*Pharmaceutical Research, Vol. 8, No. 5, 1991*

*Review*

# Stereoselectivity in Pharmacokinetics: A General Theory

**René H. Levy[1,2] and Alan V. Boddy[3]**

Stereoselectivity in pharmacokinetics may be characterized by a measurable difference between enantiomers in a pharmacokinetic parameter. We propose that pharmacokinetic parameters may be classified according to three levels of organization in the body and that the hybrid character of parameters increases with the level of organization that they represent. At the molecular level are intrinsic metabolite formation clearances and fraction of drug unbound in plasma, reflecting the selectivity of an endogenous macromolecule for the enantiomers of a chiral drug molecule. At the organ level, pharmacokinetic parameters represent the combined effects of stereoselectivity in each of their component parameters within an organ. As a result, these parameters are of intermediate hybrid character. Parameters with the highest degree of hybrid character describe the pharmacokinetic behavior of a drug in the whole body. The stereoselectivity associated with each of the component parameters could either amplify or dampen the resultant stereoselectivity in hybrid parameters. The hypothesis that kinetic differences between enantiomers are inversely correlated with the degree of hybrid character was examined for four drugs: warfarin, verapamil, mephenytoin, and propranolol. By classifying pharmacokinetic parameters according to both the level of organization that they characterize and their hybrid nature, it becomes possible to account for stereoselectivity in drug distribution and elimination.

KEY WORDS: stereoselectivity; chirality; enantiomers; drug metabolism; pharmacokinetics.

## INTRODUCTION

The stereoselectivity of many endogenous biochemical processes has been characterized (1), and recently, the implications of stereoselectivity have become apparent for the pharmacokinetics of several drugs (2–5). However, from observations of stereoselectivity in pharmacokinetics of one drug, it is not possible to predict the same phenomenon in others. The concept that would permit such a judgment does not yet exist. This paper proposes a theory of stereoselectivity in pharmacokinetics and validates it with information available in the current literature.

Differences between the enantiomers of a drug or it metabolites can influence pharmacokinetics in a number of ways. The one most often seen is substrate selectivity, which is discussed in the present paper. Other aspects of stereoselectivity, such as product selectivity (6), interactions between enantiomers (7), and interconversion (8,9), are not discussed in this paper.

## THEORY

Inherent in the determination of a pharmacokinetic parameter is the assumption that the parameter refers to a single chemical entity. For a chiral drug, this means the separate and individual determination of pharmacokinetic parameters for the two enantiomers. Substrate stereoselectivity may be said to occur when there is a measurable difference between enantiomers in the value of a given pharmacokinetic parameter. In the following discussion, a measurable difference in the parameter values for a pair of enantiomers is defined as larger than or equal to 20%. This corresponds to a value of 1.2 or greater for the ratio of the higher value to the lower value for a given parameter. This ratio is referred to as the stereoselective index (SI).

For a pair of optical isomers, some pharmacokinetic parameters may show little stereoselectivity (SI ~ 1), whereas others exhibit a marked difference. It is proposed that the factors that govern this disparity in the sensitivity of different parameters to stereoselective effects are predictable and pertain not only to the drug but also to the nature of the parameters themselves. It is further proposed that pharmacokinetic parameters should be classified according to the level of organization in the body which they characterize. There are three distinct levels to be considered:

(I) macromolecular,
(II) whole organ, and
(III) whole body.

Each of these levels of organization endows the corresponding pharmacokinetic parameters with a certain hybrid character. Using this classification, as elaborated below, stereoselectivity in pharmacokinetics can be rationalized according to the degree of hybrid character of a given parameter.

[1] Department of Pharmaceutics, School of Pharmacy, University of Washington, BG-20, Seattle, Washington 98195.
[2] To whom correspondence should be addressed.
[3] Present address: 47 St. Anne's Road, Chorlton-cum-Hardy, Manchester, U.K. M21 2TQ.



