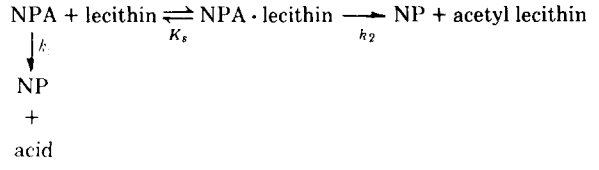
the medium was equal in both cases.

These results suggest that partition theory, which was applied to procaine and 2-diethylaminoethyl *p*-nitrobenzoate and for the evaluation of drug entrapment in liposomes, may not apply to the present case because the liposomes appear to be exhausted by the degradation of *p*-nitrophenyl acetate. The exhaustion may be due to acetylation of the phosphate group of the lecithin molecule, which prevents further orientation of the substrate on the surface of the vesicles from being favorable for the hydroxide-ion attack. Furthermore, as seen in the difference between the rates for unilamellar and multilamellar liposomes, the effective surface area of the vesicles plays a key role, and the reaction occurring on the surface is much more predominant than that in the interior lipid phase.

Binding of *p*-nitrophenyl acetate by liposomes appears to be important at the first stage of the reaction to facilitate hydrolysis. The whole reaction can be treated in a manner analogous to that used for enzymatic catalysis:



Scheme I

where NPA and NP are *p*-nitrophenyl acetate and the product, *p*-nitrophenol, respectively; NPA · lecithin is the substrate–lecithin complex; k_1 and k_2 are the rate constants for the spontaneous and facilitated reactions, respectively; and K_s is the dissociation constant of the complex.

According to Scheme I, the apparent first-order rate constant, k_{obs}, for the appearance of NP can be expressed under the condition of an excess lecithin concentration:

$$k_{obs} = \frac{k_1 K_s + k_2 [\text{lecithin}]}{K_s + [\text{lecithin}]} \qquad \text{(Eq. 1)}$$

By converting Eq. 1 to the double-reciprocal form, a Lineweaver–Burk plot makes it possible to determine K_s and k_2 values. However, since lecithin does not exist as a molecular form in water, k_{obs} does not depend on the practical lecithin concentration but instead on the effective surface area of the vesicles formed, which could be converted to the effective concentration of the lipid based on the ratio of the k_{obs} values of unilamellar and multilamellar liposomes prepared under various conditions with an equal lecithin content.

When the lecithin concentration is moderate, k_{obs} is no longer a constant but becomes a function of the effective concentration of the lipid changing with time. Therefore, the effective concentration is an adjustable parameter that is fitted best by a nonlinear optimization procedure in addition to the k_2 value.

Thus, the surface properties of liposomes, if they are prepared under the same conditions except for size reduction procedures, may greatly affect the stability of a drug, especially when the enhancement of degradation is involved.

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Quantitative Change in Metabolic Fate of Drug Related to Serum Protein Binding

Keyphrases □ Protein binding, serum—effect on drug metabolism □ Drug metabolism—effect of serum protein binding □ Biotransformation—effect of serum protein binding on drug metabolism

To the Editor:

If a drug is eliminated by renal excretion and by biotransformation, then the fraction of the dose that is metabolized, F_m, is equal to the ratio of the metabolic formation clearance to the total clearance. Thus:

$$F_m = Cl_m/Cl_T \qquad \text{(Eq. 1)}$$

If clearance is not limited or affected by the organ blood perfusion rate and the rates of the clearance processes are proportional to the concentration of free (unbound) drug in serum:

$$F_m = \frac{fCl_{m\ \text{intrinsic}}}{fCl_{T\ \text{intrinsic}}} \qquad \text{(Eq. 2)}$$

where f is the free fraction of drug in serum and the clearance terms represent intrinsic clearances of free drug (1–3). Since f cancels out, F_m is independent of serum protein binding under the stated conditions.

If the renal clearance of a drug involves glomerular filtration (the rate of which usually is proportional to the concentration of free drug in serum) as well as renal tubular secretion and if the rate of tubular secretion is proportional to the concentration of total (free plus bound) drug in serum (3), then F_m is affected by f. Specifically:

$$\text{renal clearance} = fk_g(1 - F) + k_s^*(1 - F) \qquad \text{(Eq. 3)}$$

where k_g is the glomerular filtration clearance referenced to the free drug concentration, k_s^* is the apparent renal secretion clearance referenced to the total drug concentration, and F is a dimensionless constant representing the fraction of filtered and secreted drug that is reabsorbed (3). Proportionality between the renal tubular secretion rate and the total rather than free drug concentration in plasma or serum may occur if the true renal secretion clearance is much higher than the effective renal blood flow (4).

