site has received relatively little attention. In the case of the gut and liver, the phenomenon results from the anatomical arrangement of the splanchnic circulation which allows these organs to act as a barrier, not only for drugs but also for noxious substances that might be ingested. This protective function is implicit in the naming of the portal circulation of the liver and has been recognized in general terms for centuries. It is only in the last decade, however, that the pharmacokinetic implications of presystemic elimination have been fully recognized. In 1969, Harris & Riegelman showed that the reduced plasma levels of aspirin after oral compared to intravenous administration were due to its elimination by both gut and liver before the drug could reach the systemic circulation (1). These workers coined the term *first pass effect* to describe the phenomenon. However, recognizing that the liver will continue to eliminate drug on all subsequent passes, we prefer the term *presystemic elimination.*

Criteria have now been developed to detect and quantify the extent of presystemic elimination and to indicate where it is occurring. Its detection requires only that bioavailability is less than the fraction of the dose absorbed. Bioavailability is defined as the ratio of the areas under the drug concentration/time curve in blood or plasma (AUC) after oral and intrave-

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nous administration, corrected for dose if necessary. The fraction of drug absorbed may be determined from the urinary and fecal excretion of drug and metabolites, usually as total radioactivity after oral administration of radiolabeled drug. It is on the basis of this type of information that most of the drugs undergoing presystemic elimination in man have been identified (Table 1). Identification of the organs involved is relatively simple in animals. For example, comparison of drug concentrations (AUC) after oral and intraportal or intraperitoneal drug administration will allow detection of intestinal elimination. Similarly, a difference between intravenous and intraportal AUC indicates an hepatic site. This general approach has been used to discern the hepatic and intestinal contribution to the presystemic elimination of such drugs as isoproterenol (22), aspirin (2), morphine (41), and nalorphine (42), and a full kinetic analysis has been derived recently by Gillette & Pang (70). Gügler and co-workers (33) have also used surgical protocaval anastomosis (which bypasses the hepatic contribution) to show that presystemic elimination of lidocaine occurs predominantly in the liver, while that of salicylamide occurs in both liver and intestine. Although these techniques are available for human studies, their application has been limited because of the invasive nature of such procedures. The portal vein can be catheterized transumbilically, but human studies have been confined to the measurement of drug and metabolites after oral drug administration (13, 58). Direct estimates of hepatic drug extraction using hepatic venous catherization are available for a limited number of drugs and can be used to estimate the extent of extrahepatic elimination, as well as the relative contribution of the liver to the presystemic effect. Finally, a patient with a therapeutic portocaval anastomosis has been studied to confirm that there was no intestinal metabolism of propranolol (71). Clearly, however, full evaluation in humans is seldom possible for both technical and ethical reasons. The best we can do, therefore, is to show the presence (or absence) of quantitative consistency between the magnitude of presystemic elimination and the value of the hepatic extraction ratio. The latter is estimated from the systemic drug clearance and liver blood flow. In this context it should be emphasized that a knowledge of whole blood concentrations (or the blood/plasma drug concentration ratio) is essential. While plasma levels alone can be used to quantify presystemic elimination, systemic drug clearance values must be based on blood concentrations in order to relate to blood (not plasma) flow and provide an estimate of organ extraction. Unfortunately, this information is not always available. Nonetheless, sufficient data exist to establish the principles involved and to test the general pharmacokinetic analyses that have been developed (2, 70, 72, 73). Rather than present an exhaustive review of the considerable literature now available, we seek to develop a simple quantitative approach and illustrate this with selected examples.

Table 1 Some drugs that undergo presystemic elimination

Drug	Animal model	Reference	Major site(s) of presystemic elimination	Comments
Acetylsalicylic acid	man	2	liver, gut	
	dog	1		
Alprenolol	man	3, 4	liver	availability dose dependent
Aminosalicylic acid	man	5		availability dose dependent
Chlorpromazine	man	6		metabolized in isolated rat intestinal loop in vivo (8)
	dog	7		
	rat	7		
Clonixin	rat	9		
	monkey	9		
	dog	9		
Doxepin	man	10		
Estradiol	man	11		metabolism occurs in isolated human jejunal loop in vivo
Estriol	man	12		
Flunitrazepam	dog	14		
Flurazepam	man	13		metabolism shown to occur in human intestine
Hydralazine	man	15		
Imipramine	man	16	liver	intestinal metabolism in man unlikely (17)
Isoetharine	dog	18	gut, liver	also metabolized by isolated perfused lung in dog (19)
Isoproterenol	man	20	gut, liver	also metabolized after intrabronchial administration in man and dog (21)
	dog	20, 22	gut, liver	
Isosorbide dinitrate	man	23		
Levodopa	man	24		
	dog	25	gut	metabolism occurs in rat gastric and intestinal mucosa in vitro (27); availability dose dependent in rat (26)
	rat	26	gut	
Levomeprazine	man	28		
Lidocaine	man	29–31	liver	
	dog	32, 33		
Meperidine	man	34		
Methotrimeprazine	man	35		
Methyldigoxin	man	36, 37	gut	
Methyltestosterone	man	38		
Metoprolol	man	39	liver	dose-dependent availability

Table 1 *(continued)*

Drug	Animal model	Reference	Major site(s) of presystemic elimination	Comments
Morphine	man	40		
	rat	41	gut, liver	two thirds of first-pass effects due to intestine in rat
Nalorphine	rat	42	liver, gut	60% of first-pass effect due to liver in rat
Naloxone	man	43		
	rat	44		
Naltrexone	man	45		
Nortryptyline	man	46	liver	
Oxprenolol	man	47	liver	
Oxyphenbutazone phosphate ester	dog	48		
Papaverine	man	49	liver	
Pentazocine	man	50		
Perphenazine	man	51		
Phenacetin	man	52		dose-dependent availability
Progesterone	dog	53		evidence of gut metabolism in vivo in dog
Propoxyphene	man	54, 55	liver	dose-dependent availability
Propranolol	man	56	liver	dose-dependent availability
Proscillaridin	man	57, 58	gut	may also be partly inactivated within gut lumen of man
Protryptiline	man	59		
Quinidine	man	60		
Salbutamol	man	61		
Salicylamide	man	62, 63		availability dose dependent
	dog	33	gut, liver	
Stilbestrol	rat	64		conjugation occurs in everted rat intestinal sacs in vitro
SU 13197 (Anti-arrythmic agent)	man	65		
Terbutaline	rat	66	gut, liver	
Triazolam (A benzodiazepine)	dog	68		
Trifluoperazine	rat	67	liver	
Verapamil	man	69		

HEPATIC PRESYSTEMIC ELIMINATION

The simplest and most thoroughly investigated example of presystemic elimination is the liver when it is the sole organ of metabolism. In this and all subsequent analyses, metabolism is considered to be first order (i.e. linear) and only the steady state situation is considered. The fraction of the drug which is eliminated from portal blood is given by the hepatic extraction ratio E_H, so that the remainder $(1-E_H)$ escapes into the systemic circulation. This remainder is then cleared from the circulation by the liver at a hepatic clearance rate Cl_H, equal to $Q_H E_H$ where Q_H is liver blood flow. Thus if a fraction F of the drug is absorbed and then subjected to presystemic elimination, the area under the concentration/time curve after oral administration, (AUC_o) of a dose (D_o) is given by

$$AUC_o = \frac{FD_o(1-E_H)}{Q_H E_H}. \qquad 1.$$

When the liver alone eliminates drug, hepatic clearance Cl_H can be derived after intravenous administration as

$$Cl_H = Q_H E_H = \frac{Div}{AUCiv} \qquad 2.$$

where Div is the dose administered intravenously. So substituting in equation 1,

$$AUC_o = \frac{FD_o(1-E_H)\ AUCiv}{Div}. \qquad 3.$$

Assuming absorption is complete ($F = 1$), then bioavailability (AUC_o/AUC_{iv}) is clearly dependent on the magnitude of the hepatic extraction ratio. Thus hepatic presystemic elimination is most important for highly extracted drugs. Poorly extracted compounds such as antipyrine, warfarin, and tolbutamide undergo little presystemic extraction, and their disposition is not appreciably influenced by the route of administration (74). Although presystemic hepatic metabolism has been suggested for several drugs on the basis of their high systemic clearance after intravenous administration, the data are not always complete. Direct determination of the relative contribution of the liver to presystemic elimination requires invasive catheterizations to determine organ clearances, and is therefore not frequently undertaken. Even without this information, however, an indication of the extent of extrahepatic metabolism can be obtained from the quantitative consistency in the data. For example, on the basis of bioavailability and absorption measurements, an apparent value for E_H can be obtained from

