enzyme-inducing agents to a simple increase in hepatic first-pass metabolism. Although the existence of increased first-pass clearance was supported by the present analysis, the data suggest that an alternative mechanism, increased effective linear volume, may be responsible. Due to the increased retention of lidocaine in the liver as a result of increased effective liver volume, the first-pass clearance of lidocaine was much more extensive in epileptic patients than in normal volunteers.

Although the possibility exists for a reduction in the extent of lidocaine absorption in the epileptic patient, no evidence for a similar interaction could be found in the literature. In addition, it is highly unlikely that all of the anticonvulsant drugs used in this study should have the same effect on absorption. However, there is evidence (7–9) for the increase in effective liver volume observed in the present study. An increase in liver mass during anticonvulsant therapy, as well as an increase in binding affinity by the newly synthesized protein, has been postulated as possible mechanisms.

In conclusion, changes in the pharmacokinetics of drugs due to the chronic administration of enzyme-inducing agents has been attributed solely to increases in the intrinsic metabolic activity (6–9). Concomitant changes in blood flow are sometimes postulated as complementary mechanisms for increased clearance (9–11). However, one mechanism that has generally been overlooked is the effect of enzyme-inducing agents on the effective volume of the eliminating organ, *e.g.*, the liver and/or intestinal mucosa, by increasing tissue mass or tissue binding (10–12).

The results of the present analysis indicate that first-pass clearance may be a complex interaction of several pharmacokinetic parameters including blood flow, metabolic activity, and effective tissue volume. The complexity of this interaction may help to explain the apparent discrepancies between enzyme induction observed *in vitro* and *in vivo*.

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Solubility and Partitioning V: Dependence of Solubility on Melting Point

Keyphrases □ Solubility—dependence on melting point, crystalline compounds □ Crystalline compounds—polycyclic aromatic hydrocarbons, dependence of solubility on melting point

To the Editor:

It is well known that the solubility (in any solvent) of a crystalline solute is at least partially dependent on certain properties of the crystal. The reduction in solubility that is attributable to solute crystallinity is given by:

$$\log \frac{X^C}{X^{SCL}} = \frac{-\Delta S_f (T_m - T)}{2.303RT} + \frac{\Delta C_p (T_m - T)}{2.303RT} - \frac{\Delta C_p}{2.303R} \ln \left(\frac{T_m}{T}\right) \quad \text{(Eq. 1)}$$

where X^C and X^{SCL} are the mole fractional solubilities of the crystalline solute and of the supercooled liquid, respectively; T_m and T are the melting point and temperature of interest, respectively (both in °K); ΔS_f is the entropy of fusion of the crystal; and ΔC_p is the difference in heat capacity between the crystal and the supercooled liquid.

The supercooled liquid, SCL, is the result of melting the crystal at the temperature of interest, which is assumed to be below the melting point. It is the equivalent to the "oil" form of the substance. In most cases, it is not possible to produce the oil or molten form below the melting point. For these cases, the supercooled liquid represents a hypothetical state.

To estimate the solubility of crystalline compounds, it is necessary to estimate the crystal–liquid solubility ratio, X^C/X^{SCL}. This estimation is normally facilitated by simplifying Eq. 1 to remove the ΔC_p terms. Two alternative approximations for ΔC_p are commonly used: $\Delta C_p = 0$ and $\Delta C_p = \Delta S_f$. These approximations lead to the following simplifications.

If $\Delta C_p = 0$:

$$\log \frac{X^C}{X^{SCL}} = -\frac{\Delta S_f (T_m - T)}{2.303RT} \quad \text{(Eq. 2)}$$

If $\Delta C_p = \Delta S_f$:

$$\log \frac{X^C}{X^{SCL}} = -\frac{\Delta S_f}{2.303R} \ln \left(\frac{T_m}{T}\right) \quad \text{(Eq. 3)}$$

Equation 2 was used by Yalkowsky and coworkers (1–4), whereas Eq. 3 was used by Martin *et al.* (5) and was recommended by Hildebrand *et al.* (6).

