*Ann. Rev. Pharmacol. Toxicol. 1981. 21:31–61*




# STRUCTURE-ACTIVITY RELATIONSHIPS AND DRUG DISPOSITION[1]



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## THE NATURE OF BIOLOGICAL MEMBRANES AND DRUG PERMEATION

Biological membranes can be classified into three major types: (*a*) those made up of several layers of cells, derived from ectoderm primarily for sensory and protective functions, e.g. the skin, (*b*) those derived from the endoderm primarily intended for absorption of nutrients, e.g. the epithelium of the gastrointestinal tract consisting of a single layer of cells, (*c*) those consisting of a boundary less than one cell in thickness, e.g. the membrane of blood cells, mitochondrion, or nucleus. Among these, one may consider the cell membrane or the plasma membrane as a fundamental structure (1, 2).

Overton made the first important observation on the character of living membranes in 1902 by studying the osmotic behavior of frog muscle in solutions of various substances (3). Realizing that cellular membranes are more readily penetrated by lipid-soluble substances than by lipid-insoluble substances, Overton (4) and Meyer (5, 6) independently used partition coefficients to correlate with biological activity of narcotic (depressant)

[1]Abbreviations: BUI, brain uptake index (percentage of $^3$HOH); $1/C$, a measure of the biological effect, where $C$ is the molar concentration required to cause a certain effect, e.g. erythema or vasoconstriction; $D$, the diffusion coefficient (cm$^2$/sec); $K_m$ human stratum corneum/water partition coefficient; log $P_0$, the ideal lipophilicity for maximum absorption; $PF/P$, prostatic fluid/plasma concentration ratio of the drug; $R$, $M/P$ = milk ultrafiltrate/plasma ultra filtrate ratio; $R'$, $C_m/C_p$ = total concentration of the drug in the milk/ total concentration of the drug in the plasma ratio.



0362-1642/81/0415-0031$01.00

substances. To account for the permeability of lipid-insoluble polar molecules like urea, formamide, and water, Collander & Bärland (7) later proposed that the lipid membrane is interrupted by pores filled with water. Thus the model of lipid-sieve membrane came into being.

Using as a basis the study of the surface area of the monolayer lipid derived from red cell extract, Gorter & Grendel (8) proposed that the cell membrane is a bimolecular layer. Later when the surface tension of cells in aqueous medium was measured, a much lower tension than expected from a simple lipid-water interface was observed (9). Danielli & Harvey (10) were able to reconcile the discrepancy by showing that the interfacial tension of oil droplets surrounded by protoplasm is much lower than that of oil droplets surrounded by a protein-free solution.

Danielli & Davson (11, 12) later proposed the bimolecular layer model of oriented lipid molecules with a monolayer of protein adsorbed on both sides of the bilayer. This model has been confirmed by electron microscopic and X-ray diffraction studies of various cell membranes as well as the mitochondrial and nuclear membranes. The thickness of the membranes is about 100 Å. Based on the analysis of thermodynamics of macromolecular systems and other experimental evidence, Singer (16) and Singer & Nicolson (17) proposed the fluid mosiac model of two-dimensional solutions of oriented globular proteins and lipids as the membrane structure of various plasmalemmal and intracellular membranes. According to this model, the heterogeneous set of globular protein emerges in an amphipathic structure, i.e. with the polar and ionic groups protruding from the lipid layer into the aqueous phase and the nonpolar groups mostly embedded in the hydrophobic nonpolar interior of the membrane (17). This more elaborate model is not inconsistent with the earlier lipid-sieve membrane in accounting for the permeability of lipophilic and hydrophilic drug molecules.



## MECHANISMS OF TRANSFER OF SUBSTANCES ACROSS MEMBRANES

### *Passive Transfer*

SIMPLE FILTRATION OF WATER AND SOLVENT DRUG OF WATER SOLUBLE MOLECULES THROUGH THE AQUEOUS PORES Normal capillary wall and glomerular membrane are examples of porous membranes with fairly large apertures. Both solvents and water-soluble solutes (except high molecular weight compounds like proteins) can pass through these pores by simple diffusion mechanism, aided by concentration gradient, hydrostatic, and osmotic pressure differences (18).

DIFFUSION BY DISSOLVING IN THE MEMBRANE MATERIAL (LIPID BARRIER) This appears to be the most important mechanism for most bioactive foreign molecules, except for the ones that are structural analogues to naturally occurring nutrients (e.g. 5-fluorouracil, 5-bromouracil, methotrexate, and amino acid derivatives). It is also quite conceivable that even a drug known to be transported by active mechanism will also diffuse passively until an equal concentration on both sides of the membrane is attained. This passive diffusion process is not dependent on the consumption of energy; it is not saturable and is not inhibited by structural analogues or specific metabolic inhibitors. The general principle of the pH-partition hypothesis applies to the diffusion restricted by a lipid barrier (1, 19) although even some charged molecules such as quaternary ammonium salts are known to be absorbed by the gastrointestinal tract as such or as ion pairs with negative ions (like alkyl sulfates) (20).

## *Specialized Transport*

CARRIER TRANSPORT MECHANISMS These mechanisms depend on complex formation between the solute or drug with a certain membrane component, thus facilitating the transport of lipid insoluble molecules. Three different types of carrier transport have been reported: active transport (21, 22), facilitated diffusion (21), and exchange diffusion (1, 23).

*Active transport mechanism* This mechanism depends on cellular energy in order to go against the concentration gradient. It is saturable and can be inhibited by metabolic inhibitors as well as by structural analogues of the substrates. It is in many cases stereo-specific. This mechanism is operative for many highly polar nutrients, such as sugars, amino acids, purines, pyrimidines, bile salts, vitamins (24, 25) and cardic glycosides like digitoxin and digoxin (26), 5-flurorouracil (27), L-3,4-dihydrophenylalanine (28), and L-5-hydroxytryptophan (29). LeFévre has reviewed the structure-activity relationships in substrates and antagonists of sugar transport in the red blood cell (30).

*Facilitated diffusion* This mechanism differs from active transport since it is driven by existing concentration gradient, and yet is different from passive diffusion. Because it depends on reversible binding to membrane carrier moving by thermal agitation, it is saturable (31). For example, human red cell membrane is much more permeable to polar substances such as glucose, glycerol, urea, and chloride ions than what one would expect from the simple lipid membrane model.

*Exchange diffusion* Exchange diffusion may take place in any carrier transport system that is near saturation (32). In this process, a carrier shuttles back and forth from one side of the membrane to the other, where it releases the substrate and picks up another molecule of the substrate. For example, if a different isotope of the substrate is placed on either side of the membrane, there will be a rapid exchange of the isotopes without a net transfer of substrate (23).

PINOCYTOSIS AND PHAGOCYTOSIS Amoeba and cells growing in tissue culture take up small droplets of the external medium by engulfing or sucking in process known as pinocytosis (33, 34). Phagocytosis is the process by which living cells like amoeba or leukocytes engulf other cells, particles, or minute foreign bodies. For the permeation of large molecules like proteins and chylomirons or other larger molecular aggregates pinocytosis and phagocytosis are known to be operative (35).

During phagocytosis, a part of the cell membrane is taken up as a vesicle around the particles taken up by the cell (36). This type of special transport is quite significant for drugs being delivered by liposomes. Liposome entrapped–methotrexate has been shown to hold up better in plasma and in tissue (37). The potential application of the liposome-encapsulated desferioxamine in the treatment of chronic hemosiderosis has been proposed by Guilmette et al (38).



## STRUCTURE-ACTIVITY RELATIONSHIPS FOR PASSAGE OF DRUGS ACROSS VARIOUS BODY MEMBRANES

### *Gastric Absorption*

Using the data of Brodie & Hogben (39, 40), Lien (41) derived the following correlations for the gastric absorption of drugs (Equations 1, 2):

From the Stomach of Rats

| Acids | $n$ | $r$ | $s$ |
|---|---|---|---|
| 1. $\log \%\ \text{Abs} = -6.626\ (\log P)^2 + 2.465 \log P - 0.679$<br>$\log P_0 = 1.97\ (1.78 - 2.69)$ | 9 | 0.952 | 0.129 |
| **Bases** | | | |
| 2. $\log \%\ \text{Abs} = -0.217\ (\text{pK}_a - 1) + 1.342$<br>$= +0.217 \log U/D + 1.342$ | 5 | 0.953 | 0.177 |

Where $P$ is the 1-octanol/water partition coefficient for the undissociated form, $U/D$ represents the undissociated/dissociated, $n$ the number of data points (drugs), $r$ the correlation coefficient, and $s$ the standard deviation.

Kakemi et al have studied the gastric absorption of barbiturates in rats (42). Linear correlations (19) have been obtained between log $K$ (absorption) and log $P$ measured in $CCl_4$, $CHCl_3$, or isoamylacetate and water (Equations 3–6).

Gastric Absorption of Barbiturates by Rats

| | $n$ | $r$ | $s$ |
|---|---|---|---|
| 3. $\log K_{(1/h)} = 0.307 \log P_{CHCl_3} - 1.189$ | 15 | 0.943 | 0.114 |
| 4. $\log K_{(1/h)} = 0.313 \log P_{\text{i-amyl acetate}} - 1.261$ | 16 | 0.867 | 0.147 |
| 5. $\log K_{(1/h)} = 0.268 \log P_{CCl_4} + 0.806$ | 16 | 0.933 | 0.123 |
| 6. $\log K_{(1/h)} = -0.068 (\log P)^2_{CCl_4} + 0.0303 \log P_{CCl_4} - 0.725$ | 16 | 0.958 | 0.103 |
| $\log P_{0CCl_4} = 2.21\ (1.30 - 10.08)$ | | | |
| $\log P_{0_{oct}} = 2.01$ | | | |

Similar correlations are obtained from the absorption of sulfonamides by rat stomach (43).