Equation 3. This value can be used to calculate hepatic clearance assuming a mean value for liver blood flow. If only the liver is involved, this estimate of hepatic clearance should closely approximate the determined value for intravenous (systemic) drug clearance. Alternatively, an estimate of hepatic extraction on the basis of known systemic clearance and assumed liver blood flow should be consistent with the bioavailability estimate ($1 - E_H$). It is this type of information that has been used to substantiate the predominantly hepatic presystemic elimination of propranolol (71), lidocaine (29), papaverine (49), imipramine (16), metoprolol (39), and alprenolol (4). In the case of propranolol (75), extrahepatic metabolism has been excluded by direct measurement of hepatic extraction and a similar approach showed that hepatic elimination accounted for 70% of the total body clearance of lidocaine (31).

The presystemic effect is also of great importance in determining the concentrations of metabolites formed after oral administration. Although the fraction of the dose that is metabolized is independent of the route of administration, larger doses will be required after oral drug to match unchanged drug concentration after intravenous administration. Higher metabolite concentrations will therefore be attained. This becomes important if such metabolites are either active or toxic as may occur in the case of lidocaine (32). Recently Pang & Gillette (76) derived the following relationship for the area under the metabolite(s) concentration-time curve $AUC(m)$, after administration of drug orally or intravenously

$$AUC(m) = \frac{fm(1 - E_m)D}{Cl_{s(m)}} \qquad 4.$$

where fm is the fraction metabolized, E_m the hepatic extraction of metabolite and $Cl_{s(m)}$ is clearance of metabolite from the systemic circulation. It should be noted that this analysis assumes that metabolite generated in the liver can be further metabolized before being released into the systemic circulation. That is, the metabolite also undergoes presystemic elimination giving the $(1 - E_M)$ term.

Until now, we have assumed that elimination is linear and independent of dose. However dose-dependent presystemic elimination has been described, for example, for propranolol (71), metoprolol (39), and alprenolol (3) after single oral doses. Although nonlinear availability of propranolol has been questioned (77), the phenomenon has been confirmed recently (78). With these drugs, the AUC increased with increasing oral doses, implying a saturation phenomenon which does not occur over the usual intravenous dose range. In addition, metabolic pathways may differ according to the route of administration, so that the active 4-hydroxylated metabolite of propranolol appears only after oral administration (79). These data

suggest that nonlinear hepatic extraction may involve saturation of a metabolic pathway. It has also been suggested that saturable drug binding in the liver may be involved (80, 81), but it is entirely possible that saturable binding and metabolism are linked processes. During chronic propranolol administration, drug accumulates to an unexpected extent, and accumulation is associated with a reduced presystemic extraction (82). Finally, at steady state, the ratio of 4-hydroxylated metabolite to parent drug falls with increasing doses (83). Clearly, the kinetics of presystemic elimination can be complex and difficult to assess especially since different conditions exist during chronic oral and i.v. administration. One way to overcome the problem is to concurrently administer native drug by one route and labeled compound by another. By analyzing the two moieties separately (either by scintillation counting or mass spectrometry), systemic (intravenous) and oral kinetics can thus be simultaneously assessed during oral administration. This is an extremely powerful technique and has been used to investigate the nonlinear kinetics of propranolol (82). It may also be applied to the investigation of metabolite generation by administering parent drug and labeled metabolite simultaneously (84).

In addition to its descriptive usefulness, analysis of the oral and intravenous kinetics of certain highly extracted drugs has recently found application in estimating the biological determinants of drug disposition, i.e. liver blood flow and intrinsic clearance.

Kinetic Estimation of Liver Blood Flow

Several workers have rearranged the original equation of Gibaldi et al (85) and Rowland (2) to estimate hepatic blood flow. For example, by definition

$$E_H = \frac{AUC_{iv} - AUC_{hv}}{AUC_{iv}}, \qquad 5.$$

where AUC_{hv} is the area under the whole blood concentration-time curve of drug in the hepatic veins. Substituting for E from Equation 3 and assuming complete absorption gives

$$AUC_{hv} = \frac{AUC_o\, Div}{D_o}. \qquad 6.$$

According to Fick, liver blood flow, Q_H, is given by

$$Q_H = \frac{Div}{AUC_{iv} - AUC_{hv}} \qquad 7.$$

and therefore substituting for AUC_{hv} from Equation 6 gives

$$Q_H = \frac{D_o D_{iv}}{AUC_{iv}\mathrm{D}_o - AUC_o\mathrm{D}_{iv}}. \qquad 8.$$

This method requires an indicator that is fully absorbed and metabolized only by the liver. Propranolol fulfills these conditions and has been used by Kornhauser et al (56). They administered native drug orally together with ^{3}H-labeled drug intravenously and obtained consistent estimates of liver blood flow ranging from 0.79 to 2.16 liter/min. Racemic propranolol, containing the dextro- and levorotatory isomers in equal proportions, is not an ideal compound as it lowers liver blood flow as a result of β-blockade (86). The *d*-isomer, which is almost devoid of pharmacological activity at clinical dosage, would be more suitable (87).

Intrinsic Hepatic Clearance

The realization that presystemic elimination involved highly extracted drugs refocused attention on the fact that the systemic clearance of these drugs was dependent on hepatic blood flow as well as enzyme activity (86). Enzyme activity can be described as a clearance term, intrinsic clearance (Cl_i'). This is defined as the volume of liver water cleared of drug in unit time. In terms of enzyme kinetics Cl_i' reduces to V_{max}/km under first-order conditions (88). The steady state removal rate of total drug (bound and free) by the whole organ, R, is given by definition as

$$R = Cl_i' \ f_B C_L$$

where C_L is the free drug concentration in the liver (assumed to equal that in blood) and f_B the fraction of free drug in blood. R is also given by

$$R = Q\ (C_{in} - C_{hv})$$

where C_{in} and C_{hv} are inflow and effluent (hepatic venous) concentrations. Thus assuming C_{in} is equal to C_{iv}

$$Q(C_{iv} - C_{hv}) = Cl_i' f_B C_L. \qquad 9.$$

Hepatic clearance, Cl_H, is then

$$Cl_H = \frac{Q(C_{iv} - C_{hv})}{C_{iv}} = \frac{Cl_i' f_B C_L}{C_{iv}}. \qquad 10.$$

