metabolism resulting in increased plasma concentrations—contrary to most reports in the literature, we have found that both in man and in the rat, tricyclic antidepressants are weak inducers of drug metabolism.

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Effects of tricyclic antidepressants on drug metabolism

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There have been several reports of an acute inhibitory effect of imipramine and desmethylimipramine on drug metabolism in the rat (Kato, Chiesara & Vassanelli, 1964; Shand & Oates, 1971) and a recent study in man (Vessel, Passananti & Green, 1970) demonstrated inhibition of antipyrine and bishydroxycoumarin metabolism with nortriptyline. It is conceivable that such a mechanism might contribute to the cardiotoxic effects of tricyclic antidepressants in susceptible individuals.

The present work was undertaken (a) to extend the study as carried out by Vessel *et al.* (1970), to four other commonly used tricyclic antidepressants, (b) to compare the effects of these agents in man after long and short term treatment and (c) to look at their effects on rat liver drug metabolizing enzymes. In the human studies, drug metabolizing capacity was assessed using the plasma antipyrine half life procedure as previously described (O'Malley, Crooks, Duke & Stevenson, 1971). Hexobarbitone was used as substrate in the *in vitro* rat liver studies.

TABLE 1. *Antipyrine half life values (h) in the same individuals before and after treatment for 7 and 28 days*

Drug	Number of subjects	Treatment		
		Before	7 days	28 days
Amitriptyline	6	12·7±2·8	11·8±3·3	10·9±1·9
Chlorimipramine	6	11·8±2·6	10·5±2·3	*9·3±1·9
Desmethylimipramine	7	12·4±1·4	10·6±1·9	11·3±2·6
Imipramine	6	10·3±1·7	10·0±1·8	9·5±1·9
Nortriptyline	5	10·2±1·0	9·0±1·6	9·3±2·5

Results are shown as means ± standard deviation. With each drug the dose was 50 or 75 mg/day.
* $P<0.01$.

Table 1 shows the results obtained in healthy volunteers of both sexes aged 20–30 years. It is apparent that there was a tendency towards an increase in the rate of antipyrine metabolism after either period of treatment although the difference was significant in only one case. Our findings with nortriptyline are therefore not in agreement with those of Vessel *et al.* (1970).

These results are supported, however, by our rat data in that the rate of hexobarbitone metabolism tended to be increased after chronic exposure to the antidepressants. This work indicates that in both man and the rat the 5 tricyclic antidepressants studied appear to act as weak inducers of drug metabolism.

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Digoxin dosage in patients with impaired kidney function

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Based on the so-called 'intact nephron hypothesis' (Bricker, Morrin & Kime, 1960) a linear relationship between the endogenous creatinine clearance (V_{Cr}) and the overall elimination rate constant (k_e) of many drugs can be demonstrated: $k_e = k_m + a \cdot V_{Cr}$.

In order to find the appropriate individual dose schedule of digoxin for patients with impaired kidney function, we tested this hypothesis.

Thirty-one patients with different degrees of kidney impairment (endogenous creatinine clearance ranged from 0 to 100 ml/min) were given 0·25–0·5 mg tritium labelled digoxin intravenously. The volume of distribution, the 'overall' (k_e), the renal (k_r) and extrarenal (k_m) rate constant for elimination of digoxin were determined from measurements in the plasma and in the urine. At the same time endogenous creatinine clearance (V_{Cr}) was estimated.

According to the equation $k_e = k_m + a \cdot V_{Cr}$ a linear correlation between the elimination constant and the endogenous creatinine clearance was found using the method of 'the least squares of errors'. For digoxin the following equation was calculated: $k_e = 0{\cdot}00593 + 0{\cdot}00013 \cdot V_{Cr}$; $r = 0{\cdot}91$; $S_{y/x} = \pm 0{\cdot}0019$; $P < 0{\cdot}001$. The k_e obtained from the different measurements ranged from 0·004 h^{-1} in the anurics to 0·0196 h^{-1} in normals or from 173·3 h to 35·4 h half-life respectively. The rate constant in the urine was not significantly different from the constant obtained in the plasma.

Based on this quantitative relationship between digoxin elimination and a simple clinical routine test of kidney function the individual dose schedule for patients with kidney impairment can be calculated. For practical clinical purposes, a 'bedside method' described by Dettli, Spring & Habersang (1970) is also suitable for determining the dose of digoxin.

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Plasma digoxin concentrations in children in heart failure

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Digoxin dose schedules used in paediatric units in England vary widely. We have