0724-8741/91/0500-0551$06.50/0 

### Level I: Macromolecules—Parameters of a Low Hybrid Character

The phenomenon of stereoselectivity has been defined as "the extent to which an enzyme or other macromolecule or macromolecular structure (antibody or receptor) exhibits affinity toward one molecule of a pair of stereoisomers in comparison with and in contrast to the other isomer" (10). According to this definition of stereoselectivity, differences between pairs of enantiomers will be most marked with regard to parameters that reflect interactions between drug molecules and other specific macromolecules of the body, such as binding proteins and metabolic enzymes. Examples of such parameters include unbound fraction in plasma ($f_u$) and intrinsic formation clearances of individual metabolites ($CLf_i$). This type of parameter may be said to have the lowest degree of hybrid nature. The binding affinity of a drug for a specific protein represents directly the interaction between the drug molecule and the protein binding site. The intrinsic formation clearances of individual metabolites also represent a direct interaction between drug and specific metabolizing isozymes (Fig. 1). Although direct determination of the interaction between a drug and an enzyme or protein may be performed *in vitro,* such investigations are often influenced by the conditions applied, such as substrate or protein concentration. Therefore, we restrict our considerations to parameters which have been determined *in vivo* or *ex vivo.*

### Level II: Whole Organ—Parameters of an Intermediate Hybrid Character

This class of parameters reflects the interactions of drugs with the body at the level of whole organs. Parameters such as total-organ clearance and extraction of drug across an organ are included in this category. Examples include hepatic metabolic clearance and renal clearance. With regard to their higher degree of hybrid character, these parameters represent the combined effects of several primary interactions between stereoisomers and macromolecules. Also, the value of a parameter reflecting the processes within an intact organ may be affected by factors that exhibit no stereoselectivity, such as blood flow (11).

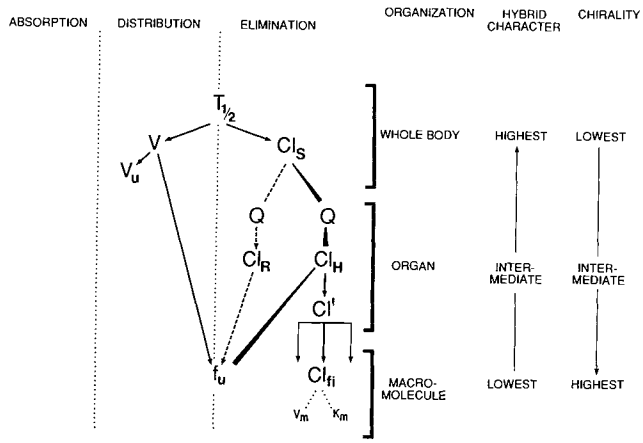


Fig. 1. Diagram showing the relation among levels of organization in the body, the hybrid nature of pharmacokinetic parameters, and the degree of chirality or stereoselectivity expected in those parameters.

### Level III: Whole Body—Parameters of a High Hybrid Character

Parameters in this category reflect processes associated with multiple organs and are determined by the specific physiological and anatomical relationships between organs. Examples include half-life, total-body clearance, and volume of distribution. The high hybrid character of this group of parameters is based on the multiplicity and sequential nature of the processes involved. Total-body clearance is the sum of all organ clearances in the body. Volume of distribution is a measure of the balance of drug distribution and binding between the site of measurement (plasma or plasma water) and the rest of the body. Perhaps the most hybrid pharmacokinetic parameter is half-life, which is determined from the ratio of volume of distribution to clearance. In this single parameter value, both distribution and elimination characteristics of the drug are reflected.

The relationships among these parameters, their hybrid character, and the level of organization that they represent are shown in Fig. 1. While the parameters in this figure are included in specific categories, it is recognized that the level of organization reflected by a particular parameter could vary from drug to drug. The factors that influence the degree of stereoselectivity observed in a pharmacokinetic parameter may be illustrated by considering some examples.