Gastric Absorption by Rats

| Sulfonamides | $n$ | $r$ | $s$ |
|---|---|---|---|
| 7. $\log K_u = 0.314 \log P_{i\text{-amyl acetate}} - 1.159$ | 17 | 0.942 | 0.122 |
| **Sulfonamides and Barbiturates** | | | |
| 8. $\log K_u = 0.286 \log P_{i\text{-amyl acetate}} - 1.179$ | 32 | 0.927 | 0.137 |

Since Equation 7 has slope and intercept very close to those of Equation 4, combination of both yields Equation 8. More than 85% ($r^2 > 0.85$) can be accounted for by Equation 8. Similar correlations can be obtained from the partition coefficients measured in $CCl_4$ or $CHCl_3$. For the gastric absorption of carbamates reported by Houston et al (44, 45) Equation 9 is obtained (46).

| Gastric Absorption of Carbamates by Rats | $n$ | $r$ | $s$ |
|---|---|---|---|
| 9. $\log K = 0.146 \log P_{oct} - 0.193$ | 16 | 0.938 | 0.195 |

## *Intestinal Absorption*

For the same series of *N*-alkyl carbamates, parabolic dependence of the log *K* on log *P* instead of linear dependence has been observed (44–46).

Intestinal Absorption by Rats (Everted Gut Sac Method)

| | | *n* | *r* | *s* |
|---|---|---|---|---|
| For $ROCONH_2$ | | | | |
| 10. | $\log K = -0.090 (\log P)^2 + 0.103 \log P - 0.833$<br>$\log P_0 = 0.56$ | 10 | 0.973 | 0.126 |
| For $ROCONHCH_3$ | | | | |
| 11. | $\log K = -0.063 (\log P)^2 + 0.198 \log P - 0.891$<br>$\log P_0 = 1.56$ | 7 | 0.917 | 0.08 |

It is interesting to note that the ideal lipophilicity log $P_0$ for maximum absorption of the *N*-methyl derivatives is about one log unit higher than that of the *N*-unsubstituted series (See Equations 10, 11).

Both the lipophilic character (log $P_{oct}$) and the extent of ionization log $D/U = (pK_a - pH)$ are needed for a significant correlation of the intestinal absorption of basic drugs (19) (Equation 12).

| | | *n* | *r* | *s* |
|---|---|---|---|---|
| 12. | $\log \%\ Abs = -0.131 (\log P)^2 + 0.362 \log P - 0.105 (pK_a - 5.3) + 1.273$<br>$\log P_0 = 1.39$ | 11 | 0.916 | 0.182 |

It is interesting to note that clindamycin, a more lipophilic antibiotic (log $P = 2.16$), has been shown to be absorbed much more rapidly than the parent compound lincomycin (log $P = 0.56$) (47). The reported better antibacterial activities and less gastrointestinal side effects of clindamycin are also related to the higher lipid solubility and greater membrane penetrability (48).

Equations 13–18 are derived from the in situ permeability coefficient data of rat intestine obtained originally by Ho et al (49). Since the uncorrected (apparent) partition coefficients were measured using 1-octanol buffer (pH 6.0), no apparent correlation could be obtained when both neutral and acidic drugs were included (Equations 13, 14). When these two groups were separated, statistically highly significant correlations were obtained, as judged from the correlation coefficient *r* and the standard deviation *s* of the regression. In these equations $P_{app}$ is the permeability coefficient through rat jejunum with a high stirring (49, 50).

| For Both Neutral and Acidic Drugs | $n$ | $r$ | $s$ |
|---|---|---|---|
| 13. $\log P_{app} = 0.090 \log P_{oct/buff} - 3.967$ | 24 | 0.407 | 0.258 |
| 14. $\log P_{app} = 0.183 \log P_{oct/buff} - 0.689 \log \text{mol wt} - 2.627$ | 24 | 0.740 | 0.195 |
| **For Neutral Molecules Only** | | | |
| 15. $\log P_{app} = 0.125 \log P_{oct/buff} - 4.082$ | 13 | 0.679 | 0.203 |
| 16. $\log P_{app} = 0.237 \log P_{oct/buff} - 0.657 \log \text{mol wt} - 2.884$ | 13 | 0.933 | 0.105 |
| **For Acidic Drugs Only** | | | |
| 17. $\log P_{app} = 0.026 \log P_{oct/buff} - 3.808$ | 11 | 0.088 | 0.105 |
| 18. $\log P_{app} = 0.106 \log P_{oct/buff} - 1.225 \log \text{mol wt} - 1.221$ | 11 | 0.903 | 0.143 |

The log mol wt term in Equations 16 and 18 is significant at 99.95 percentile level as indicated by an F-test ($F_{1,10} = 31.4$ and $F_{1,8} = 35.1$, respectively). The physical meaning of the negative dependence on log molecular weight has been attributed to the reciprocal dependence of the diffusion coefficient ($D$) on the cube root of molecular weight as shown by the Sutherland-Einstein equation (19, 50).

$$19.\ D = \frac{RT}{6\pi\eta N}\left(\frac{4N}{3M \cdot \bar{v}}\right)^{1/3}$$

Levine and her co-workers have studied the transport of quaternary ammonium compounds extensively, and attributed the poor absorption of a cationic compound like benzomethamine to the formation of a nonabsorbable complex with mucin (51, 52). On the other hand carrier transport of certain quaternary ammonium compounds like tubocurarine, pralidoxime, etc by a phosphatidopeptide fraction has also been reported by Levine et al (53–56). In addition to the effects of mucin and phosphatidopeptide, Levine et al (57) have reported that everted gut of rats sacrificed by decapitation may progressively lose its structural integrity and the barrier to absorption. Morphological changes like edema of the laminal propria were observed 5 min after incubation at 37°C in oxygenated buffer, 30 min later

50–75% of the normal epithelium disappeared, at 1 hr the epithelial border was totally disrupted. Tissue damage was found to be lower at 25°C in tissues of rats sacrificed under anesthesia or in intestinal sacs of golden hamster (57).

Plakogiannis et al (58) have reported that the presence of equimolar concentration of sodium decylsulfate inhibited the transfer of *N*-methylquinolinium derivatives. Masaki and her co-workers (59) studied the in vitro transport of different quaternary ammonium compounds across rat small intestine with and without the presence of alkyl sulfate anions. They observed that the effective rate constant ($k + k^1$) of small quaternary ammonium salts like 2-pyridine aldoxine methyl iodide (2-PAM) was increased two to three fold by the addition of sodium decylsulfate, presumably because of ion-pair formation. On the other hand, sodium octylsulfate decreased the transport of fairly bulky quaternary ammonium compounds like methantheline, propanotheline, and tridihexethyl. This was attributed to excessive hydrophobic interactions between the intestinal membrane and the highly lipophilic ion pairs. Since no significant change was observed for 3-PAM, 4-PAM, or sodium salicylate in the presence of alkylsulfate anion, the observed changes in transport could not be due to the detergent effect of the anion.

By and large, the pH-partition hypothesis can be considered as a practical rule of thumb in describing drug absorption. However, accumulated data have shown that the relationship between absorption and lipid solubility or partition coefficient is in many cases nonlinear, especially when a wide range of log *P* value is included. Furthermore, the hypothesis is not adequate in describing or predicting the transport of ionic species (59, 60), or even the lack of transport of highly lipid-soluble compounds, e.g. mineral oil (41). The so-called virtual pH has been proposed to circumvent the shortcomings of the pH hypothesis, but its validity has been questioned (61). Wagner & Sedman have proposed an *extraction theory* to describe quantitatively the rate of gastrointestinal and buccal absorption of acidic and basic molecules as a function of the pH of aqueous luminal content and time. It has been suggested that the absorption of monomeric species is rate limited by transfer of drugs out of the membrane in vivo instead of being rate limited by the unstirred aqueous diffusion layer as proposed by others (62–65). This is consistent with the parabolic dependence on log *P* observed in many cases (2, 19, 41).

Similar parabolic dependence on lipophilicity ($\log P_{oct/w}$) but with different ideal $\log P_0$ values for maximum absorption has been observed for the intestinal absorption of carbamates using everted gut and the in situ methods (2, 44) (Equations 20, 21).

In Situ Absorption (the Method of Doluisio et al) of $ROCONH_2$

| From Intestine | $n$ | $r$ | $s$ |
|---|---|---|---|
| 20. $\log K = -0.069 (\log P)^2 + 0.053 \log P - 0.855$<br>$\log P_0 = 0.39$ | 13 | 0.860 | 0.080 |
| 21. $\log K = -0.100 (\log P)^2 + 0.128 \log P + 0.108 E_s - 0.800$<br>$\log P_0 = 0.64$ | 13 | 0.948 | 0.053 |

It is interesting to note that addition of the steric parameter ($E_s$) significantly improved the correlation for the absorption data obtained in situ as indicated by the F test ($F_{1,9} = 14.2$). The positive dependence of $E_s$ indicates that unbranched small molecules will have higher absorption rates than the bulkier branched molecules. The addition of the same parameter to the in vitro (everted gut) data did not result in improved correlation (2). The everted gut method suffers the possible morphological deterioration as discussed previously. In addition, it is one step removed from the in vivo situation since the blood supply to and from the intestine is severed. The in situ method (67) on the other hand still retains the blood circulation; therefore, the absorption is closer to what may happen in intact animals. One factor that makes it more complicated than the everted gut method is that it is susceptible to physiological factors like hemodynamics. Doluisio et al have found that prolonged fasting of rats exceeding 20 hr significantly decreased the drug absorption studied under the in situ method (68).

From the original data of Nogami et al on the in situ rat intestinal absorption of various benzene derivatives (69–71) and the octanol-water partition coefficients, from the log $P$ values compiled by Shindo & Komai (46), the following parabolic equation (Equation 22) is obtained:

| In situ Intestinal Absorption of Phenols and Various Benzene Derivatives (Very Weak Acids, Bases, and Neutral Compounds) | $n$ | $r$ | $s$ |
|---|---|---|---|
| 22. $\log K = -0.120 (\log P)^2 + 0.555 \log P - 0.622$<br>$\log P_0 = 2.31$ | 39 | 0.872 | 0.125 |

This finding is in agreement with the additivity rule according to the extra thermodynamic relationships as proposed by Nogami et al (69–71). It is interesting that so many different types of compounds ranging from phenols

and sulfonamides to neutral compounds and even aniline derivatives could be correlated with such a simple equation. One should not expect such a simple correlation without taking into account different degrees of ionization if stronger acids or bases were included in the study (2, 19, 41). For the small intestinal absorption of sulfonamides by rats, log $K_u M^{1/2}$ gives slightly better than log $K_u$ (19, 43).

