

The fatty acid content of the solution was determined by gas chromatography. Each metabolite was studied over a range of albumin : metabolite ratios and control dialysis experiments were included for each study. Unbound *o*-methyl red in the diffusate was determined spectrophotometrically.

Table 1 summarises some of the results and shows that only one of the hydrophilic metabolites, indoxyl sulphate, produced a significant increase in the percentage of unbound *o*-methyl red.

A further nine hydrophilic metabolites had no effect. However, lauric acid and myristic acid both caused a marked increase in unbound dye concentration (Table 1). Renal insufficiency is accompanied by disorders of blood lipids (Cramp, Moorhead & Wills, 1975) and so lipophilic metabolites such as the fatty acids may be implicated in the decreased drug binding which occurs in uraemia. Preliminary spectroscopic investigations indicate that fatty acids inhibit the binding of *o*-methyl red to HSA by a mechanism different from that of indoxyl sulphate.

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In vivo absorption studies with paraquat and diquat in the dog

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Paraquat (1,1'-dimethyl-4,4'-bipyridilium) and diquat (1,1'-ethylene-2,2'-bipyridilium) are non-selective herbicides with a similar mode of action (Calderbank, 1964). Paraquat produces lung damage in man and in several species of laboratory animals, probably due to an energy-dependent accumulation of paraquat by the lung (Rose, Smith & Wyatt, 1974), whereas diquat is not actively accumulated by lung slices and is less toxic to the lung *in vivo*.

After i.v. administration of tracer doses of [¹⁴C]-paraquat (30–50 µg/kg) to Greyhound dogs the plasma concentration-time curve fitted a tri-exponential decline, defined by the equation:

$$C = A^{-\alpha t} + B^{-\beta t} + C^{-\lambda t}$$

and the kinetics could be characterized on the basis of a three-compartment open linear system. Assuming that elimination occurs only from compartment 1, A, B, C, α , β , and λ can be used to calculate the rate of constants of transfer between compartments (Rescigno & Segre, 1966). Employing the equations of Loo & Riegelman (1968) these rate constants can be used to calculate the amount of paraquat absorbed at any given time.

In fasting dogs the absorption of low doses of paraquat, administered in 200 ml water, was rapid but

incomplete, reaching a peak plasma concentration 75 min after dosing. Oral administration of 120 µg/kg resulted in 46–66% absorption of paraquat in 6 h, whereas at doses of 2 mg/kg and 5 mg/kg, 22–38% and 25–28% respectively were absorbed. 70–90% of the paraquat absorbed, calculated according to the Loo Riegelman equations, was excreted in the urine in 6 h and is consistent with the proportion recovered in the urine following i.v. administration. Diquat (12 µg/kg) was only 10–20% absorbed in 6 h and did not produce an early plasma peak. Administration of propantheline (15 mg i.v.) 15 min before an oral dose of paraquat altered the plasma concentration-time curve markedly, delaying the peak concentration by 3 h to 6 h, indicating that the stomach is not a major site of paraquat absorption.

The dose dependent absorption of paraquat in the dog suggests facilitated absorption, probably in the small intestine, whereas the absorption of diquat may occur solely by passive diffusion.

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