Total-body clearance ($CL_S$) represents organization at the level of the whole body and is equal to the sum of clearances, $CL_i$, by individual organs in parallel:

$$CL_S = \Sigma\, CL_i \qquad (1)$$

Since it is a sum of clearances, the stereoselectivity exhibited by total-body clearance will always be smaller than that exhibited by the most stereoselective of the component clearances. Also, stereoselective effects in relatively minor organs of elimination will be masked in $CL_S$ if there is no stereoselectivity of elimination in other organs. If, for example, $CL_S$ is composed of two clearance terms, the SI value for $CL_S$ is the ratio of the sum of those component clearances for the enantiomers:

$$SI(CL_S) = CL_{S(+)}/CL_{S(-)} = [CL_{1(+)} + CL_{2(+)}]/[CL_{1(-)} + CL_{2(-)}] \qquad (2)$$

where the (+)-isomer has a higher $CL_S$ than the (−)-isomer. If the stereoselectivity in $CL_S$ is due to stereoselectivity in $CL_1$, $SI(CL_S)$ is less than $SI(CL_1)$. If stereoselectivity in $CL_2$ is the reverse of that in $CL_1$, $SI(CL_S)$ is still less than $SI(CL_2)$. It should be noted that the latter comparison is between the ratios $[CL_{S(+)}/CL_{S(-)}]$ and $[CL_{2(-)}/CL_{2(+)}]$, according to the definition of SI given above. Therefore, it should become apparent that the SI value for a hybrid parameter cannot be directly derived from the SI values of its component parameters unless differences in the direction of stereoselectivity are taken into account.

In turn, the clearance by a single organ, such as the liver, can be defined as

$$CL_H = Q_H \cdot f_u \cdot CL_{int}/(Q_H + f_u \cdot CL_{int}) \qquad (3)$$

At high clearance values $CL_H$ is limited by hepatic blood flow ($Q_H$) and stereoselective effects in $f_u$ or $CL_{int}$ will be masked. At low values of $f_u \cdot CL_{int}$, organ clearance is

equal to this product and may be affected by stereoselectivity in binding in plasma or in intrinsic clearance. For example,

$$SI(CL_H) = CL_{H(+)}/CL_{H(-)} = [f_{u(+)} \cdot CL_{int(+)}]/[f_{u(-)} \cdot CL_{int(-)}] \quad (4)$$

Thus, stereoselectivity in the product of $f_u \cdot CL_{int}$ may be larger than, equal to, or smaller than the stereoselectivity in either of the two components, since stereoselectivity in one of these low hybrid-component parameters may amplify, dominate, or counteract stereoselectivity in the other.

Intrinsic organ clearance is equal to the sum of clearances by different routes of elimination within the organ:

$$CL_{int} = \Sigma\, CLf_i \quad (5)$$

As with total-body clearance, stereoselectivity in a single pathway, say to one metabolite, may be masked by a lack of stereoselectivity in a more dominant route of elimination. This situation is most commonly seen in the liver, where the various $CLf_i$ represent different routes of metabolism, i.e., the molecular interaction with different metabolizing enzymes. Also, as in the case of $CL_S$, stereoselectivity in $CL_{int}$ will be less than that of the most stereoselective $CLf_i$.

Volume of distribution is determined by the balance between the binding of drug in plasma and that in tissue and has been defined as:

$$V = V_P + V_T \cdot f_u/f_T \quad (6)$$

The volume of tissue ($V_T$) is a constant and the fraction unbound in tissue ($f_T$) is unlikely to show stereoselectivity since it represents the partitioning and binding of drug at a number of sites outside of plasma. Therefore, it is likely that in most instances, stereoselectivity in $V$ will be influenced principally by stereoselectivity in $f_u$.