Small Intestinal Absorption of Sulfonamides in Rats

| | | $n$ | $r$ | $s$ |
|---|---|---|---|---|
| 23. | $\log K_u = 0.381 \log P_{CHCl_3} - 0.077$ | 17 | 0.845 | 0.231 |
| 24. | $\log K_u = 0.416 \log P_{CHCl_3} - 0.149$ (including five $N^4$-acetyl derivatives) | 22 | 0.834 | 0.257 |
| 25. | $\log K_u = -0.121 (\log P)^2_{CHCl_3} + 0.333 \log P_{CHCl_3} + 0.027$ | 17 | 0.895 | 0.200 |
| | $\log P_{0CHCl_3} = 1.37$ = 2.41 (octanol) | | | |
| 26. | $\log K_u M^{1/2} = 0.407 \log P_{CHCl_3} + 1.127$ | 17 | 0.875 | 0.216 |
| 27. | $\log K_u M^{1/2} = 0.461 \log P_{CHCl_3} + 1.076$ | 22 | 0.869 | 0.236 |
| 28. | $\log K_u M^{1/2} = -0.117 (\log P)^2 + 0.361 \log P_{CHCl_3} + 1.228$ | 17 | 0.918 | 0.184 |
| | $\log P_{0CHCl_3} = 1.54$ = 2.56 (octanol) | | | |

Equations 29–31 were derived from the intestinal absorption data in rats compiled by Knoefel (72, 73).

Small Intestinal Absorption of Amides by Rats

| | | $n$ | $r$ | $s$ |
|---|---|---|---|---|
| 29. | $\log \%\ \text{Abs} = 0.307 \log P_{oil/w} + 2.461$ | 6 | 0.751 | 0.278 |
| 30. | $\log \%\ \text{Abs} = 0.473 \log P_{oil/w} - 0.013\ \text{mol wt} + 4.243$ | 6 | 0.963 | 0.131 |

Small Intestinal Absorption of Steroids in Rats

| | | $n$ | $r$ | $s$ |
|---|---|---|---|---|
| 31. | $\log \%\ \text{Abs}/100\ \text{g} = 0.304 \log P_{\text{benzene/aqMeOH}} + 1.152$ | 6 | 0.939 | 0.098 |

AMINO ACID TRANSPORT SYSTEM IN RABBIT ILEUM Hajjar & Curran (74) have studied the structural requirements for the affinity of various substrates for the amino acid site in the active transport system of the mucosal border of rabbit ileum. The affinity of amino acids for the site was proportional to the number of carbon atoms in the side chain (log molecular weight or $\pi$) for the 10 amino acids examined. Positive dependence of the affinity (log 1/ki) on the Hammett sigma ($\sigma$) constant was also found for the ring substituents on phenylalamine. Removal of either the $\alpha$-$NH_2$ or the carbonyl group greatly decreased the affinity (74).

## *Colonic Absorption of Drugs*

The pattern of colonic absorption has been shown to be similar to that in the small intestine (19, 75, 76). The following correlations were derived from the data of Schanker (75, 76).

Colonic Absorption of Barbiturates in Rats

| | | $n$ | $r$ | $s$ |
|---|---|---|---|---|
| 32. | $\log \%\ \text{Abs} = 0.248 \log P_{CHCl_3} + 1.110$ | 9 | 0.981 | 0.036 |

Colonic Absorption of Acidic Drugs in Rats

| | | $n$ | $r$ | $s$ |
|---|---|---|---|---|
| 33. | $\log \%\ \text{Abs} = 0.135\ (pK_a - 6.8) + 1.492$ | 10 | 0.780 | 0.301 |
| 34. | $\log \%\ \text{Abs} = 0.156\ (pK_a - 6.8) + 0.366 \log P + 0.755$ | 10 | 0.866 | 0.258 |

Colonic Absorption of Basic Drugs in Rats

| | | $n$ | $r$ | $s$ |
|---|---|---|---|---|
| 35. | $\log \%\ \text{Abs} = 0.076\ (6.8 - pK_a) + 1.227$ | 10 | 0.751 | 0.257 |
| 36. | $\log \%\ \text{Abs} = -0.388\ (\log P)^2 + 0.821 \log P + 1.117$ | 10 | 0.814 | 0.242 |
| 37. | $\log \%\ \text{Abs} = -0.330\ (\log P)^2 + 0.869 \log P + 0.059\ (6.8 - pK_a) + 0.817$<br>$\log P_0 = 1.32$ (0.42–2.08, 95% confidence interval) | 10 | 0.910 | 0.187 |
| 38. | $\log \%\ \text{Abs} = 0.362 \log D + 1.83$ | 10 | 0.930 | 0.143 |

Addition of the $(\log P)^2$ in Equation 37 is statistically significant at the 90th percentile level ($F_{1,6} = 5.7$). The ideal lipophilic character $\log P_0$ of 1.32 appears to be quite close to that found for the intestinal absorption of basic drugs [$\log P_0 = 1.39$ (Equation 12)]. Scherer & Howard (77) have used distribution coefficient in quantitative correlation, and obtained a slightly improved correlation from the same set of data (Eq. 38). In Equation 38

$$\log D_{base} = \log P + \log \frac{1}{1 + 10^{(pKa-pH)}}.$$

Although Equation 38 looks simpler than Equation 37, $\log D$ is a function of both $\log P$ and ($pK_a$ – pH). Equation 38 does not provide the resolution between the contributions from $\log P$ and ($pK_a$ – pH) as Equation 37 does.

Kakemi et al (78) have examined the mechanism of rectal absorption of sulfonamides. Apparent correlation was observed between the absorption rate constant ($k \times 10^2$) and the product of partition coefficient and diffusion constant ($P \cdot D$). Since both $\log k$ and $\log P$ are linearly related to free energy changes, the following equations are derived from the original data of Kakemi et al (78).

Rectal Absorption of Sulfonamides in Rats

| | $n$ | $r$ | $s$ |
|---|---|---|---|
| 39. $\log k = 0.896 \log P_{i\text{-amyl acetate}} - 1.641$ | 6 | 0.639 | 0.769 |
| 40. $\log k = 1.328 \log (P \cdot D) - 3.982$ | 6 | 0.722 | 0.681 |
| 41. $\log k = 3.140 \log P_{i\text{-amyl acetate}} + 9.472 \log D - 18.131$ | 6 | 0.961 | 0.320 |

In spite of the small number of data points examined ($n = 6$), the $\log D$ term in Equation 41 is statistically significant at the 95th percentile level ($F_{1,3} = 20.08$). The higher coefficient associated with $\log D$ suggests that the diffusion through the barrier is more important than the partition into the lipoid barrier.

The same investigators (79) also studied the effect of water-soluble bases (mostly glycols) and found that the rectal absorption rate of sulfonamides was reduced by these water-soluble bases. Apparent correlation was found between the absorption rate constant ($k \times 10^2$) and the reciprocal of the dielectric constants ($10^2/\epsilon$) of the bases. In other words, the higher the dielectric constants of the water-soluble base the lower the absorption rate

constant. The decreased absorption was attributed to the depression of the polarity in the vehicle (79).

## *Absorption of Drugs Through the Oral Mucosa (Buccal Absorption)*

By comparing the sublingual to subcutaneous dose ratios and the oil/water solubility coefficients of various alkaloids, Walton (80) reported that drugs that are poorly absorbed have relatively low oil-water partition coefficients and closely related drugs that are well absorbed have relatively high coefficients. The same author later reported (81) the efficacy of sublingual administration of drugs. The drugs with adequate degree of penetrability are organic nitrates, androgens, estrogens, anhydrohydroxyprogesterone, desoxycorticosterone acetate, fat-soluble vitamins, apomorphine, nicotine, and cocaine. Drugs that do not penetrate the oral mucosa in any practical dosage are morphine, codeine, ergot alkaloids, autonomic drugs like atropine and methacholine, barbiturates, analeptics, and cardiac glycosides (81).

From the data of Beckett & Moffat (82–85) on human subjects, Lien et al have derived Equations 42 and 43.

**Buccal Absorption of Acidic Drugs in Humans**

| | | *n* | *r* | *s* |
|---|---|---|---|---|
| 42. | $\log \%\ \text{Abs} = -0.154\ (\log P)^2 + 1.293 \log P + 0.664\ (pK_a - 6.0) - 0.013$ | 31 | 0.968 | 0.138 |
| | $\log P_0 = 4.19\ (3.82–5.92)$ | | | |

**Buccal Absorption of Basic Drugs in Humans**

| | | *n* | *r* | *s* |
|---|---|---|---|---|
| 43. | $\log \%\ \text{Abs} = -0.074\ (\log P)^2 + 0.813 \log P - 0.500$ | 10 | 0.943 | 0.108 |
| | $\log P_0 = 5.52$ (95% c.l. cannot be defined) | | | |

The ideal lipophilicity for maximum absorption ($\log P_0$) of the undissociated form is at least two units higher than the $\log P_0$ for maximum gastrointestinal absorption. This may be due, at least partially, to some adsorption and membrane binding, since only the disappearance of the drug from the solution was measured. This may be especially significant for the basic drugs existing predominantly in the protonated form. In the transport of quaternary ammonium compounds across rat small intestine, a clear-cut biphasic phenomenon was observed for the cations (20). Dearden & Tom-

linson (86) have derived a model involving protein binding, which has been shown to be consistent with the in vivo results. The same group of investigators has also reported that the analgesic activity of 16 p-substituted acetanilides is related parabolically to the extent of buccal absorption (drug absorbed/drug unabsorbed = A/U) as indicated by Equation 44 (87).

$$44.\ \log 1/ED_{50} = -1.989\,(A/U)^2 + 2.800\,A/U - 0.439$$

Even the percentage of buccal absorption was found to be linearly dependent on the lipophilic constant $\pi$, the authors found that Equation 44 was slightly better than the correlation between analgesic activity and log $P$.

For those highly lipophilic drugs (log $P \geq 2$), which are inactivated either in the gastrointestinal tract or by the first passage through the liver, sublingual administration may offer advantages over oral administration.

A few examples where sublingual tablets have been successfully used in therapeutics are erythrityl tetranitrate (log $P_{oct/w} = 2.94$), manitol hexanitrate (log $P_{oct/w} = 2.94$), and methyltestosterone (log $P_{oct/w} = 3.82$) (88). Any drug or dosage form intended for sublingual administration should be both devoid of excessive bitter taste or irritating effect and reasonably lipid-soluble.