This equation gives a model-independent description of the effects of flow, intrinsic clearance, and drug binding on hepatic clearance. Unfortunately, it cannot be solved unless an assumption about C_L is made. Two models are available with critically different assumptions: the sinusoidal model first proposed by Brauer (89) and the venous equilibration model first proposed by Rowland (2). The sinusoidal model assumes that drug concentrations decline exponentially along the sinusoids so that the relevant C_L is the logarithmic average of C_{in} and C_{hv} (90). In this case

$$Cl_H = Q(1 - e^{\frac{-Cl_i' f_B}{Q}}) \quad 11.$$

The venous equilibration model assumes that C_L equals the free drug concentration leaving the liver in the hepatic veins. In this case

$$Cl_H = \frac{Q\ Cl_i' f_B}{Q + Cl_i f_B}. \quad 12.$$

The predictions that these two models make of the effects of altered flow and intrinsic clearance have been compared by Wilkinson (91) and Pang & Rowland (92). In terms of the effects on systemic (i.v.) clearance, the predictions are not very different and are often beyond precise experimental detection. However, the effects of altered flow on drug concentrations in the hepatic veins predicted by the two models are really quite divergent. The difference becomes important because AUC_{hv} is equal to AUC_o (see Equation 7). According to the venous equilibration model AUC_{hv} (and AUC_o) should be unaffected by alterations in hepatic blood flow. In perfused rat livers this appears to be true concerning both propranolol and lidocaine kinetics (93). An important corollary of this is that the apparent clearance of an oral dose (D/AUC_o) is numerically equal to the intrinsic clearance of total drug ($Cl_i' f_B$). So that

$$\frac{D}{AUC_o} = Cl_i' f_B. \quad 13.$$

Thus a simple method would be available to measure both blood flow and intrinsic clearance independently from oral and intravenous kinetics as in the case of propranolol (56). If the sinusoidal model applies, however, the relationship between flow and AUC_o is more complex and AUC_o will fall as flow is reduced. This appears to be true in the case of galactose elimination by the perfused liver (90, 95). In this instance AUC_o is a more complex function (92).

$$AUC_o = \frac{D(e^{\frac{-Cl_i' f_B}{Q}})}{Q(1 - e^{\frac{-Cl_i' f_B}{Q}})} \quad 14.$$

An extensive comparison of the two models has been made by Pang & Rowland (92) who simulated the effects of altered flow, intrinsic clearance, and binding in blood on both oral and intravenous kinetics. At this time it is not possible to state whether one or other model is the more valid. Indeed, it appears that it will depend on the drug in question, and an intermediate model may apply for some compounds (J. R. Gillette, personal communication).

Factors Altering Presystemic Hepatic Elimination

Both models predict, however, that altering intrinsic clearance will have a greater effect on drug concentrations after oral than after intravenous administration (2, 93). This has been shown to be true concerning the stimulation of metyrapone metabolism by phenytoin (96), of alprenolol by pentobarbital (97), and for the inhibition of propranolol metabolism by chlorpromazine (98). In each case, AUC_o was markedly altered with little or no change in intravenous kinetics. This phenomenon occurs because any change in intrinsic clearance of a highly extracted drug does little to alter systemic clearance which is normally flow-dependent. On the other hand, even a small change in hepatic extraction may produce a large change in availability ($1 - E$). For example, let us assume that enzyme induction increases the extraction of a drug from 0.9 to 0.95. This would result in an insignificant change in systemic clearance (QE). However, availability ($1 - E$) would be essentially halved from 0.10 to 0.05. The effects of altering blood flow are the opposite, so that intravenous kinetics are affected more than those after oral administration. For example, although increasing blood flow increases the systemic clearance of a highly extracted drug, it does so despite a fall in the extraction ratio. The reduced extraction increases both availability and peak drug concentration and tends to offset the effect of reduction in half-time caused by increased systemic clearance. Thus AUC_o is little changed (93). No human data are available to support this although simulations in the perfused rat liver are consistent (94). It should be emphasized that these considerations apply to blood flow alterations throughout the dosage interval. Recently, McLean and co-workers (99) have suggested that a short-lived increase in hepatic blood flow, such as may occur following a meal, may cause the decrease in extraction ratio exclusively during absorption to exceed the effect of the increase in average drug clearance during the dosage interval. The AUC after oral administration and thus the bioavailability would therefore increase. These workers have postulated that such variations in hepatic blood flow could account for the increased bioavailability of single doses of metoprolol and propranolol when administered with food compared with during the fasting state (100).

Finally, the consequences of altered drug binding in blood on the disposition of highly cleared drugs are also route-dependent (92). After intravenous administration, the clearance of highly extracted drugs may be little affected by altered binding. For example, the extraction ratio for propranolol so far exceeds the free fraction (0.05–0.10) that total drug clearance is unaffected by binding changes (93). Therefore, binding displacement interactions involving highly cleared drugs should produce a permanent increase in free drug concentrations in whole blood. This contrasts sharply with the effects of altered binding in blood on poorly extracted compounds,

in which only a transient rise in free concentration is expected (93). In contrast, after oral administration of the highly extracted drugs, total drug concentrations depend on intrinsic free drug clearance (which will be unaltered) and the free drug fraction in blood (see Equation 13). Thus it would be expected that total drug levels would fall and that free drug concentration would remain relatively unchanged. To date no examples exist to verify these theoretical assumptions.

Presystemic elimination can also be profoundly altered in patients with liver disease. In addition to the effects of parenchymal damage on intrinsic clearance in cirrhosis, both intrahepatic and extrahepatic vascular shunts may develop. These shunts will increase oral drug availability because they bypass the presystemic effect. The resultant effects will be more marked after oral than after intravenous administration. This situation can be simply modeled by assuming that only a fraction (f_L) of portal blood flow passes to the functioning parts of the liver. Then

$$AUC_o = \frac{Df_L(1 - E_H)}{Cl_s} + \frac{(1 - f_L)D}{Cl_s} = \frac{D(1 - f_L E_H)}{Cl_s}. \qquad 15.$$

The most obvious form of extrahepatic shunt is produced surgically by performing an end-to-side portovaval anastomosis. Gügler and co-workers (33) showed that this procedure increased lidocaine availability in dogs from 14.8 to 81.3%. Predictably, because it is a poorly extracted compound, the kinetics of antipyrine were unaltered. Shand & Rangno (71) reported a single patient with a protocaval anastomosis in whom propranolol availability was complete. In addition, this procedure will decrease total liver blood flow, and reduced systemic clearances of the highly extracted compounds, indocyanine green and *d*-propranolol (101) have been observed in such patients.

It should be mentioned that the presence of vascular shunts renders the pharmacokinetic estimation of liver blood flow invalid. Under these circumstances apparent liver blood flow $\hat{Q}$ calculated from Equation 16 is

$$\hat{Q} = \frac{Q}{f_L}. \qquad 16.$$

Although as yet untested, it should be possible to measure blood flow in the traditional manner by catheterization of the hepatic veins and then calculate the fraction of mesenteric blood that is shunted using Equation 16.

INTESTINAL PRESYSTEMIC ELIMINATION

That drugs may be metabolized by both gut flora (102) and by the intestinal wall (103) is clearly established. However, precise quantitative descriptions of the effects of intestinal elimination are lacking, largely because of our

ignorance of the biology of the system. The critical question is whether intestinal presystemic and systemic extractions are quantitatively the same. In the case of the liver, this is true because drug is always delivered by the bloodstream. The intestine, however, is also directly exposed to drugs during the absorption process, and there is certainly no a priori reason to suggest that presystemic elimination should be quantitatively the same as elimination following systemic drug administration. In the latter case, intestinal clearance can be expressed in terms of mesenteric blood flow, intrinsic clearance, and binding in blood, and the extraction ratio has its traditional meaning. In contrast, mucosal metabolism after luminal exposure depends not only on intrinsic clearance, but also on the rate of transfer of drug across the intestine (which in turn is a complex function of permeability, surface area, and blood flow). Thus the fraction of the dose eliminated during initial absorption will not necessarily equate with the intestinal extraction ratio after systemic administration. This difference would be magnified if drug were secreted in bile or if the gut or gut flora could metabolize a biliary metabolite to the parent compound.