The half-life of a drug may be defined as

$$t_{1/2} = \ln 2 \cdot V/CL_S \quad (7)$$

Since this is a ratio of two independent parameters, the extent to which $t_{1/2}$ will reflect stereoselectivity in either clearance or volume of distribution will be variable. In those cases where it is mediated by differences in $f_u$ for the enantiomers, stereoselectivity in the last two parameters is often in the same direction [Eqs. (3) and (6)], resulting in a value of SI for $t_{1/2}$ close to unity.

It should be noted that parameters governing drug absorption from dosage form are not included in these considerations since the processes involved are dependent on a number of factors (disintegration, dissolution, gastrointestinal transit time, etc.), which do not differ between optical isomers (12,13). Only when active transport processes are involved would a stereoselective effect be anticipated, as is the case for methotrexate (14). In this case, the fraction of drug absorbed is a parameter of a low hybrid nature, as it is representative of a direct interaction with a specific endogenous macromolecule.

The hypothesis that hybrid character and extent of stereoselectivity are inversely related may be tested by considering the parameter values of the enantiomers of several optically active drugs.

## EVALUATION OF THE STEREOPHARMACOKINETIC HYPOTHESIS

Although many chiral drugs have been investigated in terms of the pharmacokinetics of their enantiomers, in this survey we have restricted ourselves to those drugs for which pharmacokinetic parameters in each of the hybrid categories have been determined in humans. The pharmacokinetic parameters of the enantiomers of warfarin, verapamil, mephenytoin, and propranolol are given in Tables I to IV. In all tables, the parameters are arranged in descending order of hybrid nature.

### Warfarin

An examination of Table I shows that the degree of stereoselectivity increases as the level of organization characterized by the parameters devolves from whole body to organ to macromolecular. A more detailed analysis reveals how stereoselectivity depends on the hybrid character of the parameters. Thus, the significant stereoselectivity in half-life is due principally to a difference in volume of distribution between the enantiomers. In turn, the values of the last parameter reflect the stereoselectivity exhibited by $f_u$. There is no significant stereoselectivity in total-body clearance, despite the stereoselectivity in the formation clearances by individual routes of metabolism. This is because total clearance is determined by several component clearances, the stereoselectivity of which is masked in their summation. The fraction excreted unchanged shows little stereoselectivity, which would be expected if this route of metabolism were dependent on the physicochemical properties of the drug molecule. The larger differences between the enantiomers in the fractions metabolized by different routes is the result of stereoselective interactions with specific metabolizing enzymes. Thus, the S-enantiomer is eliminated mostly by 7-hydroxylation and formation of warfarin alcohol 2, whereas the R-enantiomer is metabolized to 8-hydroxy warfarin and warfarin alcohol 1.

**Table I.** Pharmacokinetic Parameters for the Optical Isomers of Warfarin[a]

| Parameter | *R*-Warfarin | *S*-Warfarin | Stereoselective index |
|---|---|---|---|
| $t_{1/2}$ (hr) | 47.1 | 24.4 | 1.93 |
| $V$ (ml/kg) | 129 | 70.5 | 1.83 |
| Cl (ml/hr/kg) | 1.9 | 2.0 | 1.05 |
| $f_u$ (%) | 3.6 | 2.2 | 1.64 |
| $f_e$ (%) | 1.0 | 0.9 | 1.11 |
| $f_{m,6\text{-OH}}$ | 10.4 | 8.72 | 1.19 |
| $f_{m,7\text{-OH}}$ | 5.32 | 33.7 | 6.33 |
| $f_{m,8\text{-OH}}$ | 7.31 | 0.14 | 52.2 |
| $f_{m,WA1}$ | 8.92 | ND | ∞ |
| $f_{m,WA2}$ | 0.01 | 1.3 | 130 |

[a] Data from Ref. 15. Parameters calculated from plasma and urine data following a single oral dose of 1.5 mg/kg pseudoracemic warfarin (labeled with stable isotopes). Clearance Cl and volume $V$ were calculated from the area under the plasma concentration–time curve, assuming a bioavailability of 1. Fractions metabolized ($f_m$) refer to 6-, 7-, and 8-hydroxy warfarin and to the warfarin alcohol diastereoisomers 1 and 2.