## *Percutaneous Absorption of Drugs*

The skin is one of the largest (about 18,000 $cm^2$) and most unhomogeneous organs of the body (89, 90). It serves protective, sensory, and regulatory functions (91). Although it serves as a fairly effective self-repairing protective envelope against numerous harmful foreign substances, it may in many instances fail to do so. Even the intact skin is penetrable to many pesticides like organophosphorus compounds, and to organic solvents like benzene and toluene. It is also vulnerable to irritants, vesicants, and keratolytic agents. Even in local application, excess percutaneous absorption of chemicals may lead to irritation, sensitization, or undesired systemic side effects. On the other hand, for medicated preparations, such as creams containing hormones, vitamins, or antiperspirants, absorption into the skin is necessary for achieving the desired beneficial effect locally. More recently, a special drug delivery system based on calculated rate of transdermal absorption of scopolamine to achieve antinausea effect has been accomplished (92, 93). Further development in this area can be expected for next few years.

Because of the complexity of the structure of the skin and the multitude of vehicles (90, 91), a thorough discussion of the subject of percutaneous absorption is beyond the scope of this review. In this survey, only the physicochemical properties and the structural aspects of drug molecules and their correlation with percutaneous absorption are discussed.

Among all the physicochemical parameters, the partition coefficient of a drug has long been recognized as important in determining its penetrability through human skin (94, 95). Equations (45–47) correlate the in vitro absorption of phenylboronic acids into human skin (96, 97).

Percutaneous Absorption of Phenylboronic Acids

| | $n$ | $r$ | $s$ |
|---|---|---|---|
| 45. $\log C = 0.573 \log P - 3.749$ | 8 | 0.907 | 0.227 |
| 46. $\log C = -0.212 (\log P)^2 + 1.133 \log P - 3.999$ <br> $\log P_0 = 2.7$ | 8 | 0.919 | 0.234 |
| 47. $\log C = 0.417 \log P_{\text{benzene}} - 2.463$ | 7 | 0.954 | 0.148 |

It is clear from these equations that the degree of percutaneous absorption of these compounds is primarily determined by their lipophilic character as measured by the octanol/water or benzene/water partition coefficients. More than 80% of the variance in the data ($r^2 > 0.80$) can be accounted for by these equations. Addition of the electronic parameter ($\sigma$) to Equation 45 or 47 does not significantly improve the correlation. The $(\log P)^2$ term in Equation 46 is not statistically significant; nevertheless, the approximate optimum lipophilic character $\log P_0$ is around 2.7, not very different from the $\log P_0$ of 2.3 for the penetration of the brain by the same series of compounds, and for the maximum hypnotic of barbiturates ($\log P_0 = 2.4$) (98).

Equations 48–50 were derived from the permeability data of aliphatic alcohols through human epidermis reported by Scheuplein's group (97, 99). Equations 51–55 were from similar experiments on steroids (100).

Penetration of Aliphatic Alcohols Through Human Epidermis

| | $n$ | $r$ | $s$ |
|---|---|---|---|
| 48. $\log K_{p\,(\text{cm/hr})} = 0.420 \log K_{\text{olive oil}} - 2.354$ | 8 | 0.977 | 0.156 |
| 49. $\log K_{p\,(\text{cm/hr})} = 0.544 \log P_{\text{oct}} - 2.884$ | 8 | 0.979 | 0.150 |
| 50. $\log K_{p\,(\text{cm/hr})} = 0.934 \log K_{m\,\text{stratum corneum}} - 2.891$ | 8 | 0.986 | 0.121 |

Penetration of Steroids Through Human Epidermis

| | | $n$ | $r$ | $s$ |
|---|---|---|---|---|
| 51. | $\log K_{p_{(cm/hr)}} = 0.818 \log K_{hexadecane} - 3.556$ | 13 | 0.865 | 0.473 |
| 52. | $\log K_{p_{(cm/hr)}} = 1.262 \log K_{amyl\ caproate} - 7.537$ | 13 | 0.933 | 0.339 |
| 53. | $\log K_{p_{(cm/hr)}} = 2.626 \log K_{m\ stratum\ corneum} - 7.537$ | 14 | 0.931 | 0.377 |
| 54. | $\log K_{p_{(cm/hr)}} = 0.891 \log P_{ether} - 5.175$ | 10 | 0.964 | 0.261 |
| 55. | $\log K_{p_{(cm/hr)}} = -0.207(\log P)^2_{ether} + 1.494 P_{ether} - 5.425$ <br> $\log P_{0_{ether}} = 3.6$ | 10 | 0.978 | 0.220 |

It is interesting to note that partition coefficients measured in pure hydrocarbon (e.g. hexadecane in Equation 51) give less satisfactory correlation as compared to other solvents capable of forming hydrogen bonds with solute. The stratum corneum/water partition coefficients give the best correlations for both series (Equations 50 and 53). Equations 50 and 53 have quite different slopes as well as intercepts. Upon the addition of the log molecular weight term to account for the difference in molecular size (50) (see Table 1) Equations 56–58 are obtained.

Penetration of Alcohols and Steroids Through Human Epidermis

| | | $n$ | $r$ | $s$ |
|---|---|---|---|---|
| 56. | $\log K_{p_{(cm/hr)}} = 0.109 \log K_{stratum\ corneum} - 3.372$ | 23 | 0.068 | 1.156 |
| 57. | $\log K_{p_{(cm/hr)}} = 2.240 \log K_{stratum\ corneum} - 4.662 \log mol\ wt + 4.774$ | 23 | 0.945 | 0.359 |

58. $\log K_{p\,(cm/hr)} = -0.454\,(\log K)^2_{\text{stratum corneum}} + 3.160 \log K_{\text{stratum corneum}} - 5.160 \log \text{mol wt} + 5.635$ 23 0.958 0.348

$$\log P_0 = 3.48\ (2.3\text{–}17.4)$$

The $(\log K)^2$ term in Equation 58 is statistically significant at 95th percentile level ($F_{1,19} = 6.07$). From Equation 57 and 58 it appears that the lower permeability of the steroids as compared to the isolipophilic alcohol is primarily due to the bulk as represented by higher molecular weight and



**Table 1** Physicochemical properties and in vitro permeability of alcohols and steroids through human epidermis

| Compound | log M.W. | log $K_m$[a] | log $K_p$ (cm/hr) Obsd[b] | log $K_p$ (cm/hr) Calcd[c] |
|---|---|---|---|---|
| Water | 1.26 | −0.52 | −3.00 | −2.63 |
| Methanol | 1.51 | −0.22 | −3.00 | −2.87 |
| Ethanol | 1.66 | −0.22 | −3.00 | −3.65 |
| *n*-Propanol | 1.78 | 0.30 | −2.85 | −2.64 |
| *n*-Butanol | 1.87 | 0.40 | −2.60 | −2.82 |
| *n*-Pentanol | 1.94 | 0.70 | −2.22 | −2.39 |
| *n*-Hexanol | 2.01 | 1.00 | −1.89 | −2.03 |
| *n*-Heptanol | 2.06 | 1.48 | −1.49 | −1.31 |
| *n*-Octanol | 2.11 | 1.70 | −1.28 | −1.19 |
| Progesterone | 2.50 | 2.02 | −2.82 | −2.73 |
| Pregnenolone | 2.49 | 1.70 | −2.82 | −3.15 |
| Hydroxypregnenolone | 2.52 | 1.63 | −3.22 | −3.42 |
| Hydroxyprogesterone | 2.52 | 1.60 | −3.22 | −3.47 |
| Cortexone | 2.52 | 1.59 | −3.35 | −3.49 |
| Testosterone | 2.46 | 1.36 | −3.40 | −3.60 |
| Cortexolone | 2.54 | 1.36 | −4.12 | −4.01 |
| Corticosterone | 2.54 | 1.23 | −4.22 | −4.27 |
| Cortisone | 2.56 | 0.93 | −5.00 | −5.03 |
| Hydrocortisone | 2.60 | 0.85 | −5.52 | −5.42 |
| Aldosterone | 2.56 | 0.83 | −5.52 | −5.27 |
| Estrone | 2.43 | 1.66 | −2.44 | −2.91 |
| Estradiol | 2.44 | 1.66 | −3.52 | −2.96 |
| Estriol | 2.46 | 1.36 | −4.40 | −3.60 |

[a] $K_m$ = Stratum corneum/water partition coefficient from Refs. (99, 100).
[b] From Refs. (99, 100).
[c] Calculated from Equation 58.

consequently lower diffusion through the epidermis. Hingson & Diamond have also reported that branched compounds are much less permeant than straight-chain analogues in gall bladders of four different species, whereas this effect is small in the intestine and negligible in choroid plexus (101).

Equations 59–61 were derived from Treherne's permeability data of rabbit whole skin to nonelectrolytes like urea, glucose, alcohols, etc (97, 102).

Permeability of Rabbit Whole Skin to Nonelectrolytes

| | | $n$ | $r$ | $s$ |
|---|---|---|---|---|
| 59. | $\log K_{p\,(cm/hr)} = 0.392 \log P - 2.761$ | 7 | 0.928 | 0.318 |
| 60. | $\log K_{p\,(cm/hr)} = -0.060 (\log P)^2 + 0.309 \log P - 2.591$; $\log P_0 = 2.6$ | 7 | 0.957 | 0.278 |
| 61. | $\log K_{p\,(cm/hr)} = 0.385 \log P - 0.856 \log \text{mol wt} - 1.151$ | 7 | 0.975 | 0.214 |

The $(\log P)^2$ term in Equation 60 is not statistically significant. It is interesting, however, to note that the $\log P_0$ of 2.6 in this series is quite close to that of the phenylboronic acids ($\log P_0 = 2.7$, Equation 46). The log molecular weight term in Equation 61 is significant at the 90th percentile level ($F_{1,4} = 7.01$). The positive coefficient of $\log P$ and the negative coefficient of log molecular weight suggest that small molecules with high lipophilicity will penetrate through the skin most easily. Similar linear equations 62–63 were derived from the permeability data of these compounds through rabbit dermis alone (97, 102).