To verify one or the other of these approximations, it is necessary to find a set of crystalline solutes and a solvent for which X^{SCL} is known. The crystalline polycyclic aromatic hydrocarbons (pah) in benzene are such a system. Since the solutes and solvent have no permanent dipoles, the major cohesive interactions will be the result of London dispersion forces. Dispersion forces are primarily dependent on polarizability, which is proportional to volume for hydrocarbons. Thus, the cohesive energy density of the solutes and the solvent is very similar, and the solutions are very nearly ideal. Because the components of an ideal solution are completely miscible (if they are liquids), it can be assumed that $X^{SCL} = 1.0$ for the polycyclic aromatic hydrocarbons in benzene.

It has been shown that the entropy of fusion of confor-

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Table I—Entropies of Fusion of Some Polycyclic Aromatic Hydrocarbons

	Reference 8	Reference 9	Reference 10
Diphenyl	—	13.2	13.0
Naphthalene	13.0	24.7	13.1
Anthracene	14.0	14.1	14.1
Phenanthrene	10.8	10.5	12.1
Pyrene	9.6	8.6	—
Triphenylene	12.7	—	—
Chrysene	11.8	—	14.9
Fluorene	11.6	12.1	—
Acenaphthene	14.3	14.4	13.6
Fluoranthrene	11.8	—	—

mationally rigid molecules is reasonably constant. Most large aromatic molecules have $\Delta S_f \simeq 13.5$ cal/°K/mole. The values of the entropy of fusion of some polycyclic aromatic hydrocarbons are shown in Table I.

Equations 2 and 3 can be tested by regression analysis of $X^{pah}_{benzene}$ as a function of $(T_m - T)/2.303RT$ and $\ln(T_m/T)/2.303R$, respectively, and comparison of the slopes with the expected value of 13.5 cal/°K/mole.

The values of $(T_m - T)/2.303RT$ and $\ln(T_m/T)/2.303R$ do not differ greatly for low melting solutes studied at room temperature. However, they can significantly deviate from one another at higher temperatures. The values of the two terms as a function of melting point at $T = 300$ and 400 °K are shown in Table II.

The solubilities of 14 polycyclic aromatic hydrocarbons in benzene as determined previously (7) at several temperatures are given in Table III. These data provide an excellent opportunity to test and compare the described equations. Table IV provides a summary of the least-squares regression analysis of the data in Table III against Eqs. 2 and 3. Both curves were forced through the origin.

It is apparent that both equations give excellent correlations with the data. The statistical parameters show better fit with Eq. 2, although the difference is not significant. The major difference between the two equations lies in the value of the slope. If the entropy of fusion of the polycyclic aromatic hydrocarbons is constant, as appears to be the case, the slope is equal to that value. The entropy of fusion calculated from Eq. 2 (16.19 cal/°K/mole) is much closer to the expected value of 13.5 cal/°K/mole than the slope of Eq. 3 (19.58 cal/°K/mole).

The slight difference between the slope obtained with Eq. 2 and 13.5 cal/°K/mole is probably due to a systematic change in cohesive energy density with increasing molecular size and, thus, with increasing melting point. This change would cause the larger and higher melting hydrocarbons to have X^{SCL} progressively less than the ideal value of unity. It would also cause X^C/X^{SCL} to appear to be artifactually high and thus increase the slope over the

Table II—Dependence of $(T_m - T)/2.303RT$ and $\ln(T_m/T)/2.303R$ on T_m and T

	T = 300 °K		T = 400 °K	
T_m	$\frac{(T_m - T)}{2.303RT}$	$\frac{\ln(T_m/T)}{2.303RT}$	$\frac{(T_m - T)}{2.303RT}$	$\frac{\ln(T_m/T)}{2.303RT}$
300	0	0	—	—
400	0.07	0.06	0	0
500	0.15	0.11	0.05	0.05
600	0.22	0.15	0.11	0.09
700	0.29	0.19	0.16	0.12