Table II. Pharmacokinetic Parameters of the Optical Isomers of Verapamil[a]

| Parameter | (+)-Verapamil | (−)-Verapamil | Stereoselective index |
|---|---|---|---|
| $t_{1/2}$ (hr) | 4.1 | 4.8 | 1.17 |
| $V_{SS}$ (L/kg) | 2.74 | 6.42 | 2.34 |
| Cl (L/min) | 0.80 | 1.41 | 1.77 |
| $f_u$ (%) | 6.30 | 11.5 | 1.82 |
| $Cl_O$ (L/min) | 1.72 | 7.46 | 4.34 |
| $F$ (%) | 50 | 20 | 2.50 |
| $\Sigma Cl_{f \cdot dealk}$ (L/min) | 0.67 | 1.97 | 2.95 |
| $\Sigma Cl_{f \cdot demet}$ (L/min) | 0.02 | 0.73 | 33.0 |

[a] Data from Refs. 16–18. Half-life, clearance, and volume of distribution calculated following separate iv administration of the individual enantiomers at a dose of 5 mg. Oral clearance ($CL_O$) and bioavailability calculated from AUC following an oral 160-mg dose of a pseudoracemic mixture of the unlabeled (−) and dideuterated (+) enantiomers. Total fractional clearances ($\Sigma Cl_f$.) refer to dealkylation and demethylation reactions.

## Verapamil

The overall relationship between stereoselective index and degree of hybrid nature is also found for verapamil, where stereoselectivity is largest for those parameters with the lowest degree of hybrid character. This is often explained by the mathematical relationships between parameters where stereoselectivity in parameters of a low hybrid character is not transferred to the parameters of a higher hybrid nature. Thus, there is no significant stereoselectivity in half-life, despite that seen for both clearance and volume of distribution [Eq. (7)]. Stereoselectivity in volume of distribution is due to stereoselectivity in $f_u$, but binding has little influence on the systemic clearance values for the enantiomers of this highly extracted drug. However, $CL_O$, which more closely reflects $CL_{int}$ and is not limited by blood flow, does show significant stereoselectivity. The difference in $F$ between the enantiomers is also a reflection of the stereoselectivity in $CL_{int}$. As predicted, the largest stereoselective effects are seen in the formation (or fractional) clearances associated with specific pathways of metabolism.

Table IV. Pharmacokinetic Parameters for Optical Isomers of Propranolol[a]

| Parameter | (+)-Propranolol | (−)-Propranolol | Stereoselective index |
|---|---|---|---|
| $t_{1/2}$ (hr) | 3.57 | 3.53 | 1.01 |
| CL (L/min) | 1.21 | 1.03 | 1.17 |
| $V$ (L/kg) | 4.82 | 4.08 | 1.18 |
| $f_u$ (%) | 0.203 | 0.176 | 1.15 |
| $\alpha_1$-$AGP_u$ (%) | 0.162 | 0.127 | 1.28 |
| $HSA_u$ (%) | 0.607 | 0.649 | 1.06 |
| $Cl_O$ (L/min) | 2.78 | 1.96 | 1.42 |
| $Cl_{O,gluc}$ (L/min) | 0.24 | 0.27 | 1.12 |
| $Cl_{O,NLA}$ (L/min) | 0.38 | 0.31 | 1.23 |
| $Cl_{O,4\text{-}OH}$ (L/min) | 1.16 | 0.48 | 2.51 |
| $Cl_{O,4\text{-}OH,G}$ (L/min) | 0.30 | 0.32 | 1.04 |
| $Cl_{O,4\text{-}OH,S}$ (L/min) | 0.85 | 0.17 | 5.17 |

[a] Data from Refs. 24 and 25. Fractions unbound determined *in vitro* by equilibrium dialysis of deuterated pseudoracemate and refer to plasma or to solutions of $\alpha_1$-acid glycoprotein ($\alpha_1$-$AGP_u$) or human serum albumin ($HSA_u$). Partial metabolic clearances refer to glucuronidation ($Cl_{O,gluc}$), N-dealkylation ($Cl_{O,NLA}$), 4-hydroxylation ($Cl_{O,4\text{-}OH}$), and subsequent glucuronide and sulfate conjugation ($Cl_{O,4\text{-}OH,G}$ and $Cl_{O,4\text{-}OH,S}$).