Permeability of Nonelectrolytes Through Rabbit Dermis

| | | $n$ | $r$ | $s$ |
|---|---|---|---|---|
| 62. | $\log K_{p\,(cm/hr)} = 0.100 \log P - 0.970$ | 6 | 0.823 | 0.097 |
| 63. | $\log K_{p\,(cm/hr)} = -0.575 \log \text{mol wt} - 0.098$ | 6 | 0.982 | 0.032 |

For the in situ data of nicotinic acid derivatives causing erythema on human skin, no significant correlation, either linear or parabolic, could be obtained when $\log P_{ether}$ was used (97, 103). For the six compounds with water solubility available, addition of the molar solubility term ($\log S$) significantly improved the correlation.

In Situ Testing of Nicotinic Acid Derivatives Causing Erythema on Human Skin

| | $n$ | $r$ | $s$ |
|---|---|---|---|
| 64. $\log 1/C = 0.416 \log P_{ether} + 2.281$ | 8 | 0.598 | 0.757 |
| 65. $\log 1/C = -0.339 (\log P)^2_{ether} + 0.502 \log P_{ether} + 2.792$ | 8 | 0.793 | 0.656 |
| 66. $\log 1/C = 0.431 \log P_{ether} + 2.025$ | 6 | 0.725 | 0.680 |
| 67. $\log 1/C = 1.008 \log P_{ether} + 1.230 \log S + 6.604$ | 6 | 0.967 | 0.289 |

This reflects the importance of adequate water solubility as well as a proper lipophilic character for local erythema effect. Similar correlation between the vasoconstriction activity and the solubility and partition coefficient of corticosteroids has also been reported (97, 104).

Corticosteroids Causing Vasoconstriction on Human Skin

| | $n$ | $r$ | $s$ |
|---|---|---|---|
| 68. $\log 1/C = 1.617 \log P_{ether} + 2.743$ | 11 | 0.816 | 0.566 |
| 69. $\log 1/C = 2.553 \log P_{ether} + 1.139 \log S + 6.101$ | 11 | 0.924 | 0.396 |

Roberts et al (105) have found the following correlations between the stratum corneum-water partition coefficients and the octanol-water partition coefficients of various types of compounds. It is interesting to note that the steroids give quite different slope and intercept as compared to the others.

Distribution of Various Drugs Between Human Stratum Corneum and Water

| | $n$ | $r$ |
|---|---|---|
| For Aromatic Alcohols and Phenols | | |
| 70. $\log K_m = 0.57 \log P - 0.1$ | 21 | 0.992 |
| For Aliphatic Alcohols and Acids | | |
| 71. $\log K_m = 0.66 \log P - 0.1$ | 13 | 0.982 |
| For Steroids | | |
| 72. $\log K_m = 0.37 \log P + 0.6$ | 14 | 0.874 |

The same group of investigators (106) has also reported that the penetration of some phenolic compounds is concentration dependent. The increase in the permeability coefficient beyond a threshold is attributed to "damage" to the epidermis and a reduction in the resistance to diffusion. Thermodynamic analysis of the percutaneous absorption of phenolic compounds based on the temperature effect (Arrhenius plot) has also been reported (107).

## *Diffusion of Drugs from Plasma Into Milk*

Lien (108) has recently done a survey on the physiological and physicochemical factors affecting secretion of different types of drugs into milk. It has been suggested that if free drug concentrations in both milk and plasma are used (i.e. milk ultrafiltrate/plasma ultrafiltrate ratio), the theoretical value can be calculated as follows:

For Weak Organic Acids

$$73.\quad R = M/P = \frac{1 + 10^{(pH_1 - pK_a)}}{1 + 10^{(pH_2 - pK_a)}}$$

For Weak Organic Bases

$$74.\quad R = M/P = \frac{1 + 10^{(pK_a - pH_1)}}{1 + 10^{(pK_a - pH_2)}},$$

where $pH_1$ and $pH_2$ are the pH values of the milk and the plasma, respectively. However, using the data of constant infusion in cows, it is necessary to include the partition coefficient term to get statistically significant correlation for acidic drugs. For basic drugs, only the ionization appears to be the predominating factor for the limited number of drugs examined (108).

For Sulfonamides (Acids)

| | $n$ | $r$ | $s$ |
|---|---|---|---|
| 75. $\log M/P = 0.129 \log P + 2.224\ U/D - 0.406$ | 8 | 0.93 | 0.16 |
| 76. $\log M/P = -0.123\ (\log P)^2 + 0.136 \log P + 0.191 \log U/D - 0.330$ | 8 | 0.98 | 0.11 |

For Basic Drugs

| | | | |
|---|---|---|---|
| 77. $\log M/P = -0.098 \log U/D + 0.585,$ | 5 | 0.96 | 0.14 |

where $\log U/D = pK_a - 7.4$ for acids, $\log U/D = 7.4 - pK_a$ for bases.

If the total concentrations of the drugs in both compartments are measured, the following equations are needed to correct for the protein binding (109).

For Acidic Drugs

$$78.\quad R' = \frac{C_m}{C_p} = \frac{1 + 10^{(pH_1 - pK_a)}}{1 + 10^{(pH_2 - pK_a)}} \cdot \frac{f_p}{f_m}$$

For Basic Drugs

$$79.\quad R' = \frac{C_m}{C_p} = \frac{1 + 10^{(pK_a - pH_1)}}{1 + 10^{(pK_a - pH_2)}} \cdot \frac{f_p}{f_m}$$

where $f_p$ and $f_m$ are the fraction of free (unbound) drug in plasma and milk, respectively.

## *Diffusion of Drugs into Prostatic Fluid*

From the data of Winningham & Stamey on sulfonamides and nitrofurantoin in dogs, equations 78 and 79 have been derived (110, 111).

Sulfonamides and Nitrofurantoin

| | $n$ | $r$ | $s$ |
|---|---|---|---|
| 80. $\log PF/P = -0.214\ (\log P)^2 + 0.097 \log P + 0.330 \log U/D - 0.572$<br>$\log P_0$ for maximum $PF/P = 0.23$ | 16 | 0.905 | 0.211 |
| 81. $\log PF/P = -0.065\ (\log U/D)^2 + 0.376 \log U/D - 0.526$<br>optimum $\log U/D = 2.9$,<br>optimum $pK_a = 10.3$ | 16 | 0.922 | 0.24 |

For eight antibacterial agents and antibiotics a reversed parabolic equation is obtained (111).

| | $n$ | $r$ | $s$ |
|---|---|---|---|
| 82. $\log PF/P = 0.419\ (\log P)^2 - 0.262 \log P + 0.556 \log U/D - 0.545$ | 8 | 0.970 | 0.218 |

$\log P_0$ for minimum $PF/P = 0.43$ (0.15 – 0.69). The reversed parabolic dependence on $\log P$ has been attributed to plasma protein binding ($\log P_0 = 0.70$) (111).

## *Penetration of Drugs Through Blood-Brain Barrier*

Rapoport & Levitan (112) have reported that neurotoxicity of several contrast media with approximately the same pKa's is correlated with their lipid solubility as measured by the true octanol/water partition coefficients of the undissociated form. Using radiolabeled drugs, Oldendorf has investigated the lipid solubility and penetration of drugs through the blood-brain barrier (BBB) (113). From his data the following correlations are obtained in this study.

Penetration of Drugs Through BBB

| | $n$ | $r$ | $s$ |
|---|---|---|---|
| 83. $\log \text{BUI} = 0.373 \log P_{\text{olive oil/w}} + 1.749$ | 20 | 0.774 | 0.499 |
| 84. $\log \text{BUI} = -0.076 (\log P_{\text{olive oil/w}})^2 + 0.186 \log P_{(\text{olive oil/w})} + 1.817$ | 20 | 0.830 | 0.453 |
| 85. $\log \text{BUI} = 0.346 \log P_{\text{olive oil/w}} - 0.814 \log \text{mol wt} + 3.587,$ | 20 | 0.844 | 0.436 |

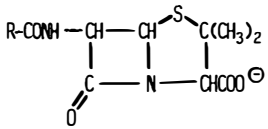
where BUI = brain uptake index (percentage of $^3$HOH).

Equation 85 is considered as the "best" equation. The log molecular term is statistically significant at 97.5 percentile level ($F_{1,17} = 6.64$). Equation 85 suggests that under isolipophilic condition, a compound with lower molecular weight will have higher brain uptake.

## *Physicochemical Properties and Protein Binding of Drugs*

Accumulated data have shown that hydrophobic interaction is a major driving force for protein binding of various drugs. In many cases when the degree of ionization is held constant or not involved, excellent correlation can be obtained between protein binding and partition coefficients. For example, for 79 penicillins with different side-chains, Bird & Marshall (114) derived Equation 86.

Binding of Penicillins by Human Serum Albumin



| | $n$ | $r$ | $s$ |
|---|---|---|---|
| 86. $\log (B/F) = 0.504 \Sigma\pi - 0.665,$ | 79 | 0.924 | 0.066 |

where $B/F$ is the ratio of bound penicillin/free penicillin and $\Sigma\pi$ represents the sum of Hansch $\pi$ values for the side chain $R$.

| Binding of Spriolactones to Human Serum Albumin | $n$ | $r$ | $s$ |
|---|---|---|---|
| 87. $\log K = 0.223 \log P_{oct/buffer} + 3.914$ | 9 | 0.845 | 0.030 |

Equation 87 correlates the equilibrium binding constant ($K$) of spirolactones to human plasma protein (115). When the $pK_a$ values of the drugs vary over a wide range, correction for different degrees of ionization is necessary for meaningful correlation (116, 117). For congeneric series of drugs indices obtained from molecular orbital methods (HMO-LCAO) have been used in correlating with protein binding (118).