Metabolism within the lumen would also seem less likely to recur once the drug has been fully absorbed or after systemic administration. Intraluminal metabolism would then simply act to reduce the fraction of the dose that is absorbed. Again, however, biliary secretion of drug or metabolites could complicate the situation.

On the basis of this discussion, we can distinguish two possible types of presystemic intestinal elimination. The first is the situation in which the fraction eliminated presystemically is equal to the extraction ratio after systemic administration. Kinetically this is identical with the situation in the lung and the liver, and we would propose the term *postabsorptive* to describe it. The second situation involves intestinal metabolism either in the gut lumen or wall that results in presystemic elimination of a fraction of the dose that is *not* equal to the systemic intestinal extraction ratio. We suggest the term *preabsorptive* to describe this phenomenon. It seems likely that preabsorptive extraction would generally be greater than systemic extraction, but the opposite is at least theoretically possible, depending on the anatomical relationship between the sites of absorption and metabolism.

Clearly, pharmacokinetic analyses must account for these two alternatives and the equations are quite easy to derive (104). Unfortunately, the available data do not always lend themselves to easy interpretation since few workers publish whole blood concentrations. In addition many drugs that are metabolized by the gut are also extracted by the liver. Despite these limitations, the literature contains some data to support both pre- and postabsorptive metabolism.

Curry and his co-workers (7) have investigated the kinetics of chlorpromazine in the rat. They suggested that presystemic elimination occurs entirely in the intestine because the AUCs after intravenous and intraperitoneal administration (which results in presystemic hepatic elimination) are identical, while oral availability is less than 50%. Metabolism of the drug was also demonstrated in isolated loops of intestine (8). The general equation describing blood concentrations after oral administration of drugs metabolized only by the gut is

$$AUC_o = \frac{f_I D}{Q_M E_I}, \qquad 17.$$

where f_I is the fraction eliminated presystemically by the gut, Q_M is the mesenteric flow, and E_I is intestinal extraction. In cases where presystemic and systemic extractions are equal (postabsorptive), then $f_I = (1 - E_I)$ and

$$AUC_o = \frac{(1 - E_I)D}{Q_M E_I}. \qquad 18.$$

Although the problems with reanalysis of published data are obvious, this equation would seem to describe the situation with chlorpromazine metabolism in the rat. Presystemic extraction of 50% is generally consistent with a plasma clearance of about 30 ml/kg/min. Assuming a blood/plasma ratio of about unity and a mesenteric flow of 45 ml/kg/min in the rat (105), this would give an intestinal extraction of about 66%. Certainly, the presystemic effect does not appear any greater than that which would be compatible with systemic clearance. A similar situation appears to apply to the kinetics of aspirin. As mentioned, this drug appears to be metabolized in both liver and gut in which case

$$AUC_o = \frac{f_I(1 - E_H)D}{Q_M E_I + Q_H E_H}. \qquad 19.$$

The contribution of the intestine to presystemic elimination can be judged from the AUCs after oral and intraportal drug administration. In three dogs studied by Harris & Riegelman (1) intestinal extraction after oral administration averaged 28% (E_I). The hepatic extraction (E_H) was 36%. In those same animals the systemic clearance can be calculated as 30 ml/kg/min (assuming a blood/plasma concentration similar to man of 0.8) (2) in dogs weighing 20 kg. Assuming a hepatic blood flow of about 50 ml/kg/min, hepatic clearance would equal 18 ml/kg/min leaving 12 ml/kg/min as intestinal clearance ($Q_M E_I$). Assuming a mesenteric flow of 35 ml/kg/min (70% of portal flow), then E_I can be calculated as 0.34, which is not too dissimilar to the 28% presystemic extraction found experimentally. A similar conclusion, that presystemic and systemic extractions were similar in

man, was reached by Rowland and co-workers (106). In this type of situation, we may consider the liver and gut as a single functional unit, so that Equation 19 reduces to

$$AUC_o = \frac{(1 - E_s)D}{Q_H E_s} \qquad 20.$$

in which E_s is the combined, splanchnic extraction. This can be verified experimentally by showing compatibility between presystemic extraction, known liver blood flow, and systemic whole blood clearance.

In contrast with these examples, several drugs appear to undergo true preabsorptive elimination, that is, when $(1 - f_I)$ does not equal E_I in Equations 18 and 19. One of the more clear-cut examples involves β-methyldigoxin. Hinderling and co-workers (36, 37) investigated the drug's kinetics in man using whole blood concentrations and calculated only an 8% metabolic extraction after intravenous administration. This was much less than the 20% presystemic extraction observed to occur after oral administration. The relative role of gut wall and intestinal contents is unclear. L-Dopa is also not eliminated to any significant extent by the liver (107), yet it undergoes significant presystemic elimination in man (24) and dog (25). Evidence exists for metabolism in the gut lumen and intestinal wall (27). Quantitative data obtained in the dog showed no difference between the kinetics of the drug after intravenous or intraperitoneal administration but only a 44% availability after oral administration (25). Clearly, acid hydrolysis, bacterial degradation, and intestinal metabolism could all contribute to this high extraction.

Another line of evidence suggesting that preabsorptive metabolism may occur in the gut involves quantitative changes in metabolite excretion. Provided that presystemic elimination is postabsorptive (be this in liver, lung, or intestine) then the fraction of the administered dose that is excreted as a given metabolite should remain constant irrespective of the route of administration. This statement applies only when elimination remains first order, when the metabolite represents the final product, and provided other pathways are not operative. Thus differences can appear when unequal doses are used for the various routes of administration and metabolic pathways become saturated. Under these conditions even drugs metabolized only by the liver can show altered metabolic pathways after oral administration. 4-Hydroxypropranolol is seen in plasma only after oral administration because the higher concentrations attained presumably saturate an alternate pathway. When both liver and gut metabolism occurs, such problems of nonlinearity tend to confound the issue. Some very large differences in metabolite excretion after administration orally and intravenously have been noted, however, indicating that gut wall metabolism may be preab-

sorptive. Conway and co-workers (66) investigated the metabolism of terbutaline in rats after the same dose was administered intravenously, intraperitoneally, and orally. They found that only one metabolite, the glucuronide, was formed; that absorption was complete; and that the ratio of metabolite to parent compound was 1:1 i.v. 2:1 i.p., and 13:1 after oral administration. The reason for the difference between the intravenous and the intraperitoneal values is unclear, although greater biliary secretion and subsequent metabolism by gut wall may occur. The very much greater ratio of metabolite to unchanged drug after oral administration does strongly suggest, however, that a greater fraction is metabolized after direct exposure to the mucosa than after recycling in blood. This would account for the low (3%) bioavailability. Similarly, Evans and co-workers (61) found a greater excretion of the major metabolite of salbutamol after oral (61%) compared to intravenous administration (27%) in man. Considerable information on the kinetics of isoproterenol is available in both animals and man. This drug is metabolized by both liver and gut, but the pathways differ in that the liver O-methylates isoproterenol while the gut produces sulfate conjugates (22). These workers also compared the excretion of these metabolites after intravenous, intraportal, and oral administration in the dog. The fraction of conjugates was greater (50%) after oral than after intravenous or intraportal administration (less than 10%). Conolly and co-workers (20) found that only unchanged isoproterenol (60%), 3-O-methyl isoproterenol, and its conjugates were excreted after intravenous administration in man. In marked contrast, the sulfate conjugate appeared only after oral administration of similar doses. Essentially the same results were obtained in dogs. That sulfate conjugation occurs in the gut of dogs was shown directly by George and co-workers (108). The finding of sulfate conjugates only after oral administration strongly suggests that this pathway is used largely after direct mucosal exposure and not on recycling. Interestingly salicylamide is also sulfated, and its administration can compete for available sulfate, thereby increasing absorption of unchanged isoproterenol from gut loop (108) or after oral drug administration in dogs (109). This inhibition could be reversed by giving the sulfate donor cysteine. Cysteine also prevents the saturation of the conjugation of salicylamide with sulfate that occurs after oral drug administration in man (62).