Table III—Solubility of Polycyclic Aromatic Hydrocarbons in Benzene

Solute	Melting Point (T_m), °K	Temperature (T), °K	Mole Fraction Solubility (X)
Diphenyl	69	37.0	0.5118
	69	47.6	0.6478
	69	59.2	0.8195
	69	63.2	0.8916
o-Terphenyl	56	28.0	0.5852
	56	32.4	0.6442
	56	44.8	0.8012
	56	50.4	0.9013
m-Terphenyl	87	36.8	0.2827
	87	47.0	0.3338
	87	60.8	0.5466
	87	67.4	0.6407
	87	74.2	0.7571
	87	77.6	0.8344
p-Terphenyl	213	38.0	0.0071
	213	60.2	0.0156
	213	64.2	0.0178
	213	68.0	0.0204
	213	77.6	0.0279
1,3,5-Triphenylbenzene	175	25.2	0.0299
	175	28.6	0.0351
	175	40.4	0.0483
	175	46.2	0.0562
	175	59.4	0.0795
	175	66.6	0.0960
Naphthalene	80	35.0	0.3766
	80	45.0	0.4806
	80	47.4	0.5094
	80	63.2	0.7119
	80	75.8	0.9180
Anthracene	218	35.8	0.0103
	218	42.4	0.0130
	218	50.6	0.0173
	218	59.6	0.0225
	218	70.2	0.0315
Phenanthrene	98	32.0	0.2239
	98	40.2	0.2836
	98	41.8	0.2990
	98	50.2	0.3750
	98	58.0	0.4572
Pyrene	150	32.4	0.0734
	150	58.6	0.1506
	150	66.8	0.1896
	150	76.2	0.2441
	150	84.6	0.3014
Triphenylene	198	39.4	0.0140
	198	47.6	0.0181
	198	63.8	0.0289
	198	69.4	0.0341
	198	82.8	0.0497
Chrysene	254	35.6	0.0021
	254	45.8	0.0032
	254	60.6	0.0052
	254	72.2	0.0079
Fluorene	113	33.6	0.1604
	113	54.4	0.2778
	113	58.4	0.3095
	113	69.4	0.4059
	113	72.8	0.4405
Acenaphthene	94	30.6	0.1815
	94	41.4	0.2540
	94	63.2	0.4731
	94	69.4	0.5552
Fluoranthene	110	44.8	0.2174
	110	56.0	0.3011
	110	64.4	0.3826
	110	77.2	0.5331

Table IV—Summary of Regression Analyses

	Equation 2	Equation 3
Slope = ΔS_f	16.19	19.58
Correlation coefficient	0.9945	0.9903
Coefficient of variation	13.49	17.91
Standard deviation	0.120	0.159
Number of data points	67	67

expected value. (If the analysis is restricted to hydrocarbons that melt at or below 150, the observed slopes are 13.96 for Eq. 2 and 15.40 for Eq. 3.)

Thus, it appears that Eq. 2 is more meaningful than Eq. 3 for quantitating the effects of solute crystallinity on solubility. This finding implies that the value of ΔC_p for the polycyclic aromatic hydrocarbons is closer to zero than it is to ΔS_f. These results are in agreement with the results obtained for the aqueous solubility of a large number of organic nonelectrolytes of widely varying structure (1).

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BOOKS

REVIEWS

Analytical Profiles of Drug Substances, Vol. 9. Edited by KLAUS FLOREY. Academic, 111 Fifth Ave., New York, NY 10003. 1980. 618 pp. 15 × 23 cm.