## PHYSICOCHEMICAL PROPERTIES AND DRUG METABOLISM

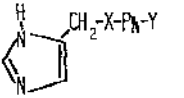
The ability of microsomal enzymes in converting lipid-soluble foreign molecules into more polar metabolites has been long recognized by pharmacologists and toxicologists. Hansch (119) has reviewed the quantitative relationships between lipophilic character and metabolism of various amines, phenols, and barbiturates. Tong & Lien (120) have reported the following equations correlating metabolic oxidations with various physicochemical parameters (Equations 88–91).

| Inhibition of Beef Heart Submitochondrial NADH Oxidation by Barbiturates | $n$ | $r$ | $s$ |
|---|---|---|---|
| 88. $\log K/I_{50} = 0.88 \log P_{\text{corn oil/w}} + 2.78$ | 14 | 0.961 | 0.133 |

| Stimulation of Rat Liver Microsomal NADPH Oxidation by Barbituartes (Excluding Allyl-Derivatives) | | | |
|---|---|---|---|
| 89. log oxid rate $= 0.58 \log P_{\text{corn oil/w}} + 0.79$ | 9 | 0.944 | 0.116 |

| Pork Liver Microsomal NADPH Dependence N-Oxidation of Tertiary Amines | | | |
|---|---|---|---|
| 90. log oxid rate $= -0.03 (\log P)^2 + 0.37 (\log P) - 7.06$<br>$(\log P) = 5.69 (5.12 - 6.64)$ | 10 | 0.962 | 0.106 |

Inhibition of Rat Liver Microsomal Epoxidation of Aldrin by Imidazole Derivatives



91. $\log I/I_{50} = 2.15\Sigma\sigma_{(m,p)} + 0.86\,Es_{(p)} + 0.39\log P \quad 13 \quad 0.930 \quad 0.125$
$+ 4.00,$

where $\sigma$ is the Hammett sigma constant and *Es* is the Taft steric constant; *m* and *p* refer to the position of *y* on the benzene ring.

Figure 1 shows the parabolic dependence of the oxidation rate of tertiary amines on log *P* including molecules ranging from trimethylamine to morphine and chlorpromazine.

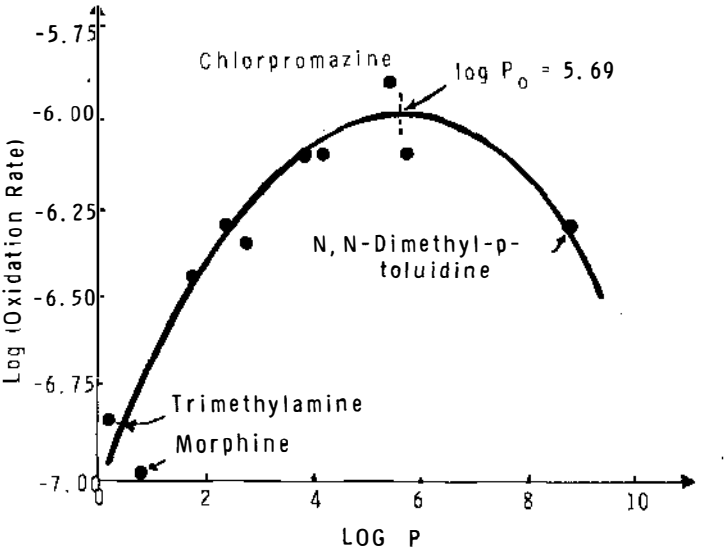



*Figure 1* Parabolic dependence of the N-oxidation rate of various tertiary amines on log *P* (Equation 90).

## PHYSICOCHEMICAL PROPERTIES AND EXCRETION OF DRUGS

### *Renal Excretion*

Glomerular filtration in the kidney allows the free passage of compounds with molecular weight of 5000 or less while large molecules like albumin (mol wt 69,000) barely appear in the filtrate. Molecules of intermediate size are partially filtered (121). Since most synthetic drugs or bioactive sub-

stances have molecular weights of less than 500, practically all the free drug in the plasma will be filtered. Besides passive diffusion and glomerular filtration, in the proximal tubule, organic acids and bases are actively secreted (122). Many organic acids are known to be secreted by this mechanism and can be inhibited by probenecid (123). The active secretion of probenecid is also competitively suppressed by p-aminohippurate. The clearance ratio of probenecid analogues has been shown to be parabolically dependent on partition coefficient.

Renal Excretion of Probenecid Analogues

| | | $n$ | $r$ | $s$ |
|---|---|---|---|---|
| 92. | $\log (C_x/\text{GFR}) = -0.242 (\log P_{\text{CHCl}_3})^2 + 0.035 \log P_{\text{CHCl}_3} + 0.578$ | 5 | 0.980 | 0.163 |

Similar nonlinear dependence of the absorption from the urinary bladder of a series of *n*-alkyl carbamates on log *P* has been shown by Bridges et al (124). This may have significance in the recirculation of drugs as well as implication in toxic effects of drugs in the bladder.

## *Biliary Excretion of Drugs*

Both biliary excretion and renal excretion are important routes for the elimination of drugs, food colors, pesticides, and environmental chemicals from the body. It is known that carboxylic acids and the metabolities of foreign chemicals that are readily excreted in bile have molecular weights of about 300–400 (19). Intermediary metabolites like glucuronides and bile salts of various endogenous and exogenous compounds that are excreted in bile in significant quantity have molecular weights ranging from 500 to 1000. Small molecules (mol wt 300) on the other hand are not excreted in bile in quantity, probably because of a greater degree of biliary reabsorption at the level of the peribiliary plexus (125), and to a greater degree of renal excretion. The following equations are derived for the biliary excretion in rats (19).

Sulfathiazole Derivatives

| | | $n$ | $r$ | $s$ |
|---|---|---|---|---|
| 93. | $\log \%\,\text{Exc} = -0.719 (\log P)^2 + 0.860 \log P - 0.401\ \text{pK}_a + 3.214$ | 9 | 0.937 | 0.242 |
| | $\log P_0 = 0.60$ (for maximum excretion) | | | |

For Penicillins

| | | | | |
|---|---|---|---|---|
| 94. $\log \%\ \text{Exc} = 0.132\ (\log P)^2 - 0.792 \log P + 2.269$ | 9 | 0.931 | 0.083 |
| $(\log P_0 = 2.99$ for minimum excretion) | | | |

Lin et al (126) have studied the biliary excretion of cholecystographic agents in rhesus monkeys. Iodoxamic acid and iopanoic acid appear to compete for plasma protein binding sites as well as for binding sites on intrahepatic proteins.



## SUMMARY

Drug disposition is of prime concern to pharmacologists, toxicologists, and clinicians. In many cases the variation in absorption, distribution, metabolism, and excretion of a series of congeners is governed by the molecular structure and the physicochemical properties of the drug molecule. When reproducible results of sufficient spread are available, these data can be analyzed in quantitative terms. In order to achieve a high degree of selective toxicity in designing better and safer therapeutic agents, the multifacet effects of molecular modification on drug disposition must be thoroughly investigated. It is hoped that more systematic effort will be directed toward the correlation of various pharmacokinetic parameters and therapeutic and toxicological effects of drugs with their physicochemical properties and molecular structures.

*Literature Cited*

1. Schanker, L. S. 1962. Passage of drugs across body membranes, *Pharmacol. Rev.* 14:501–30
2. Lien, E. J. 1974. The relationship between chemical structure and drug absorption, distribution and excretion. In *Medicinal Chemistry IV. Proc. Int. Symp. Med. Chem.*, ed. J. Maas, pp. 319–42. Amsterdam: Elsevier
3. Overton, E. 1902. Beitrage zur allgemeinen Muskel- und Nervenphysiologie, *Pfluegers Arch. Gesamte Physiol. Menschen Tiere* 92:115–280
4. Overton, E. 1901. *Studen über Narkose.* Jena: Fischer
5. Meyer, H. 1899. Zur Theorie der Alkoholnarkose. *Arch. Exp. Pathol. Pharmakol.* 42:109–18, 119–37
6. Meyer, H. 1901. Zur Theorie der Alkoholnarkose. *Arch. Exp. Pathol. Pharmakol.* 46:338–46
7. Collander, R., Bärland, H. 1933. Permeabilitätsstudien an Chara ceratophylla. II. Die Permeabilitat fur Nichtelektrolyte. *Acta Bot. Fenn.* 11:1–114
8. Gorter, E., Grendel, F. 1925. On bimolecular layers of lipoids on the chromocytes of the blood. *J. Exp. Med.* 41:439–43
9. Cole, K. S. 1932. Surface forces of the arbacia eggs. *J. Cell. Comp. Physiol.* 5:483–94
10. Danielli, J. F., Harvey, E. N. 1935. The tension at the surface of mackerel egg oil, with remarks on the nature of the cell surface. *J. Cell. Comp. Physiol.* 5:483–94
11. Danielli, J. F., Davson, H. 1935. A contribution to the theory of permeability of thin films. *J. Cell. Comp. Physiol.* 5:495–508