The most obvious examples of preabsorptive elimination might be expected to occur with drugs that are metabolized by the gut flora. More than 60 bacterial species have been identified in the gut or feces of animals and man, many of which are capable of carrying out a wide variety of metabolic reactions with foreign organic compounds (110). These include hydrolytic, reductive, and degradative reactions, which may result in the production of metabolites more pharmacologically active than the parent compound,

in addition to decreasing the bioavailability of unchanged drug after oral administration (111). If the metabolites produced by these reactions are poorly absorbed, radiolabel tracer studies will reveal a large proportion of administered radioactivity as metabolites in the feces. If, however, these metabolites are well absorbed from the gut, a large discrepancy between urinary radioactivity and levels of unchanged drug will be seen so that presystemic elimination will be more obvious. Such a phenomenon will truly be preabsorptive if it occurs only once before the drug is either completely absorbed or excreted in the feces. Exceptions will occur, however, if the drug is actively transported back into the gut lumen or if enterohepatic recycling takes place.

Evidence is accumulating that the gut flora are implicated in the metabolism of L-dopa in man (112, 113) as well as animals (114), thus contributing to its high presystemic metabolism.

Salicylazosulfapyridine (sulfasalazine) is used widely in the treatment of ulcerative colitis, and analysis of plasma and urinary levels after oral administration in man indicates no absorption of unchanged drug (115) although cumulative excretion of metabolites in urine indicates good absorption of the metabolites. The parent compound appears to reach the colon before being cleaved at the azo linkage by intestinal bacteria to form 5-aminosalicylic acid and sulfapyridine. These products may then be further metabolized before or after absorption occurs. In the same way, prontosil and Neoprontosil® are converted to sulfanilimide by rat intestinal bacteria (116). Clearly, the role of bacterial degradation in the metabolism of other poorly available compounds warrants further study.

PULMONARY PRESYSTEMIC METABOLISM

Compounds administered by the oral or intravenous route or by inhalation must first pass through the lung before being available to the systemic circulation. If metabolism occurs during the passage through this organ, bioavailability will be decreased. In a situation analogous to the gut, orally or intravenously administered drug will also undergo metabolism during each pass through the pulmonary vascular bed, whereas inhaled drug may undergo a "once only" preabsorptive effect.

Drug administered by the oral or intravenous route has to traverse the pulmonary capillary bed where it is exposed to a vast surface area of endothelial cells. Metabolic transformation can occur either to inactive or more active compounds and it appears that the lung also shows a degree of specificity (117). Although the metabolic reactions are varied and involve amines, peptides, fatty acids, nucleotides, and steroids, certain compounds in each class escape biotransformation. Norepinephrine is inactivated by

passing through the pulmonary circulation while epinephrine is not. Halothane appears to reduce the degree of inactivation of norepinephrine (118). Angiotensin I is activated to angiotensin II on passage through the pulmonary vascular bed, and the latter peptide is not then acted on at the same site (119). Metabolism occurring during passage through the lung circulation must be distinguished from an uptake process which mainly involves basic, lipophilic amines such as chlorpromazine, propranolol, imipramine, mepacrine, quinine, emetine, methadone, and others (120). Such compounds are eventually released to be metabolized elsewhere. Of these compounds, only methadone has been shown to be metabolized (in isolated perfused rabbit lungs) and the contribution of the lung to the total systemic clearance of methadone was small (121). Since the uptake process is reversible, the area under the blood concentration-time curve after oral administration of these compounds will not be affected and availability will not change.

Drugs administered by inhalation will first be exposed to the epithelial cells of the trachea, bronchi, and small airways. It is evident that the efficiency of delivery of drug by aerosol to these sites is poor and less than 10% of inhaled isoproterenol reaches the small airways (21), the rest being swallowed and absorbed from the gastrointestinal tract. When ^{3}H-labeled isoproterenol was introduced directly into the small airways by bronchoscope in man, however, 3-O-methylisoproterenol was the main radioactive species identified in the urine. After intravenous administration, a much larger proportion of the dose was excreted as free isoproterenol and after oral administration, conjugated isoproterenol was the predominant compound. When isoproterenol was introduced into the vascular system of isolated dog lungs perfused with plasma, isoproterenol predominated in the plasma at early times. When the drug was introduced intrabronchially, 3-O-methylisoproterenol was the predominant plasma metabolite and its concentration always exceeded that of isoproterenol (19). These findings suggest that a preabsorptive effect does occur and that this is quantitatively different from the postabsorptive elimination that occurs after intravenous administration.

SUMMARY

The presystemic elimination of a large number of compounds is clearly established and represents a common and unavoidable cause of reduced bioavailability. The liver, intestine, and lungs have been identified as potential organs contributing to this effect but only in the case of the liver are sufficient data available for comprehensive analysis. More information on intestinal and pulmonary metabolism is clearly needed. Simple methods of

kinetic analysis already exist, however, to assess the relative importance of these organs in presystemic elimination, especially in relation to the pre- and postabsorptive types of elimination that may occur.