## Mephenytoin

Table III lists parameter values and stereoselective index values for mephenytoin in both extensive and poor metabolizers of the drug. In addition to following the trend of increased value of the stereoselective index with decreasing degree of hybrid nature, this drug provides an illustration of Pfeiffer's rule. This rule states that as the specificity of an enantiomer–macromolecule interaction increases, so does the degree of enantioselectivity (23). Thus, the stereoselective index for a given parameter is dramatically greater for extensive metabolizers than for poor metabolizers, principally due to the high affinity for the S-enantiomer of the enzyme responsible for 4-hydroxylation. In poor metabolizers this enzyme is functionally absent and the majority of the drug is metabolized by the relatively nonenantioselective N-demethylation reaction. In extensive metabolizers, metabolism by 4-hydroxylation dominates the elimination mephenytoin, leading to a significant degree of stereoselectivity in all of the parameters. Indeed, the competition for 4-

Table III. Pharmacokinetic Parameters for the Optical Isomers of Mephenytoin[a]

| | Extensive metabolizer | | | Poor metabolizer | | |
|---|---|---|---|---|---|---|
| Parameter | S-Isomer | R-Isomer | Index | S-Isomer | R-Isomer | Index |
| $t_{1/2}$ | 2.1 | 76 | 36.2 | 63 | 77 | 1.22 |
| $Cl_O$ (L/min) | 4.7 | 0.03 | 174 | 0.029 | 0.020 | 1.49 |
| $f_{m,4\text{-}OH}$ (%) | 83.6 | 10 | 8.36 | — | — | — |
| $Cl_{f,4\text{-}OH}$ (L/min) | 3.93 | 0.003 | 1456 | — | — | — |
| $f_{m,PEH}$ (%) | 0.25 | 17.9 | 71.6 | 41.7 | 66.9 | 1.60 |
| $Cl_{f,PEH}$ (L/min) | 0.012 | 0.048 | 4.0 | 0.012 | 0.013 | 1.08 |

[a] Data from Refs. 19–22. Half-life, oral clearance, and the formation parameters of 4-hydroxymephenytoin were calculated from plasma and urine data collected after a single oral dose of 300 mg (EM) or 200 mg (PM) of racemic mephenytoin. The formation parameters for the PEH metabolite (5-phenyl, 5-ethyl hydantoin) were recalculated from the data from two papers, each using a single oral dose of pseudoracemic mephenytoin.

hydroxylation of the S-isomer by the 4-hydroxylase enzyme is so effective that the fraction of this isomer, relative to R-mephenytoin, which is metabolized by N-demethylation is drastically reduced (0.25%). This phenomenon of stereoselective competition for substrate may lead to an apparent stereoselectivity in $f_m$ values (SI = 71.6) which does not reflect the stereoselectivity of the enzyme–drug interaction.

### Propranolol

There is no significant difference between the enantiomers of propranolol in the parameters of a high hybrid nature (half-life, systemic clearance, volume of distribution). While the overall fraction unbound in plasma or to albumin is not different for the two enantiomers, there is a significant difference in the more specific binding to α-1-acid glycoprotein. This illustrates again the principle that the stronger the interaction with a particular macromolecule, the more likely is a difference between optical isomers. Parameters that are less dependent on whole-body organization, such as oral clearance and individual metabolite formation clearances, are significantly different for the different enantiomers. This is to be expected from the low hybrid nature of these parameters.