12. Davson, H., Danielli, J. F. 1952. *The Permeability of Natural Membranes.* London: Cambridge Univ. Press. 2nd ed.
13. Robertson, J. D. 1955. The ultrastructure of adult vertebrate peripheral myelinated nerve fibers in relation to myelinegenesis. *J. Biophys. Biochem. Cytol.* 1:271–78
14. Bernhard, W. 1958. Ultrastructure aspects of nucleocytoplasmic relationship. *Exp. Cell. Res. Suppl.* 6:17–50
15. Danielli, J. F. 1958. Surface chemistry and cell membrane. In *Surface Phenomena in Chemistry and Biology,* ed. J. F. Danielli, K. G. A. Pankhurst, A. C. Riddiford, pp. 246–65. New York: Pergamon
16. Singer, S. J. 1971. The molecular organization of biological membranes. In *Structure and Function of Biological Membranes,* ed. L. I. Rothfield, pp. 145–222. New York: Academic
17. Singer, S. J., Nicolson, G. L. 1972. The fluid mosaic model of the structure of cell membrane. *Science* 175:720–30
18. Van Os, G. A. T., Ariëns, E. J., Simonis, A. M. 1964. Drug transfer: Distribution of drugs in the organism. In *Molecular Pharmacology,* ed. E. J. Ariëns, 1:7–52. New York: Academic
19. Lien, E. J. 1975. Structure-absorption-distribution relationships, significance for drug design. In *Drug Design,* ed. E. J. Ariëns, 5:81–32. New York: Academic
20. Masaki, B. W., Lien, E. J., Biles, J. A. 1973. Transport of quaternary ammonium-alkylsulfate and sodium salicylate across small intestine. *Acta Pharm. Suec.* 10:43–52
21. Kilter, M. E., Lamy, P. P. 1969. Methods used in the study of gastrointestinal absorption, a review. *Hosp. Pharm.* 4:19–26
22. Danielli, J. F. 1954. Morphological and molecular aspects of active transport. *Symp. Soc. Exp. Biol.* 8:502–16
23. Ussing, H. H. 1947. Interpretation of the exchange of radiosodium in isolated muscle. *Nature* 160:262–63
24. Jollow, D. J., Brodie, B. B. 1972. Mechanisms of drug absorption and of drug solution. *Pharmacology* 8:21–32
25. Bates, T. R., Gibaldi, M. 1970. In *Current Concept in the Pharmaceutical Sciences: Biopharmaceutics,* ed. J. Swarbrick. pp. 63. Philadelphia: Lea & Febiger
26. Mentz, P., Witzleben, H., Förster, W. 1972. Untersucheungen zur Frage einen aktiven oder passiven enteralen Resorption von Herzglykosiden. *Arch. Int. Pharmacodyn.* 200:126–40
27. Schanker, L. S., Jeffery, J. J. 1961. Active transport of foreign pyrimidines across the intestinal epithelium. *Nature* 190:727–28
28. Shindo, H., Komai, T., Kawai, K. 1973. Studies on the metabolism of D- and L-isomers of 3,4-dihydroxyphenylalanine (DOPA). V. Mechanism of intestinal absorption of D- and L-DOPA-$^{14}$C in rats. *Chem. Pharm. Bull.* 21:2031–38
29. Shindo, H., Komai, T., Kawai, K. 1977. Mechanism of intestinal absorption and brain uptake of L-5-hydroxytryptophan in rats, as compared to those of L-3,4-dihydroxyphenylalanine. *Chem. Pharm. Bull.* 25:1417–25
30. LeFévre, P. G. 1961. Sugar transport in the red blood cell: Structure reactivity relationships in substrate and antagonists. *Pharmacol. Rev.* 13:39–70
31. Wilbrandt, W. 1959. Permeability and transport systems in living cells. *J. Pharm. Pharmacol.* 11:65–79
32. Wilbrandt, W., Rosenberg, T. 1961. The concept of carrier transport and its corollaries in pharmacology. *Pharmacol Rev.* 13:109–83
33. Lewis, W. H. 1931. Pinocytosis. *Johns Hopkins Hosp. Bull.* 49:17–27
34. Lewis, W. H. 1937. Pinocytosis by malignant cells. *Am. J. Cancer* 29:666–79
35. Park, C. R. 1961. In *Membrane Transport and Metabolism,* ed. A. Kleinzeller, A. Kotyk, p. 19. New York: Academic
36. Sbarra, A. J., Shirley, W., Bardawil, W. A. 1962. "Piggy-back" phagocytosis. *Nature* 194:255–56
37. Kimelberg, H. K. 1976. Differential distribution of liposome-entrapped [$^3$H]-methotrexate and labelled lipids after intravenous injection in a primate. *Biochem. Biophys. Acta* 448:531–50
38. Guilmette, R. A., Cerny, E. A., Rahman, Y. E. 1978. Pharmacokinetics of the iron chelator desferrioxamine as affected by liposome encapsulation: Potential in treatment of chronic hemosiderosis. *Life Sci.* 22:313–20
39. Brodie, B. B., Hogben, C. A. M. 1957. Some physicochemical factors in drug action. *J. Pharm. Pharmacol.* 9:345–89
40. Brodie, B. B. 1964. *In Animal and Clinical Pharmacology Technique in Drug Evaluation,* ed. J. H. Nodine, P. E. Siegler, p. 69. Chicago: Yearbook Publ.
41. Lien, E. J. 1970. Physicochemical properties and gastrointestinal absorption of drugs. *Drug. Intell.* 4:7–9

42. Kakemi, K., Arita, T., Hori, R., Konishi, R. 1967. Absorption and excretion of drugs. XXX. Absorption of barbituric acid derivatives from rat stomach. *Chem. Pharm. Bull.* 15:1534–39
43. Koizumi, T., Arita, T., Kakemi, K. 1964. Absorption and excretion of drugs. XIX. Some pharmacokinetic aspects of absorption and excretion of sulfonamides (1) absorption from rat stomach. *Chem. Pharm. Bull.* 12:413–20
44. Houston, J. B., Upshall, D. G., Bridges, J. W. 1974. A re-evaluation of the importance of partition coefficients in the gastrointestinal absorption of anutrients. *J. Pharmacol. Exp. Ther.* 189: 244–54
45. Houston, J. B., Upshall, D. G., Bridges, J. W. 1975. Further studies using carbamate esters as model compounds to investigate the role of lipophilicity in the gastrointestinal absorption of foreign compounds. *J. Pharm. Exp. Ther.* 195: 67–72
46. Shindo, H., Komai, T. 1979. Structural factors affecting the absorption and distribution of drugs. In *Structure-Activity Relationships—Quantitative Approaches. The Significance in Drug Design and Mode-of-Action Studies,* ed. T. Fujita, pp. 365–404. Tokyo: Nankodo
47. Hansch, C., Leo A. J. 1979. *Substituent Constants for Correlation Analysis in Chemistry and Biology,* pp. 300. New York: Wiley
48. Birknmeyer, R. D., Kagan, F. 1970. Lincomycin. XI. Synthesis and structure of clindamycin, a potent antibacterial agent. *J. Med. Chem.* 13:616–19
49. Ho, N. F. H., Park, J. Y., Morozowich, W., Higuchi, W. I. 1977. Physical model approach to the design of drug with improved intestinal absorption. In *Design of Biopharmaceutical Properties Through Prodrugs and Analogs,* ed. E. B. Roche, pp. 136–227. Washington DC: APhA Acad. Pharm. Sci.
50. Lien, E. J., Wang, P. H. 1980. Lipophilicity, molecular weight and drug action, reexamination of parabolic and bilinear models. *J. Pharm. Sci.* 69:648–50
51. Levine, R. R., Blaie, M. R., Clark, B. B. 1955. Factors influencing the intestinal absorption of certain monoquaternary anticholinergic compounds with special reference to benzomethamine [N-diethylaminoN'-methyl-benzilamide methobromide (MC-3199)]. *J. Pharmacol. Exp. Ther.* 114:78–86
52. Levine, R. R., Pelikan, E. W. 1961. The influence of experimental procedures and dose on the intestinal absorption of an onium compound, benzomethamine. *J. Pharmacol. Exp. Ther.* 131:319–27
53. Levine, R. R., Spencer, A. F. 1961. Effect of a phosphatido-peptide fraction of intestinal tissue on the intestinal absorption of a quaternary ammonium compound. *Biochem. Pharmacol.* 8: 248–50
54. Levine, R. R. 1963. Facilitation of intestinal absorption of tubocurarine produced by phosphatidyl-peptide fraction. *Fed. Proc. Fed. Am. Soc. Exp. Biol.* 22:310
55. Levine, R. R., Steinberg, G. M. 1966. Intestinal absorption of pralidoxime and other aldoximes. *Nature* 209: 269–71
56. Levine, R. R. 1966. Mechanism of intestinal absorption as they relate to quaternary ammonium compounds. *Arzneim. Forsch.* 16:1373–75
57. Levine, R. R., McNary, W. F., Kornguth, P. J., LeBlanc, R. 1970. Histological reevaluation of everted gut technique for studying intestinal absorption. *Eur. J. Pharmacol.* 9:211–19
58. Plakogiannis, F. M., Lien, E. J., Harris, C., Biles, J. A. 1970. Partition of alkylsulfates of quaternary ammonium compounds: structure dependence and transport study. *J. Pharm. Sci.* 59:197–200
59. Masaki, B. W., Lien, E. J., Biles, J. A. 1973. Transport of quaternary ammonium-alkylsulfate and sodium salicylate across rat small intestine. *Acta Pharm. Suec.* 10:43–52
60. Crouthamel, W. G., Tan, G. H., Dittert, L. W., Doluisio, J. T. 1971. Drug absorption. IV. influence of pH on absorption kinetics of weakly acidic drugs. *J. Pharm. Sci.* 60:1160
61. Smolen, V. F. 1973. Misconceptions and thermodynamic untenability of deviations from pH-partition hypothesis. *J. Pharm. Sci.* 62:77–79
62. Suzuki, A., Higuchi, W. I., Ho, N. F. H. 1970. Theoretical model studies of drug absorption and transport in the gastrointestinal tract I. *J. Pharm. Sci.* 59:644–51
63. Suzuki, A., Higuchi, W. I., Ho, N. F. H. 1970. Theoretical model studies of drug absorption and transport in the gastrointestinal tract. II. *J. Pharm. Sci.* 59:651–59
64. Ho, N. F. H., Higuchi, W. I. 1971. Quantitative interpretation of *in vivo* buccal absorption of n-alkanoic acids by the physical model approach. *J. Pharm. Sci.* 60:537–41