Literature Cited

1. Harris, P. A., Riegelman, S. 1969. Influence of the route of administration on the area under the plasma concentration-time curve. *J. Pharm. Sci.* 58: 71–75
2. Rowland, M. 1972. Influence of route of administration on drug availability. *J. Pharm. Sci.* 61:70–74
3. Åblad, B., Ervik, M., Hallgren, J., Johnsson, G., Sölvell, L. 1972. Pharmacological effects and serum levels of orally administered alprenolol in man. *Eur. J. Clin. Pharmacol.* 5:44–52
4. Åblad, B., Borg, K. O., Johnsson, G., Regardh, C. G., Sölvell, L. 1974. Combined pharmacokinetic and pharmacodynamic studies on alprenolol and 4-hydroxyalprenolol in man. *Life Sci.* 14:693–704
5. Engeberg-Pederson, H., Mörch, P., Tybring, L. 1964. Kinetics of serum aminosalicylic acid levels. *Br. J. Pharmacol.* 23:1–13
6. Dahl, S. G., Strandjord, R. E. 1977. Pharmacokinetics of chlorpromazine after single and chronic dosage. *Clin. Pharmacol. Ther.* 21:437–48
7. Curry, S. H., Derr, J. E., Maling, H. M. 1970. The physiological disposition of chlorpromazine in the rat and dog. *Proc. Soc. Exp. Biol. Med.* 134:314–18
8. Curry, S. H., D'Mello, A., Mould, G. P. 1971. Destruction of chlorpromazine during absorption in the rat *in vivo* and *in vitro*. *Br. J. Pharmacol.* 42:403–11
9. Katchen, B., Buxbaum, S., Meyer, J., Ning, J. 1973. Metabolism and pharmacokinetics of a new nonsteroid, anti-inflammatory agent. 2-(3-chloro-o-toluidino) nicotinic acid (clonixin) in rats, dogs, and monkeys. *J. Pharmacol. Exp. Ther.* 184:453–64
10. Ziegler, V. E., Biggs, J. T., Wylie, L. T., Rosen, S. H., Hawf, D. J., Coryell, W. H. 1978. Doxepin kinetics. *Clin. Pharmacol. Ther.* 23:573–79
11. Diczfalusy, E., Franksson, C., Lisboa, B. P., Martinsen, B. 1962. Formation of oestrone glucosiduronate by the human intestinal tract. *Acta Endocrinol. Copenhagen* 40:537–51
12. Diczfalusy, E., Franksson, C., Martinsen, B. 1961. Oestrogen conjugation by the human intestinal tract. *Acta Endocrinol. Copenhagen* 38:59–72
13. Mahon, W. A., Inaba, T., Stone, R. M. 1977. Metabolism of flurazepam by the small intestine. *Clin. Pharmacol. Ther.* 22:228–33
14. Kaplan, S. A., Alexander, K., Jack, M. L., Puglisi, C. V., deSilva, J. A. F., Lee, T. L., Weinfeld, R. E. 1974. Pharmacokinetic profiles of clonazepam in dog and humans and of flunitrazepam in dog. *J. Pharm. Sci.* 63:527–32
15. Talseth, T. 1976. Studies on hydralazine. iii. Bioavailability of hydralazine in man. *Eur. J. Clin. Pharmacol.* 10:395–401
16. Gram, L. F., Christiansen, M. 1975. First-pass metabolism of imipramine in man. *Clin. Pharmacol. Ther.* 17:555–63
17. Dencker, H., Dencker, S. J., Green, A., Nagy, A. 1976. Intestinal absorption, demethylation and enterohepatic circulation of imipramine. *Clin. Pharmacol. Ther.* 19:584–86
18. Williams, F. M., Briant, R. H., Dollery, C. T., Davies, D. S. 1974. The influence of the route of administration on the urinary metabolites of isoetharine. *Xenobiotica* 4:345–53
19. Briant, R. H., Blackwell, E. W., Williams, F. M., Davies, D. S., Dollery, C. T. 1973. The metabolism of sympathomimetic bronchodilator drugs by the isolated perfused dog lung. *Xenobiotica* 3:787–99
20. Conolly, M. E., Davies, D. S., Dollery, C. T., Morgan, C. D., Paterson, J. W., Sandler, M. 1972. Metabolism of isoprenaline in dog and man. *Br. J. Pharmacol.* 46:458–72
21. Blackwell, E. W., Briant, R. H., Conolly, M. E., Davies, D. S., Dollery, C. T. 1973. Metabolism of isoprenaline after aerosol and direct intrabronchial administration in man and dog. *Br. J. Pharmacol.* 50:581–91
22. Conway, W. D., Minatoya, H., Lands, M., Shekowski, J. 1968. Absorption and elimination profile of isoproterenol. iii. The metabolic fate of dl-isoproterenol-7-^{3}H in the dog. *J. Pharm. Sci.* 57: 1135–41
23. Assinder, D. F., Chasseaud, L. F., Taylor, T. 1977. Plasma isosorbide dinitrate concentrations in human subjects after administration of standard and sus-

tained-release formulations. *J. Pharm. Sci.* 66:775–78
24. Abrams, W. B., Coutinho, C. B., Leon, A. S., Spiegel, H. E. 1971. Absorption and metabolism of levodopa. *J. Am. Med. Assoc.* 218:1912–14
25. Cotler, S., Holazo, A., Boxenbaum, H. G., Kaplan, S. A. 1976. Influence of route of administration on physiological availability of levodopa in dogs. *J. Pharm. Sci.* 65:822–27
26. Cheng, L. K., Fung, H. 1976. Dose-dependent pharmacokinetics of laevodopa and its metabolities in the rat. *Xenobiotica* 6:237–48
27. Rivera-Calimlim, L., Morgan, J. P., Dujovne, C. A., Bianchine, J. R., Lasagna, L. 1971. L-3,4-Dihydroxyphenylalanine metabolism by the gut *in vitro*. *Biochem. Pharmacol.* 20:3051–57
28. Dahl, S. G., Strandjord, R. E., Sigfusson, S. 1977. Pharmacokinetics and relative bioavailability of levomepromazine after repeated administration of tablets and syrup. *Eur. J. Clin. Pharmacol.* 11:305–10
29. Boyes, R. N., Scott, D. B., Jebson, P. J., Godman, M. J., Julian, D. G. 1971. Pharmacokinetics of lidocaine in man. *Clin. Pharmacol. Ther.* 12:105–16
30. Thompson, P. D., Rowland, M., Melmon, K. L. 1971. The influence of heart failure, liver disease, and renal failure on the disposition of lidocaine in man. *Am. Heart J.* 82:417–21
31. Stenson, R. E., Constantino, R. T., Harrison, D. C. 1971. Interrelationships of hepatic blood flow, cardiac output, and blood levels of lidocaine in man. *Circulation* 43:205–11
32. Boyes, R. N., Adams, H. J., Duce, B. R. 1970. Oral absorption and disposition kinetics of lidocaine hydrochloride in dogs. *J. Pharmacol. Exp. Ther.* 174:1–8
33. Gügler, R., Lain, P., Azarnoff, D. L. 1975. Effect of portocaval shunt on the disposition of drugs with and without first-pass effect. *J. Pharmacol. Exp. Ther.* 195:416–23
34. Mather, L. E., Tucker, G. T. 1976. Systemic availability of orally administered meperidine. *Clin. Pharmacol. Ther.* 20:535–40
35. Dahl, S. G. 1976. Pharmacokinetics of methotrimeprazine after single and multiple doses. *Clin. Pharmacol. Ther.* 19:435–42
36. Hinderling, P. H., Garrett, E. R., Webster, R. C. 1977. Pharmacokinetics of β-methyldigoxin in healthy humans. I. Intravenous studies. *J. Pharm. Sci.* 66:242–53
37. Hinderling, P. H., Garrett, E. R., Webster, R. C. 1977. Pharmacokinetics of β-methyldigoxin in healthy humans. II. Oral studies and bioavailability. *J. Pharm. Sci.* 66:314–25
38. Alkalay, D., Khemani, L., Wagner, W. E. Jr., Bartlett, M. F. 1973. Sublingual and oral administration of methyltestosterone. A comparison of drug bioavailability. *J. Clin. Pharmacol.* 13: 142–51
39. Johnsson, G., Regardh, C. G., Sölvell, L. 1975. Combined pharmacokinetic and pharmacodynamic studies in man of the adrener ic beta-1 receptor antagonist metoprolol. *Acta Pharmacol. Toxicol.* 36: Suppl. 5, pp. 31–44
40. Brunk, S. F., Delle, M. 1974. Morphine metabolism in man. *Clin. Pharmacol. Ther.* 16:51–57
41. Iwamoto, K., Klaassen, C. D. 1977. First-pass effect of morphine in rats. *J. Pharmacol. Exp. Ther.* 200:236–44
42. Iwamoto, K., Klaassen, C. D. 1977. First-pass effect of nalorphine in rats. *J. Pharmacol. Exp. Ther.* 203:365–76
43. Fishman, J., Roffwarg, H., Hellman, L. 1973. Disposition of naloxone-7,8^{3}H in normal and narcotic dependent men. *J. Pharmacol. Exp. Ther.* 187:575–89
44. Weinstein, S. H., Pfeffer, M., Schor, J. M., Franklin, L., Mintz, M., Tutko, E. R. 1973. Absorption and distribution of naloxone in rats after oral and intravenous administration *J. Pharm. Sci.* 62: 1416–19
45. Kogan, M. J., Verebey, K., Mulé, S. J. 1977. Estimation of the systemic availability and other pharmacokinetic parameters of naltrexone in man after acute and chronic oral administration. *Res. Commun. Chem. Pathol. Pharmacol.* 18:29–34
46. Gram, L. F., Overo, K. F. 1975. First-pass metabolism of nortriptyline in man. *Clin. Pharmacol. Ther.* 18:305–14
47. Mason, W. N., Winer, N. 1976. Pharmacokinetics of oxprenolol in normal subjects. *Clin. Pharmacol. Ther.* 20: 401–12
48. Hook, R. H., Eastwood, C. J. Jr., Wright, G. J. 1975. The objective and timing of drug disposition studies, appendix. II. Plasma concentrations of oxyphenbutazone in dogs, given oxyphenbutazone or the calcium or sodium salts of its phosphate ester. *Drug Metab. Rev.* 4:249–65
49. Garrett, E. R., Roseboom, H., Green, J. R. Jr., Schuermann, W. 1978. Pharmacokinetics of papaverine hydrochloride and the biopharmaceutics of its