Since total clearance is the sum of the renal and metabolic clearances for drugs eliminated entirely by those two

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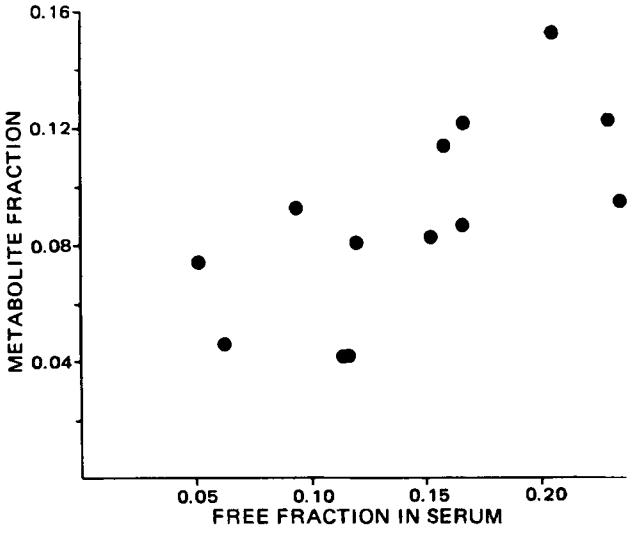

Figure 1—*Relationship between the fraction of a 20-mg/kg iv dose of sulfisoxazole excreted in the urine as metabolites and the free fraction of sulfisoxazole in serum. Data were obtained from 13 rats (6). The correlation coefficient is 0.68;* $p < 0.02$.

types of processes:

$$Cl_T = fk_g(1 - F) + k_s^*(1 - F) + fCl_{m\ \text{intrinsic}} \qquad \text{(Eq. 4)}$$

and the fraction of a dose metabolized is equal to $fCl_{m\ \text{intrinsic}}$ divided by all of the terms on the right side of Eq. 4. Dividing the numerator and denominator of that ratio by f yields:

$$F_m = \frac{Cl_{m\ \text{intrinsic}}}{k_g(1 - F) + Cl_{m\ \text{intrinsic}} + \frac{k_s^*(1 - F)}{f}} \qquad \text{(Eq. 5)}$$

Examination of Eq. 5 reveals that as f increases, F_m also increases. Thus, the fraction of a dose of drug converted to metabolite(s) increases if the serum protein binding of that drug is decreased in blood flowing through the eliminating organs (5)[1]. This conclusion applies only to drugs that are excreted in part by a process whose rate is proportional to the total rather than the free drug concentration in plasma or serum while the rates of other, parallel elimination processes are proportional to the free drug concentration. Sulfisoxazole appears to exhibit such characteristics in rats (6).

In 13 male Sprague–Dawley rats receiving a single intravenous injection of 20 mg of sulfisoxazole/kg, the fraction of the dose recovered in the urine as metabolites ranged from 0.042 to 0.152 and f ranged from 0.0518 to 0.235 (6). Drug concentrations in serum declined biexponentially with no downward curvature, which would occur if renal excretion, the major pathway of elimination, were saturable in the concentration range studied. Reexamination of the experimental data revealed a significant positive correlation between F_m and f (Fig. 1), as predicted by Eq. 5.

One important implication of these findings relates to the mechanism of certain drug interactions. Increased conversion of a drug (A) to its metabolite(s) caused by prior or concomitant administration of another drug (B) usually will be interpreted as resulting from either induction of biotransformation or inhibition of the renal clearance of A. However, if Drug B displaces Drug A from plasma protein binding sites, then the increased biotransformation of Drug A also could occur by the mechanism described in this communication. Another implication concerns the effect of the dose or dosing rate on the metabolic fate of a drug. For drugs that exhibit significant concentration dependence of plasma protein binding (f increases with increasing drug concentration), F_m may increase with increasing dose or dosing rate due to decreased protein binding.

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[1] The opposite would occur if biotransformation is blood flow rate limited while the renal excretion rate is proportional to the free drug concentration in plasma.

Polyethylene Glycols as Solvents in Implantable Osmotic Pumps

Keyphrases □ Polyethylene glycols—use as solvents in implantable osmotic pumps □ Solvents—polyethylene glycols, use in implantable osmotic pumps □ Drug delivery systems—implantable osmotic pumps, use of polyethylene glycols as solvents

To the Editor:

Implantable osmotic pumps[1] are useful for short-term delivery of water-soluble drugs and hormones (1–4). However, many compounds such as steroids are too insoluble in water to be administered as aqueous solutions (5). Although 5% ethanol and 5% dimethyl sulfoxide increase the concentration range over which lipophilic molecules can be delivered (6), the maximum dose still is quite low. Polyethylene glycols 400 and 600 are excellent solvents for many steroids (Table I) (1,5) and also are useful *in vivo* since they have very low toxicities (7). The objective of these experiments was to evaluate the suitability of polyethylene glycols as solvents with implantable pumps *in vivo*. Since the polyethylene glycols are known to influence fluid balance *in vivo*, the potential effects of the solvents and the pumps also were examined.

The ability of the pumps to function *in vivo* with polyethylene glycols as solvents was evaluated in two ways. Mineralocorticoids are known to induce the amiloride-

[1] Model 1701, Alza Corp., Palo Alto, CA 94304.