65. Ho, N. F. H., Higuchi, W. I., Turi, J. 1972. Theoretical model studies of drug absorption and transport in the GI tract. III. *J. Pharm. Sci.* 61:192–97
66. Flynn, G. L., Yalkowsky, S. H. 1972. Correlation and prediction of mass transport across membrances. I. Influence of alkyl chain length on flux-determining properties of barrier and diffusant. *J. Pharm. Sci.* 61:838–52
67. Doluisio, J. T., Billups, N. F., Dittert, L. W., Sugita, E. T., Swintosky, J. V. 1969. Drug absorption. I. An *in situ* rat gut technique yielding realistic absorption rates. *J. Pharm. Sci.* 58:1196–1200
68. Doluisio, J. T., Tan, G. H., Billups, N. F., Diamond, L. 1969. Drug absorption. II. Effect of fasting on intestinal drug absorption. *J. Pharm. Sci.* 58:1200–2
69. Nogami, H., Hanano, M. Yamada, H. 1968. Studies on absorption and excretion of drugs. IX. Relation between chemical structure and absorption rate. 1. Effect of the number and the postion of OH-groups on the intestinal absorption rate of benzoyl derivatives. *Chem. Pharm. Bull.* 16:389–95.
70. Nogami, H., Hanano, M., Yamada, H. 1968. Studies on absorption and excretion of drugs. X. Relation between chemical structure and absorption rate. 2. Substituent constant for absorption rate coefficient of foreign organic compounds. *Chem. Pharm. Bull.* 16:580–85
71. Nogami, H., Hanano, M., Yamada, H. 1968. Studies on absorption and excretion of drugs. XI. Relation between chemical structure and absorption rate. 3. Intramolecular interaction constant, additivity rule and prediction for intestinal absorption rate coefficient. *Chem. Pharm. Bull.* 16:586–91
72. Knoefel, P. K., ed. 1972. *Absorption, Distribution Transformation and Excretion of Drugs,* p. 17. Springfield, Ill: Thomas
73. Knoefel, P. K. 1972. See Ref. 72, p. 45
74. Hajjar, J. H., Curran, P. F. 1970. Characteristics of the amino acid transport system in the mucosal border of rabbit ileum. *J. Gen. Physiol.* 56:673–91
75. Schanker, L. S. 1960. On the mechanism of absorption of drugs from the gastrointestinal tract. *J. Med. Pharm. Chem.* 2:343–59
76. Schanker, L. S. 1959. Absorption of drugs from the rat colon. *J. Pharmcol. Exp. Ther.* 126:283–90
77. Scherer, R. A., Howard, S. M. 1977. Use of distribution coefficients in quantitative structure-activity relationships. *J. Med. Chem.* 20:53–58
78. Kakemi, K., Arita, T., Muranishi, S. 1965. Absorption and excretion of drugs. XXV. On the mechanism of rectal absorption of sulfonamides, *Chem. Pharm. Bull.* 13:861–69
79. Kakemi, K., Arita, T., Muranishi, S. 1965. Absorption and excretion of drugs. XXVI. Effect of water-soluble basis on rectal absorption of sulfonamides. *Chem. Pharm. Bull.* 13:969–75
80. Walton, R. P. 1935. Absorption of drugs through the oral mucosa. III. Fat-water solubility coefficient of alkaloids. *Proc. Soc. Exp. Biol. Med.* 32:1488–92
81. Walton, R. P. 1944. Sublingual administration of drugs. *J. Am. Med. Assoc.* 124:138–43
82. Beckett, A. H., Moffat, A. C. 1968. The influence of alkyl substitution in acids on their performance in the buccal absorption test. *J. Pharm. Pharmacol.* 20:S239–47 (Suppl.)
83. Beckett, A. H., Moffat, A. C. 1969. The influence of substitution in phenylacetic acids on their performance in the buccal absorption test. *J. Pharm. Pharmacol.* 21:S139–43 (Suppl.)
84. Beckett, A. H., Moffat, A. C. 1969. Correlation of partition coefficients in n-heptane-aqueous systems with buccal absorption data for a series of amines and acids. *J. Pharm. Pharmacol.* 21: S144–50 (Suppl.)
85. Beckett, A. H., Moffat, A. C. 1970. Kinetics of buccal absorption of some carboxylic acids and the correlation of the rate constants and n-heptane aqueous phase partition coefficients. *J. Pharm. Pharmacol.* 22:15–19
86. Dearden, J. C., Tomlinson, E. 1971. A new buccal absorption model. *J. Pharm. Pharmacol.* 23:S68–72 (Suppl.)
87. Dearden, J. C., Tomlinson, E. 1971. Buccal absorption as a parameter of analgesic activity of some p-substituted acetanilides. *J. Pharm. Pharmacol.* 23:S73–76 (Suppl.)
88. Leo, A., Hansch, C., Elkins, D. 1971. Partition coefficients and their uses. *Chem. Rev.* 71:525–616
89. Calnan, C. D. 1970. The significance of assay methods for the dermatologist. *Br. J. Dermatol.* 82: Suppl. 6, pp. 43–44
90. Katz, M., Poulsen, B. J. 1971. Absorption of drugs through the skin. In *Handbook of Experimental Pharmacology,* Vol. XXVIII/1, ed. B. B. Brodie, J. Gillette, pp. 103–74. Berlin: Springer
91. Flynn, G. L. 1979. Topical drug absorption and topical pharmaceutical systems. *In Modern Pharmaceutics,* ed. G.

S. Banker, C. T. Rhodes. New York: Dekker.
92. Chandrasekaran, S. K., Bayne, W., Shaw, J. E. 1978. Pharmacokinetics of drug permeation through human skin. *J. Pharm. Sci.* 67:1370–74
93. Chandrasekaran, S. K., Capozza, R., Wong, P. S. L. 1978. Therapeutic systems and controlled drug delivery. *J. Membr. Sci.* 3:271–86
94. Rothman, S. 1943. The principles of percutaneous absorption. *J. Lab. Clin. Med.* 28:1305–19
95. Valette, G., Savel, J. 1954. Percutaneous absorption and chemical constitution: Hydrocarbons, alcohols and esters. *Arch. Int. Pharmacodyn.* 97: 232–40
96. Clendenning, W. E., Stoughton, R. B. 1962. Importance of the aqueous lipid partition coefficient for percutaneous absorption of weak electrolytes. *J. Invest. Dermatol.* 30:47–49
97. Lien, E. J., Tong, G. L. 1973. Physicochemical properties and percutaneous absorption of drugs. *J. Soc. Cosmet. Chem.* 24:371–84
98. Hansch, C., Steward, A. R., Iwasa, J., Deutsch, E. W. 1965. The use of a hydrophobic bonding constant for structure-activity correlations. *Mol. Pharmacol.* 1:205–13
99. Scheuplein, R. J. 1965. Mechanism of percutaneous absorption. I. Routes of penetration and the influence of solubility. *J. Invest. Dermatol.* 45:334–48
100. Scheuplein, R. J., Blank, I. H., Brauner, G. J., MacFarlane, D. J. 1969. Percutaneous absorption of steroids. *J. Invest. Dermatol.* 52:63–70
101. Hingson, D. J., Diamond, J. M. 1972. Comparison of nonelectrolyte permeability patterns in several epithelia. *J. Membr. Biol.* 10:93–135
102. Treherne, J. E. 1956. The permeability of skin to some non-electrolytes. *J. Physiol.* 133:171–80
103. Stoughton, R. B., Clendenning, W. E., Kruse, D. 1960. Percutaneous absorption of nicotinic acid and derivatives, *J. Invest. Dermatol.* 35:337–41
104. Katz, M., Shaikh, Z. I. 1965. Percutaneous corticosteroid absorption correlated to partition coefficient. *J. Pharm. Sci.* 54:591–94
105. Roberts, M. S., Anderson, R. A., Moore, D. E., Swarbrick, J. 1977. The distribution of non-electrolytes between human stratum corneum and water. *Aust. J. Pharm. Sci.* 6:77–82.
106. Roberts, M. S., Anderson, R. A., Swarbrick, J. 1977. Permeability of human epidermis to phenolic compounds. *J. Pharm. Pharmacol.* 29:677–83
107. Roberts, M. S., Anderson, R. A., Swarbrick J., Moore, D. E. 1978. The percutaneous absorption of phenolic compounds: The mechanism of diffusion across the stratum corneum. *J. Pharm. Pharmacol.* 30:486–90
108. Lien, E. J. 1979. The excretion of drugs in milk: A survey. *J. Clin. Pharmacol* 4:133–44
109. Matin, S. B., Wan, S. H., Karam, J. H. 1974. Pharmacokinetics of tolbutamide: prediction by concentration in saliva. *Clin. Pharmacol. Ther.* 16:1052–58
110. Winningham, D. G., Stamey, T. A. 1970. Diffusion of sulfonamides from plasma into prostatic fluid. *J. Urol.* 104:559–63
111. Lien, E. J., Kuwahara, J., Koda, R. T. 1974. Diffusion of drugs into prostatic fluid and milk. *Drug Intell.* 8:470–75
112. Rapoport, S. I., Levitan, H. 1974. Neurotoxicity of x-ray contrast media, relation to lipid solubility and blood-brain barrier permeability. *Am. J. Roentgenol.* 122:186–93
113. Oldendorf, W. H. 1974. Lipid solubility and drug penetration of the blood brain barrier. *Proc. Soc. Exp. Biol. Med.* 147:813–16
114. Bird, A. E., Marshall, A. C. 1967. Correlation of serum binding of penicillins with partition coefficients. *Biochem. Pharmacol.* 16:2275–90
115. Chien, Y. W., Hofmann, L. M., Lambert, H. J., Tao, L. C. 1976. Binding of spirolactones to human plasma proteins. *J. Pharm. Sci.* 65:1337–40
116. Hansch, C., Keihs, K., Lawrence, G. L. 1965. The role of substituents in the hydrophobic bonding of phenols by serum and mitochondrial proteins. *J. Am. Chem. Soc.* 87:5770–73
117. Fujita, T. 1972. Hydrophobic bonding of sulfonamide drugs with serum albumin. *J. Med. Chem.* 15:1949–56
118. Von Schultz, O. E., Gottfried, W. 1976. Schätzung der Proteinbinding über die HMO-LCAO-Methode. *Arzneim. Forsch.* 26:1–5
119. Hansch, C. 1973. Quantitative relationships between lipophilic character and drug metabolism. *Drug Metab. Rev.* 1:1–13
120. Tong, G. L., Lien, E. J. 1976. Biotransformation of drugs in quantitative structure activity relationships for barbituates, tertiary amines, and substituted imidazoles. *J. Pharm. Sci.* 65: 1651–54

121. Pitts, R. F. 1968. *Physiology of the Kidney and Body Fluids.* Chicago: Yearbook Publ. 2nd ed.
122. Weiner, I. M., Mudge, G. H. 1964. Renal tubular mechanisms for excretion of organic acids and bases. *Am. J. Med.* 36:743–62
123. Weiner, I. M., Washington, J. A. II, Mudge, G. H. 1960. On the Mechanism of action of probenecid renal tubular secretion. *Bull. John Hopkins Hosp.* 106:333–46
124. Bridges, J. W., Sargent, N. S. E., Upshall, D. G. 1979. Rapid absorption from the urinary bladder of a series of n-alkyl carbamates: A route for the recirculation of drugs. *Br. J. Pharmacol.* 66:283–89
125. Smith, R. L. 1971. Excretion of drugs in bile. In *Handbuch der experimentellen Pharmakologie,* ed. B. B. Brodie, J. R. Gillette, H. S. Ackerman, Vol. 28, Part I, pp. 354–89. Berlin: Springer
126. Lin, S. K., Moss, A. A., Riegelman, S. 1979. Kinetics of drug-drug interactions: Biliary excretion of iodoxamic acid and iopanoic acid in rhesus monkeys. *J. Pharm. Sci.* 68:1430–33