This book is the ninth in a continuing series that covers the analytical aspects of specific drug entities. It was compiled under the auspices of the Pharmaceutical Analysis and Control Section of the Academy of Pharmaceutical Sciences. The individual profiles or monographs are much more complete than those found in the compendia. The information in the *Analytical Profiles* series not only includes compendial tests but also important supplemental information including synthesis, additional physical properties, data on stability, absorption, metabolism, and excretion, and various analytical methods. In general, each profile is a literature review, but IR, mass spectrometric, UV, and NMR spectra are reproduced along with appropriate crystallographic data. The coverage of the quantitative analytical procedures is usually very complete and includes dosage forms, biological fluids, foodstuffs where appropriate, and related information.

Volume 9 includes 19 new monographs: bacitracin, bretylium tosylate, carbamazepine, cefaclor, cefamandole nafate, cyproheptadine, dibenzepine hydrochloride, digoxin, doxorubicin, fluphenazine decanoate, gentamicin sulfate, haloperidol, khellin, lorazepam, methoxsalen, nadolol, nitrazepam, nitroglycerin, and trifluoperazine hydrochloride. In addition, the *Addendum* contains monographs for griseofulvin and methadone hydrochloride.

While praising *Analytical Profiles* in general, and Volume 9 in particular, this reviewer believes it is time for the editorial board to define more carefully what they want *Analytical Profiles* to become. Some of the drugs covered in Volume 9 are relatively new entities. Others, such as bacitracin, digoxin, haloperidol, khellin, and nitroglycerin, could be called classics. One would have thought that these drugs would have been covered years ago. It is not clear from reading the two monographs on griseofulvin and methadone hydrochloride in the *Addendum* what has been added. Furthermore, a review of the bibliography for griseofulvin shows 18 of 29 references published prior to 1969, six prior to 1974, four prior to 1979, and one unpublished paper authored by the individuals who wrote the monograph. Griseofulvin also appeared in Volume 8 of *Analytical Profiles*. What new information appears that was not published a year ago? This question is not answered. The other drug published in the *Addendum*, methadone hydrochloride, first appeared in Volumes 3 and 4 and probably is in need of updating. But, again, the updated information is not specified. Indeed, this monograph does not even reference the previous material found in Volumes 3 and 4.

The two drugs covered in the *Addendum* brings up another point. There does not seem to be a systematic plan to update the older monographs. With the rapid changes occurring in analytical methodology and instrumentation, such a plan seems to be imperative.

Nevertheless, this series meets a real need by bringing together a concise literature review of the analytical description of important drug entities. Volume 9 is no exception. Its purchase is recommended highly for appropriate libraries, workers in pharmaceutical analysis, and teachers of pharmaceutical chemistry who want to maintain excellent personal libraries.

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Clinical Pharmacokinetics: Concepts and Applications. By MALCOLM ROWLAND and THOMAS N. TOZER. Lea & Febiger, 600 Washington Square, Philadelphia, PA 19106. 1980. 331 pp. 17 × 25 cm. Price U.S. $29.50 (Canada $35.50).

This book is an important contribution that will facilitate teaching a clinically relevant introductory course in pharmacokinetics. The goal of the authors was to fill a void which, in their own words, "has been the lack of a book that teaches the application of pharmacokinetics in drug therapy" to students, practitioners, and researchers. They are to be congratulated for achieving their goal.

The book is divided into four sections: Concepts, Disposition and Absorption Kinetics, Therapeutic Regimens, and Individualization. Each section is well supported with literature data and computer simulations. Chapters 5, 6, and 11 present a detailed, yet readable, description of clearance concepts (*i.e.*, the factors that determine steady-state plasma concentration). In contrast to most books written in the area of pharmacokinetics, college calculus is not needed to appreciate the textual material. Indeed, the authors remove much of the "mathematical fog" that has shrouded pharmacokinetics.

Several minor limitations to the text should be listed. Nonlinear kinetics is discussed quite briefly; *i.e.*, after reading the text, it is likely that