is less readily dissipated from the paws causing a greater rise in paw temperature and consequently greater injury.

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Some observations on blood level data following oral administration of aspirin as tablets and capsules

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Experimentally prepared capsules and commercially available tablets of aspirin, each of 500 mg, were tested and were shown to conform to the British Pharmacopia tests for uniformity of weight, uniformity of active ingredient and five single-capsule assays yielded results of 97·7% (S.D.=0·62%) active ingredient. From single-tablet assays they contained 100·6% of aspirin (S.D.=1·72%).

Two capsules or two tablets, were administered in a randomized cross-over experiment, to 9 healthy volunteers, two weeks being allowed before the second test was commenced. Venous blood was withdrawn before and at various times after administration, and plasma salicylate levels determined after alkaline hydrolysis.

In every subject, the tablet preparation produced a higher concentration of salicylate in the plasma 0·5 and 1 h after administration than did the capsule formulation, and the peak levels occurred earlier and more consistently for the tablet at about 2 h.

The time to reach maximum blood level varied from about 2 to 4 h for the capsules. Average peak salicylate levels between the two groups were virtually identical (66·2 μg/ml and 64·1 μg/ml; S.D., 10·8 and 10·3).

Extrapolation of the log concentration *vs.* time graph, after peak levels to a common time scale, showed similar elimination rates for the two formulations, and confirms that the individual peak levels obtained differed little between the formulations.

A polynomial regression of the first few points up to the maximum indicated a lag time in the appearance of salicylate in the plasma, and this was significantly higher for the capsule which averaged 0·23 h and 0·07 h for the tablet. The disintegration time in water of the experimental formulation was 519–524 s, and that of the commercial preparation only 14–18 s, but, whereas the tablet almost immediately became dispersed in water, it was approximately 45 s before the edges of the capsule broke open to release some of the contents. Thus, the delayed and less consistent maxima plasma salicylate levels of the capsule formulation may be due to the slow release of the drug from the dosage form. Quantitative pharmacokinetic data and dissolution rate profiles are being evaluated.

Hepatic clearance of propranolol in dogs

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Studies in which ^{14}C-propranolol was given to man indicate that this drug is almost totally absorbed after oral dosing (Paterson *et al.*, 1970). However, peak plasma con-

centrations vary seven-fold in different patients given the same oral dose (Shand, Nuckolls & Oats, 1970). This observation, together with an analysis of areas under the time concentration curves after I.V. and oral dosing, led to the suggestion that propranolol was extensively extracted or metabolized at the first pass through the liver (Gibaldi, Boyes & Feldman, 1971). We have therefore studied hepatic extraction, hepatic clearance, and whole body clearance of propranolol under (a) steady state conditions and (b) during logarithmically declining infusion into the hepatic portal vein.

In 4 anaesthetized dogs a constant I.V. infusion of (+)-propranolol was given after a loading dose of 0·3 mg/kg. Hepatic extraction was determined from the difference between the arterial and hepatic venous concentrations. Liver blood flow was estimated by the Fick principle using ^{198}Au colloidal gold and hepatic clearance of propranolol was calculated by multiplying liver blood flow by the extraction ratio. Whole body clearance of propranolol was obtained by dividing the infusion rate by the blood level at steady state. The results of these studies and four similar experiments in which (−)-propranolol was given are shown in the Table 1.

TABLE 1. *Kinetics of propranolol under steady state conditions*

Isomer	Vd (a) l/kg	Hepatic extraction %	Hepatic clearance (ml/kg)/min	Whole body clearance (ml/kg)/min	Hepatic clearance (%) whole body
Dextro					
Mean ± S.E. n=4	2·07 ± 03·5	87·8 ± 1·5	18·2 ± 1·7	24·0 ± 1·7	75·6 ± 2·3
Laevo					
Mean ± S.E. n=4	2·62 ± 0·60	80·0 ± 4·6	17·8 ± 4·1	20·0 ± 3·8	86·3 ± 8·0

Hepatic extraction of propranolol varied from 69 to 92% and hepatic clearance accounted for 65–103% of the whole body clearance. Since the major site of clearance of propranolol is in the liver and extraction by this organ so high, the half-life of propranolol will be largely dependent on liver blood flow.

After oral (or portal venous) dosing the amount of propranolol reaching the systemic circulation will depend upon variations in the efficiency of extraction by the liver. However, it appears that the process of extraction by the liver can be saturated and stored propranolol may then be released into the circulation.

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Histamine release by MCDP (401), a peptide from the venom of the honey bee

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Mast cell degranulating peptide (MCDP), first isolated from bee venom (Breithaupt & Haberman, 1968), is made up of twenty-two amino acids and has two disulphide bridges (Hanson & Vernon, 1969). It contains a relatively high proportion of the more basic amino acids, a property generally associated with histamine releasing activity.

The present work has been initiated by tests on the isolated blood leucocytes of research workers handling the peptide, some of whom developed symptoms suggestive of rhinitis and bronchospasm. No significant release of histamine was obtained from these patients' leucocytes. This led to the conclusion that these patients were not allergic to the peptide; their symptoms possibly being due to direct release of histamine from tissue mast cells.