The 4-hydroxylation of propranolol and subsequent conjugation reactions have an interesting pattern of stereoselectivity. The total metabolism to 4-hydroxy propranolol, including conjugates, has an SI value of 2.51. The SI value for the glucuronide conjugate is nearly unity, suggesting that the glucuronidation reaction has a stereoselectivity in the opposite direction to the 4-hydroxylation reaction. Similarly, the SI value for sulfate conjugates of 5.17 implies that the stereoselectivity in sulfation is in the same direction and probably amplifies the stereoselectivity in 4-hydroxylation.

The relative extent of formation of different metabolites of propranolol enantiomers has also been studied in subjects that have been classified as extensive (EM) or poor metabolizers of debrisoquin ($PM_D$) or of mephenytoin ($PM_M$) (25). This study showed that, although clearance of propranolol by several metabolic routes was lower in the poor metabolizers, the ratio of formation clearances for the two enantiomers was not different among the metabolizer subpopulations. This indicates that, while $PM_D$ and $PM_M$ subjects are less able to metabolize propranolol, the stereoselectivity of the metabolizing enzymes in poor-metabolizer subjects is not different from EM subjects. This is in contrast to the situation with mephenytoin (see above), where the functional absence of a strongly stereoselective enzyme in $PM_M$ subjects alters markedly the metabolic fate of the S-enantiomer.

## CONCLUSIONS

The theoretical framework that is suggested in this paper proposes some principles for interpreting the degree of stereoselectivity observed in pharmacokinetic parameters. The degree of stereoselectivity observed for a given pharmacokinetic parameter depends on the level of body organization (macromolecular, organ, or whole body) which is reflected by the parameter. The drug disposition processes associated with these three levels of organization determine the hybrid character of the parameter. In general, the greater the degree of hybrid character, the smaller is the value of the stereoselectivity index. This hypothesis should be tested further as stereopharmacokinetic data become available for other chiral drugs.

## ACKNOWLEDGMENT

We should like to thank Miss M.-H. Lin for assistance with the survey of the literature.

