operative care except 30 000 units of long-acting penicillin G (i.m.) every 2 days for 8 days.

Patency of each cannula was tested 14 to 17 days after surgery. Under light ether anaesthesia each rat was connected to an infusion pump. Following a 5 min period required to regain normal ambulatory activity, the rat was infused with 0·5 ml min^{-1} of physiological saline (0·9% NaCl) containing 60 mg ml^{-1} of pentobarbitone. The latency between the start of the infusion and loss of righting reflex was measured. Rats with patent cannulae responded with loss of righting reflex between 20 and 42 s after start of the infusion. Rats with non-functional cannulae did not show a loss of righting reflex even after 60 s and the infusion was accompanied by seepage of fluid at the point of entry into the rat.

The results of the test for patency carried out on 48 rats that did not dislodge their cannulae are summarized in Table 1. Chi square statistical tests indicated a significant effect of length ($P < 0.01$) and outer diameter ($P < 0.05$). Cannulae consisting of the two smaller diameters and the 40 mm length were all functional, whereas none of those consisting of the two larger diameters and 25 mm length were. Dissection of four to five animals in each group revealed that all cannulae regardless of dimensions were encapsulated in a sheath of dense tissue between the vessel wall and the cannula, and in the case of cannulae that did not work the tissue completely enclosed the open end of the cannula. Thus, as the fluid was infused it was forced along a pathway between the silicone tubing and the vessel wall and out of the vein. The functioning cannulae were also completely covered over, but the tissue was not as dense and therefore not impervious to the fluid.

Thus, it was concluded that jugular cannulae constructed of small diameter silicone tubing and terminating in the heart have the greatest probability of remaining patent.

September 22, 1978

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Further consideration of the existence of an optimal partition coefficient for intestinal absorption of foreign compounds

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A number of workers have reported that a linear relationship exists between the rate of absorption from the small intestine and partition coefficient of foreign compounds (Schanker 1960; Kakemi et al 1967; Bates & Gibaldi 1970). Houston et al (1974, 1975) using a homologous series of aliphatic carbamates, covering a much wider span of partition coefficients than investigated by previous workers, have proposed that the true relationship between rate of absorption and partition coefficient is a parabolic one.

The findings of Houston et al are not directly comparable with those of other workers for the following reasons: fed rather than starved animals were used and although the intestines were rinsed thoroughly before use intestinal absorption characteristics could vary between the fed and starved states. Because of the lack of sensitivity of the g.l.c. procedure for measuring the carbamates, relatively high concentrations (10 mM) were used for the higher homologues, these concentrations are greater than the water solubility of these compounds. To keep these compounds in solution small amounts of Tween-80 were added and although the detergent did not appear to alter the rate of absorption of the lower carbamates (in which its addition was not required for solubilization purposes) it might have influenced the absorption of the higher homologues thus contributing to the parabolic relationship between absorption rate and partition coefficient.

In view of the fact that the relationship of rate of absorption to the partition coefficient may be an important consideration in drug design we have re-investigated the absorption characteristics of the carbamates studied by Houston et al at concentrations well below their water solubility limits (i.e. 0·1 mM) with and without added detergent in both fed and starved animals.

[^{14}C-carbonyl] Ethyl carbamate (specific activity 31·4 mCi mM^{-1}) was supplied by Fluorechem Ltd., Glossop, Derby. [^{14}C-carbonyl]n-Butyl, n-hexyl and n-octyl carbamates (specific activity 1·5 mCi mM^{-1}) were synthesized by the Chemistry Division, Chemical Defence Establishment. Techniques for studying absorption were those described by Houston et al (1974) unless otherwise stated.

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The absorption rate constants obtained with the [^{14}C] carbamates at concentration of 0·1 mM in the absence of detergent (see Table 1) did not differ significantly (by application of the *t*-test) from those found employing 10 mM carbamate in which 5% w/v Tween 80 was used to maintain the higher carbamates in solution. The concentration of carbamate absorbed on the intestinal membrane was very small. The relationship between rate of absorption and partition coefficient under the standard mixing conditions described by Diamond et al (1970) is therefore truely parabolic and not due to precipitation of the higher carbamates from the mucosal solution or their binding

Table 1. Carbamate absorption rate constants from in situ small intestine of unstarved and starved rats.

	0·1 mM		10 mM	
Carbamate	Absorption rate constant (min^{-1})	% carbamate found bound to intestinal membrane after 30 min	Absorption rate constants found in present study (min^{-1})	% carbamate found bound to intestinal membrane after 30 min in present study
Ethyl[a]	0·130 (0·013)	1·22 (0·60)	0·129 (0·019)	0·62 (0·33)
Ethyl[b]	0·140 (0·021)	0·41 (0·17)		
n-Butyl[a]	0·186 (0·011)	0·61 (0·32)	0·175 (0·020)	0·94 (0·47)
n-Butyl[b]	0·182 (0·024)	0·89 (0·32)		
n-Hexyl[a]	0·097 (0·009)	1·14 (0·33)	0·093 (0·007)	0·38 (0·26)
n-Hexyl[b]	0·101 (0·011)	1·38 (0·73)		
n-Octyl[a]	0·052 (0·002)	1·06 (0·44)	*0·054 (0·003)	*1·36 (0·65)
n-Octyl[b]	0·055 (0·004)	1·72 (0·52)		

Mean (with s.d.) for four animals determined at pH 6 using 0·1 M citrate-phosphate buffer initial [^{14}C]carbamate concentration was 0·1 mM. Normal mixing of sample in the intestine was carried out as described by Diamond et al 1970.

[a] Rats were allowed free access to food and water before experiment.

[b] Rats only allowed access to water 16–20 h before experiment.

* 5% Tween 80 used.

to the intestinal wall. The present study also demonstrates that at a concentration of 5% v/v (well above the critical micelle concentration) the addition of Tween 80, a non-ionic detergent, has no apparent effect on the absorption rate of n-octyl carbamate. This result is in contrast to the findings of Yamada & Yamamoto (1965), who found 5% Tween 80 to markedly decrease drug absorption, but tends to support those of Hikal et al (1976) who reported 2% Tween 80 to have no effect upon salicylate absorption. (For a general review on this topic see Gibaldi & Feldman 1970).

Most studies on the intestinal absorption of drugs have used rats starved for 8–20 h in an attempt to clear the small intestine of food particles. In order to discover what influence starvation would have on the absorption rate of the four radiolabelled carbamates, their absorption rates were determined using rats starved for between 16 and 20 h, but with access to water. The results found were (mean with s.d. n = 3 animals; pH 6, 0·1M citrate buffer; initial carbamate concentration 0·1mM): ethyl 0·043 (0·002); n-butyl 0·056 (0·003); n-hexyl 0·088 (0·006); n-octyl 0·106 (0·006). Although standard deviations were slightly greater than those using fed rats the absorption rate constants were not significantly different (*t*-test). This finding is in agreement with those of Diamond et al (1970) who found significant decreases in intestinal absorption rates only in rats starved in excess of 24 h. In view of these findings it seems unlikely that the linear correlations between log k_a and log P found by other workers are the result of this method of pretreatment of their animals.

We acknowledge the financial support of the Procurement Executive, Ministry of Defence.

September 1, 1978

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