size distribution may well be introduced as well as the bulk inhomogeneities: for example, larger particles will have entered the lower parts of the cake under conditions where gravity settling has taken place. Secondly, it is quite possible that these same variations could occur when a filter is pre-coated with a filter-aid. Normally this is assumed to form a uniform coat, but it can be seen that this is not necessarily so.

We are grateful to Messrs, D. Hunt, L. Morris and D. J. Tulett for assistance with the cutting, and to Mr. J. Hardyman who took the photographs.

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Relation between binding to plasma protein, apparent volume of distribution, and rate constants of disposition and elimination for chlorpromazine in three species

Several recent investigations from this and other laboratories have established that, for each unit of dose, wide interspecies differences occur in chlorpromazine concentrations in plasma after intravenous doses (Curry, Derr & Maling, 1970; Curry, D'Mello & Mould, 1971; Maxwell, Carrella, & others, 1972). Concentrations are highest in man, intermediate in dogs, and lowest in rats. Plasma protein binding of chlorpromazine is also highest in man and lowest in rats (Curry, 1970a). Binding of drugs to plasma proteins is thought to control drug localization in tissues (Curry, 1970b), so a pharmacokinetic analysis of chlorpromazine concentrations in plasma has been conducted, to quantify the relation implicit in the data. The calculations have also concerned disposition and elimination rate constants.

The data were taken from the original publications. The analysis involved comparison with a two-compartment model (Riegelman, Loo & Rowland, 1968a, b). The pharmacokinetics in man were discussed by Maxwell & others (1972). The treatment of the dog and rat data was methodologically identical with the treatment of the human data.

It was appropriate to calculate: (i) the apparent volume of distribution at steady-state (Vd_{ss}) as an assessment of tissue localization; (ii) the disposition rate constant (β), which is the same as the rate constant of the second phase of the double-exponential semilogarithmic plot of concentration against time, and which assesses the rate of removal from the body as a whole; and (iii) the elimination rate constant (k_{el}), which is the best assessment of the combined processes of metabolism and excretion. The elimination rate constant is greater than the disposition rate constant, because of continual replenishment of the drug concentration in plasma consequent on loss from tissue stores.

Vd_{ss} was highest in the rat and lowest in man (Table 1). The differences were significant ($P < 0{\cdot}05$), as were the differences in protein binding. Thus a high degree of tissue localization occurred in the species in which binding to plasma protein was low and *vice versa*. These data were further used to calculate the fractions of the body content of chlorpromazine occurring in plasma water. These were similar: rat,

Table 1. *Plasma protein binding, apparent volume of distribution (Vd_{ss}), elimination rate constant (k_{el}) and disposition rate constant (β) for chlorpromazine in three species.*

Species	Plasma protein binding at 0·100 μg/ml (fraction bound)	Vd_{ss} (multiple of body weight)	k_{el} (h^{-1})	β (h^{-1})
Rat	0·894 ± 0·001	29·1 ± 1·0	0·174 ± 0·080	0·125 ± 0·060
Dog	0·941 ± 0·001	18·6 ± 2·0	0·217 ± 0·029	0·064 ± 0·007
Man	0·957 ± 0·003	11·2 ± 2·8	0·086 ± 0·018	0·023 ± 0·003

Mean ± s.e.

0·0036; dog, 0·0032; and man, 0·0038. Thus, in spite of differences in tissue and plasma amounts, comparable differences were not seen in the amounts in plasma water.

The data therefore support the idea that binding to plasma protein exerts an influence over tissue localization, or, conversely, that tissue localization exerts an influence over protein binding. The first idea is favoured, as protein binding was the same *in vitro*, and in samples collected from treated animals and man. A similar control over the rate of disappearance of drugs from the body is commonly supposed, as the combined rate of metabolism and excretion is a function of the concentration in plasma water, and in a restricted situation this concentration is inversely related to protein binding. In this study, the amounts in plasma water were similar in three species. The values for k_{el} were not significantly different in rats and dogs, although the values for β were significantly different from each other ($P < 0.05$), with the highest in rats and the lowest in man. Thus there was no obvious relation between k_{el} and the degree of binding or tissue localization, while β was highest in the species with low binding and high tissue localization, and *vice versa*. This suggested that, of the possibilities, binding and tissue localization had little or no effect on the processes of metabolism and excretion, although binding to plasma proteins might have inhibited removal of the drug from the body by restricting the availability of substrate to the metabolic and excretory organs. But protein binding equilibria are reached in milliseconds, while tissue localization equilibrium can require several hours. Hence, tissue localization, not protein binding would be expected to exert an inhibitory effect. But in this case, high degrees of tissue localization occurred with a fast rate of elimination. So these data lend no support to the idea that binding to plasma protein and tissue localization exert a major influence on rates of removal of drugs from the body.

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July 27, 1972

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