## REFERENCES

1. F. P. A. Lehman. Stereoselective molecular recognition in biology, In P. Cuatrecasas and M. Greaves (eds.), *Receptors and Recognition, Vol. 5, Ser. A,* Chapman Hall, London, 1978, pp. 1–77.
2. A. M. Evans, R. L. Nation, L. N. Snasom, F. Bochner, and A. A. Somogyi. Stereoselective drug disposition: Potential for misinterpretation of drug disposition data. *Br. J. Clin. Pharmacol.* 26:771–780 (1988).
3. F. Jamali, R. Mehvar, and F. M. Pasutto. Enantioselective aspects of drug action and disposition: Therapeutic pitfalls. *J. Pharm. Sci.* 78:695–715 (1989).
4. D. E. Drayer. Pharmacodynamic and pharmacokinetic differences between drug enantiomers: An overview. *Clin. Pharmacol. Ther.* 40:125–132 (1986).
5. E. J. Ariens. Stereochemistry, a basis for sophisticated nonsense in pharmacokinetics and clinical pharmacology. *Eur. J. Clin. Pharmacol.* 26:663–668 (1984).
6. P. Jenner and B. Testa. The influence of stereochemical factors on drug disposition. *Drug Metab. Rev.* 2:117–184 (1974).
7. K. M. Giacomini, W. L. Nelson, R. A. Pershe, L. Valdivieso, K. Turner-Tamiyasu, and T. F. Blaschke. *In vivo* interaction of the enantiomers of disopyramide in human subjects. *J. Pharmacokinet. Biopharm.* 14:335–356 (1986).
8. R. Mehvar and F. Jamali. Pharmacokinetic analysis of the enantiomeric inversion of chiral non-steroidal antiinflammatory drugs. *Pharm. Res.* 5:76–79 (1988).
9. A. J. Hutt and J. Caldwell. The metabolic chiral inversion of 2-arylproprionic acids—a novel route with pharmacological consequences. *J. Pharm. Pharmacol.* 35:693–704 (1983).
10. A. G. Rauws. In E. J. Ariens, W. Sondijn, and M. Timmermans (eds.), *Stereochemistry and the Biological Activity of Drugs,* Blackwell, Oxford, 1983.
11. G. R. Wilkinson and D. Shand. A physiological approach to hepatic drug clearance. *Clin. Pharmacol. Ther.* 18:304–315 (1978).
12. K. Williams and E. Lee. Importance of drug enantiomers in clinical pharmacology. *Drugs* 30:333–354 (1985).
13. F. Jamali, N. N. Singh, F. M. Pasutti, A. S. Russel, and R. T. Coutts. Pharmacokinetics of ibuprofen enantiomers in humans following oral administration of tablets with different absorption rates. *Pharm. Res.* 5:40–43 (1988).
14. J. Hendel and H. Brodthagen. Enterohepatic cycling of methotrexate estimated by use of the D-isomer as a reference marker. *Eur. J. Clin. Pharmacol.* 26:103–107 (1984).
15. S. Toon, L. K. Low, M. Gibaldi, W. F. Trager, R. A. O'Reilly, C. H. Motley, and D. A. Goulart. The warfarin-sulphinpyrazone interaction: Stereochemical considerations. *Clin. Pharmacol. Ther.* 39:15–24 (1986).
16. M. Eichelbaum, G. Mikus, and B. Vogelgesang. Pharmacokinetics of (+)-, (−)- and (+/−)-verapamil after intravenous administration. *Br. J. Clin. Pharmacol.* 17:453–458 (1984).
17. B. Vogelgesang, H. Echizen, E. Schmidt, and M. Eichelbaum. Stereoselective first-pass metabolism of highly cleared drugs: studies of the bioavailability of L- and D-verapamil examined with a stable isotope technique. *Br. J. Clin. Pharmacol.* 18:733–740 (1984).
18. M. Eichelbaum. Pharmacokinetic and pharmacodynamic consequences of stereoselective drug metabolism in man. *Biochem. Pharmacol.* 37:93–96 (1988).

19. P. J. Wedlund, W. S. Aslanian, E. Jacqz, C. B. McAllister, R. A. Branch, and G. R. Wilkinson. Phenotypic differences in mephenytoin pharmacokinetics in normal subjects. *J. Pharmacol. Exp. Ther.* 234:662–669 (1985).
20. E. Jacqz, S. D. Hall, R. A. Branch, and G. R. Wilkinson. Polymorphic metabolism of mephenytoin in man: Pharmacokinetic interaction with a co-regulated substrate, mephobarbital. *Clin. Pharmacol. Ther.* 39:646–653 (1986).
21. A. Kupfer, R. K. Roberts, S. Schenker, and R. A. Branch. Stereoselective metabolism of mephenytoin isomers. *J. Pharmacol. Exp. Ther.* 218:193–199 (1981).
22. A. Kupfer, P. Desmond, R. Patwardhan, S. Schenker, and R. A. Branch. Mephenytoin hydroxylation deficiency: Kinetics after repeated doses. *Clin. Pharmacol. Ther.* 35:33–39 (1984).
23. C. C. Pfeiffer. Optical isomerism and pharmacological action, a generalization. *Science* 124:29–31 (1956).
24. T. Walle, J. G. Webb, E. E. Bagwell, U. K. Walle, H. B. Daniell, and T. E. Gaffney. Stereoselective delivery and action of beta-receptor antagonists. *Biochem. Pharmacol.* 37:115–124 (1988).
25. S. A. Ward, T. Walle, U. K. Walle, G. R. Wilkinson, and R. A. Branch. Propranolol's metabolism is determined by both mephenytoin and debrisoquin hydroxylase activities. *Clin. Pharmacol. Ther.* 45:72–79 (1989).