vein, and lithium chloride was administered in a dose of 40 mg/kg in the same manner. Hepatic extraction ratios of propranolol and lithium chloride were measured by obtaining blood samples simultaneously from the portal vein and the hepatic veins at various intervals after administration.

The portal venous blood of the rat can be taken through a cannula introduced *via* the pyloric vein into the hepatic portal vein (8, 9). Propranolol and lithium concentrations in whole blood were determined by the spectrophotofluorometric method of Shand *et al.* (10) and by the flame-photometric method of Amdisen (11), respectively. The hepatic extraction ratio was calculated from drug concentrations of the portal venous and hepatic venous blood samples taken simultaneously. The drug concentrations in the portal venous and hepatic venous blood and the mean hepatic extraction ratios are shown in Table I.

Propranolol concentrations in the mixed hepatic venous blood were always much lower than those in the portal venous blood, while lithium concentrations in the two venous blood samples were almost equal. Hepatic extraction of propranolol was essentially complete in the dose of 5 mg/kg, and it was more than 85% even in the dose of 12.5 mg/kg. On the other hand, lithium was essentially not extracted in the dose of 40 mg/kg.

A method for sampling hepatic venous blood may also be used for measurement of hepatic blood flow. In humans and in dogs, blood samples from a hepatic vein may be easily taken under direct fluoroscopic visualization by catheterization of a hepatic vein *via* the median basilic vein and the superficial jugular vein, respectively. However, in the rat, several technical problems arise on account of the small size of the vessels and liver. A major problem is to place a cannula in such a manner as to avoid trauma to the liver and to prevent contamination by the blood of the inferior vena cava.

For sampling hepatic venous blood, Dhumeaux and Berthelot (12) applied a catheter to one of the small hepatic veins through an incision made in the central lobe of the liver. The main disadvantage of the hepatic vein catheterization as well as this transhepatic vein catheterization is that one does not sample the mixed blood draining from all of the hepatic veins, since the hepatic veins empty themselves separately into the inferior vena cava. Drug concentrations in blood samples obtained by these methods are not always representative of the level in the entire hepatic venous outflow (13). Therefore, data obtained from such localized samplings may not be satisfactory for estimation of true hepatic extraction of a drug by the whole liver.

The technique of the double cannulation of the inferior vena cava presented here overcomes the disadvantage inherent in the previous methods, since the mixed hepatic venous blood, instead of blood from only one hepatic vein, can be obtained. This improved method for sampling the mixed hepatic venous blood is simple and practical. When applied in the rat, this method has proved useful for the determination of the drug hepatic extraction ratio in the study of *in vivo* drug metabolism as well as for measurement of hepatic blood flow in the rat. Details of these studies will be reported.

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Concentration Dependence of Ethanol Effect on Intestinal Absorption of Theophylline in Rats

Keyphrases □ Ethanol—effect on intestinal absorption of theophylline, concentration dependence, rats, □ Theophylline—intestinal absorption, concentration dependence of ethanol, rats □ Absorption, intestinal—theophylline, concentration dependence of ethanol, rats

To the Editor:

Koysooko and Levy (1) recently reported that the rate of absorption of theophylline from the perfused small intestine of anesthetized rats is increased significantly in the presence of a constant 2% concentration of ethanol and that there is a positive rank-order correlation between theophylline absorption from the ligated small intestine of rats and water net flux from

Table I—Effect of a Constant Concentration of Ethanol in the Perfusion Solution on Theophylline Absorption from *In Situ* Perfused Rat Small Intestine

Ethanol Concentration, %	Water Net Flux[b], ml cm^{-1} hr^{-1}	Theophylline Intestinal Clearance, ml cm^{-1} min^{-1} × 10^3	Number of Rats	Body Weight, g
0	0.051 (0.024)[c]	5.25 (0.73)[c]	6	279 (50)[c]
0[a]	0.048 (0.017)	5.27 (0.62)	6	297 (41)
0.25 ± 0.03	0.070 (0.023)	6.66 (0.40)[d]	6	270 (56)
1.08 ± 0.27	0.133 (0.011)[d]	9.77 (0.70)[d]	4	252 (54)
1.88 ± 0.14	0.103 (0.014)[d]	9.02 (1.97)[d]	4	282 (43)
1.93 ± 0.35[a]	0.116 (0.013)[d]	8.33 (1.09)[d]	6	296 (29)

[a] Data from Ref. 1. [b] Slope of a plot of cumulative water net flux *versus* time during the first 60 min. [c] All results are expressed as means (standard deviation). [d] Statistically significant difference from control value ($p < 0.02$).

the intestine at initial ethanol concentrations of 0, 5, 10, and 20%. A subsequent study determined the concentration profile for the effect of ethanol on water flux and showed that ethanol concentrations as low as 0.05% can increase water net flux from the intestine (2). These findings suggested that even very low concentrations (<1%) of ethanol might increase theophylline absorption.

To investigate this possibility, we determined the effects of 0, 0.25, 1, and 2% ethanol on theophylline absorption from the *in situ* perfused small intestine of anesthetized rats, using the methodology described previously (1). The results of these investigations (Table I) show that ethanol in 1% and even in 0.25% concentrations significantly increases the absorption rate of theophylline from the rat small intestine. Results obtained previously with 0 and 2% ethanol (Table I) are in agreement with the results obtained in this study.

There is a perfect rank-order correlation between theophylline intestinal clearance and water net flux for the four sets of experiments in the present investigation. The results of studies concerning the effect of ethanol on the absorption of other drugs and of studies concerning the mechanism of the absorption-enhancing effect of ethanol and other alcohols will be described in subsequent reports.

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