oral dosage forms. *Int. J. Clin. Pharmacol. Biopharm.* 16:193–208
50. Ehrnebo, M., Boréus, L. O., Lonroth, U. 1977. Bioavailability and first-pass metabolism of oral pentazocine in man. *Clin. Pharmacol. Ther.* 22:888–92
51. Hansen, C. E., Christensen, T. R., Elley, J., Hansen, L. B., Kragh-Sorensen, P., Larsen, N. E., Naestoft, J., Hvidberg, E. F. 1976. Clinical pharmacokinetic studies of perphenazine. *Br. J. Clin. Pharmacol.* 3:915–23
52. Raaflaub, J., Dubach, U. C. 1975. On the pharmacokinetics of phenacetin in man. *Eur. J. Clin. Pharmacol.* 8:261–65
53. Nienstedt, W., Hartiala, K. 1969. Steroid metabolism by the canine intestine. 1. Qualitative experiments with progesterone. *Scand. J. Gastroenterol.* 4:483
54. Wolen, R. L., Gruber, C. M. Jr., Kiplinger, G. F., Scholz, N. E. 1971. Concentration of propoxyphene in human plasma following oral, intramuscular, and intravenous administration. *Toxicol. Appl. Pharmacol.* 19:480–92
55. Perrier, D., Gibaldi, M. 1972. Influence of first-pass effect on the systemic availability of propoxyphene. *J. Clin. Pharmacol.* 12:449–52
56. Kornhauser, D. M., Wood, A. J. J., Vestal, R. E., Wilkinson, G. R., Branch, R. A., Shand, D. G. 1978. Biological determinants of propranolol disposition in man. *Clin. Pharmacol. Ther.* 23: 165–74
57. Andersson, K. E., Bertler, A., Redfors, A. 1975. On the pharmacokinetics of proscillaridin A in man. *Eur. J. Clin. Pharmacol.* 8:421–25
58. Andersson, K. E., Bergdahl, B., Dencker, H., Wettrell, G. 1977. Proscillardin activity in portal and peripheral venous blood after oral administration to man. *Eur. J. Clin. Pharmacol.* 11:277–81
59. Ziegler, V. E., Biggs, J. T., Wylie, L. T., Coryell, W. H., Hanifl, K. M., Hawf, D. J., Rosen, S. H. 1978. Protryptyline kinetics. *Clin. Pharmacol. Ther.* 23: 580–84
60. Ueda, C. T., Williamson, B. J., Dzindzio, B. S., 1976. Absolute quinidine bioavailability. *Clin. Pharmacol. Ther.* 20:260–65
61. Evans, M. E., Walker, S. R., Brittain, R. T., Paterson, J. W. 1973. The metabolism of salbutamol in man. *Xenobiotica* 3:113–20
62. Levy, G., Matsuzawa, T. 1967. Pharmacokinetics of salicylamide elimination in man. *J. Pharm. Exp. Ther.* 156:285–93
63. Barr, W. H., Riegelman, S. 1970. Intestinal drug absorption and metabolism. II. Kinetic aspects of intestinal glucuronide conjugation. *J. Pharm. Sci.* 59: 164–68
64. Fischer, L. J., Millburn, P. 1970. Stilboestrol transport and glucuronide formation in everted sacs of rat intestine. *J. Pharmacol. Exp. Ther.* 175:267–75
65. Shand, D. G., Cavanaugh, J. H., Oates, J. A. 1971. The fate of SU. 13197, a new antiarrhythmic drug in rat and man. *Clin. Pharmacol. Ther.* 12:769–78
66. Conway, W. D., Singhvi, S. M., Gibaldi, M., Boyes, R. N. 1973. The effect of route of administration on the metabolic fate of terbutaline in the rat. *Xenobiotica* 3:813–21
67. Schmalzing, G. 1977. Metabolism and disposition of trifluoperazine in the rat. ii. Kinetics after oral and intravenous administration in acutely and chronically treated animals. *Drug. Metab. Dispos.* 5:104–15
68. Eberts, F. S. Jr. 1977. Disposition of triazolam, 8-chloro-6-(0-chlorophenyl)-1-methyl-4H-s-triazolo (4,3-a)(1,4) benzodiazepine, in the dog. *Drug Metab. Dispos.* 5:547–55
69. Schomerus, M., Spiegelhalder, B., Stieren, B., Eichelbaum, M. 1976. Physiological disposition of verapamil in man. *Cardiovasc. Res.* 10:605–12
70. Gillette, J. R., Pang, K. S. 1977. Theoretical aspects of pharmacokinetic drug interactions. *Clin. Pharmacol. Ther.* 22:623–39
71. Shand, D. G., Rangno, R. E. 1972. The disposition of propranolol. I. Elimination during oral absorption in man. *Pharmacology* 7:159–68
72. Gibaldi, M., Boyes, R. N., Feldman, S. 1972. Influence of first-pass effect on availability of drugs on oral administration. *J. Pharm. Sci.* 60:1338–40
73. Wilkinson, G. R., Shand, D. G. 1975. A physiological approach to hepatic drug clearance. *Clin. Pharmacol. Ther.* 18: 377–90
74. Andreasen, P., Vesell, E. 1974. Comparison of plasma levels of antipyrine, tolbutamide, and warfarin after oral and intravenous administration. *Clin. Pharmacol. Ther.* 16:1059–65
75. Pessayre, D., Lebrec, D., Descatoire, V., Peignoux, M., Benhamou, J. 1978. Mechanism for reduced drug clearance in patients with cirrhosis. *Gastroenterology* 74:566–71
76. Pang, K. S., Gillette, J. R. 1978. Theoretical relationships between area under the curve and route of administration of

drugs and their precursors for evaluating sites and pathways of metabolism. *J. Pharm. Sci.* 67:703–4

77. Gomeni, R., Bianchetti, G., Sega, R., Morselli, P. L. 1977. Pharmacokinetics of propranolol in normal healthy volunteers. *J. Pharmacokinet. Biopharm.* 5:183–92
78. Mackichan, J., Pyszczynski, D. R., Jusko, W. J. 1978. Analysis and disposition of low dose oral propranolol. *Res. Commun. Chem. Pathol. Pharmacol.* 20:531–38
79. Paterson, J. W., Conolly, M. E., Dollery, C. T., Hayes, A., Cooper, R. G. 1970. The pharmacodynamics and metabolism of propranolol in man. *Pharmacol. Clin.* 2:127–33
80. Shand, D. G., Evans, G. H., Rangno, R. E., Wilkinson, G. R. 1972. Importance of tissue binding in the hepatic clearance of propranolol. *5th Int. Cong. Pharmacol.* July 23–28
81. Anderson, J. H., Anderson, R. C., Iben, L. S. 1978. Hepatic uptake of propranolol. *J. Pharmacol. Exp. Ther.* 206:172–80
82. Wood, A. J. J., Carr, K., Vestal, R. E., Belcher, S., Wilkinson, G. R., Shand, D. G. 1978. Direct measurement of propranolol bioavailability during accumulation to steady-state. *Br. J. Clin. Pharmacol.* 6:345–50
83. Walle, T., Conradi, E., Walle, K., Fagan, T., Gaffney, T. E. 1977. Steady-state kinetics of the active propranolol metabolite, 4-hydroxypropranolol and its glucuronic acid conjugate in patients with hypertension and coronary artery disease. *Clin. Res.* 25:10A
84. Dutcher, J. S., Strong, J. M., Lucas, S. V., Lee, W., Atkinson, A. J. Jr. 1977. Procainamide and N-acetyl-procainamide kinetics investigated simultaneously with stable isotope methodology. *Clin. Pharmacol. Ther.* 22:447–57
85. Gibaldi, M., Boyes, R. N., Feldman, S. 1971. Influence of first-pass effect on availability of drugs on oral administration. *J. Pharm. Sci.* 60:1338–40
86. Nies, A. S., Evans, G. H., Shand, D. G. 1973. The hemodynamic effects of beta adrenergic blockade on the flow dependent hepatic clearance of propranolol. *J. Pharmacol. Exp. Ther.* 184:716–20
87. Weiss, Y. A., Safar, M. E., Lehner, J. P., Levenson, J. A., Simon, A., Alexandre, J. M. 1978. (t)-Propranolol clearance, an estimation of hepatic blood flow in man. *Br. J. Clin. Pharmacol.* 5:457–60
88. Gillette, J. R. 1971. Factors affecting drug metabolism. *Ann. NY Acad. Sci.* 179:43–66
89. Brauer, R. W. 1963. Liver circulation and function. *Physiol. Rev.* 43:115–213
90. Keiding, S., Johansen, S., Winkler, K., Tonensen, K., Tygstrup, N. 1976. Michaelis-menten kinetics of galactose elimination by the isolated perfused pig liver. *Am. J. Physiol.* 230:1302–13
91. Wilkinson, G. R. 1976. In *The Effect of Disease States on Drug Pharmacokinetics,* ed. L. Z. Benet, pp. 13–32. Washington DC: Am. Pharm. Assoc. 252 pp.
92. Pang, K. S., Rowland, M. 1977. Hepatic clearance of drugs. I. Theoretical considerations of a "well-stirred" model and a "parallel tube" model. Influence of hepatic blood flow, plasma and blood cell binding and the hepatocellular enzymatic activity on hepatic drug clearance. *J. Pharmacokinet. Biopharm.* 5:625–53
93. Shand, D. G., Mitchell, J. R., Oates, J. A. 1975. In *Concepts in Biochemical Pharmacology, Part 3.* ed. J. R. Gillette, J. R. Mitchell, pp. 272–314. New York: Springer. 480 pp.
94. Shand, D. G., Kornhauser, D. M., Wilkinson, G. R. 1975. Effects of route of administration and blood flow on hepatic drug elimination. *J. Pharmacol. Exp. Ther.* 195:424–32
95. Keiding, S., Chiarantini, E. 1978. Effect of sinusoidal perfusion on galactose elimination kinetics in perfused rat liver. *J. Pharmacol. Exp. Ther.* 205:465–70
96. Meikle, A. W., Jubiz, W., Matsukura, S., West, C. D., Tyler, F. H. 1969. Effect of diphenylhydantoin on the metabolism of metyrapone and release of ACTH in man. *J. Clin. Endocrinol.* 29:1553–58
97. Alvan, G., Piafsky, K., Lind, M., Von Bahr, C. 1977. Effect of pentobarbital on the disposition of alprenolol. *Clin. Pharmacol. Ther.* 22:316–21
98. Vestal, R. E., Kornhauser, D. M., Hollifield, J. W., Shand, D. G. Inhibition of propranolol metabolism by chlorpromazine. *Clin. Pharmacol. Ther.* In press
99. McLean, A. J., McNamara, P. J., du Souich, P., Gibaldi, M., Lalka, D. 1978. Food, splanchnic blood flow, and bioavailability of drugs subject to first-pass metabolism. *Clin. Pharmacol. Ther.* 24:5–10
100. Melander, A., Danielson, K., Scherstén, B., Wahlin, E. 1977. Enhancement of the bioavailability of pro-

pranolol and metoprolol by food. *Clin. Pharmacol. Ther.* 22:108–12
101. Branch, R. A., Shand, D. G. 1976. Propranolol disposition in chronic liver disease: A physiological approach. *Clin. Pharmacokinet.* 1:264–79
102. Goldman, P., Peppercorn, M. A., Goldin, B. R. 1974. In *Drug Interactions*, ed. P. L. Morselli, S. Garattini, S. N. Cohen. New York. Raven. 406 pp.
103. Hartiala, K. 1973. Metabolism of hormones, drugs and other substances by the gut. *Physiol. Rev.* 53:496–534
104. Colburn, W. A., Gibaldi, M. 1978. Pharmacokinetic model of presystemic metabolism. *Drug Metab. Dispos.* 6: 193–96
105. Sapirstein, L. A. 1958. Regional blood flow by fractional distribution of indicators. *Am. J. Physiol.* 193:161–68
106. Rowland, M., Benet, L. Z., Graham, G. 1973. Clearance concepts in pharmacokinetics. *J. Pharmacokinet. Biopharm.* 1:123–36
107. Mearrick, P. T., Graham, G. G., Wade, D. N. 1974. The role of the liver in the clearance of L-dopa from plasma. *J. Pharmacokinet. Biopharm.* 3:13–23
108. George, C. F., Blackwell, E. W., Davies, D. S. 1974. Metabolism of isoprenaline in the intestine. *J. Pharm. Pharmacol.* 26:265–67
109. Bennett, P. N., Blackwell, E. W., Davies, D. S. 1975. Competition for sulphate during detoxification in the gut wall. *Nature* 258:247–48
110. Donaldson, R. M. 1964. Normal bacterial populations of the intestine and their relation to intestinal function. *N. Engl. J. Med.* 270:938–45, 994–1001, 1050–56
111. Scheline, R. R. 1973. Metabolism of foreign compounds by gastrointestinal microorganisms. *Pharmacol. Rev.* 25: 451–523
112. Sandler, M., Karoum, F., Ruthven, C. R. J., Calne, D. B. 1969. m-Hydroxyphenlacetic acid formation from L-dopa in man: suppression by neomycin. *Science* 166:1417–18
113. Sandler, M., Goodwin, B. L., Ruthven, C. R. J., Calne, D. B. 1971. Therapeutic implications in parkinsonism of m-tyramine formation from L-dopa in man. *Nature* 229:414–16
114. Goldin, B. R., Goldman, P. 1973. The metabolism of dopa: The role of the intestinal microflora. *Fed. Proc.* 32:798
115. Schröder, H., Campbell, D. E. S. 1972. Absorption, metabolism, and excretion of salicylazosulfapyridine in man. *Clin. Pharmacol. Ther.* 13:539–51
116. Gingell, R., Bridges, J. W., Williams, R. T. 1971. The role of the gut flora in the metabolism of prontosil and neoprontosil in the rat. *Xenobiotica* 1:143–56
117. Bakhle, Y. S. 1975. In *Lung Metabolism*, ed. A. F. Junod, R. de Haller, pp. 293–99. New York: Academic. 501 pp.
118. Naito, H., Gillis, C. N. 1973. Effects of halothane and nitrous oxide on removal of norepinephrine from the pulmonary circulation. *Anesthesiology* 30:575–80
119. Ryan, J. W., Ryan, U.S., 1975. See Ref. 117, pp. 399–422
120. Vane, J. R. 1968. In *Importance of Fundamental Principles in Drug Evaluation*. New York: Raven
121. Wilson, A. G. E., Law, F. C. P., Eling, E. 1976. Uptake, metabolism and efflux of methadone in "single pass" isolated perfused rabbit lungs. *J. Pharmacol. Exp. Ther.* 199:360–67