The drop in concentrations after the first fortnight may reflect induction of drug hydroxylase activity in the liver. The correlations with peripheral measurements show that concentration data are useful during appraisal of marked side effects such as postural hypotension, but further studies are needed to evaluate the usefulness of plasma chlorpromazine estimations in the clinical management of psychiatric patients.

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Cardiotoxicity of tricyclic antidepressants

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Since the introduction of psychotropic drugs into medicine, many reports of cardiovascular complications resulting from their administration have appeared in the literature. These effects have ranged from minor electrocardiographic changes to sudden unexplained death in psychiatric patients. Because of the need to confirm or refute a suggestion by the Committee on Safety of Drugs that the administration of tricyclic antidepressants was associated with adverse cardiac effects, a hospital-based drug information system has been used to determine the incidence of sudden death of cardiac origin in patients receiving these drugs. In a preliminary study, the incidence of sudden unexpected death was found to be six out of fifty-three patients with cardiac disease who received amitriptyline compared with no such deaths in a matched control group (Coull, Crooks, Dingwall-Fordyce, Scott & Weir, 1970). This study has now been extended.

All inpatients in the Aberdeen General Hospitals Group who had received amitriptyline during the 40 months' period ending September, 1971 were identified and their hospital records studied. Eight hundred and sixty-four patients had received amitriptyline of whom 119 had cardiac disease. Those patients who had not received the drug during the two weeks immediately before death or discharge were not included. A control group was matched for sex, age, diagnosis and duration of hospital stay. There were twenty-four deaths in the amitriptyline group, thirteen of which were sudden and unexpected (duration of terminal illness <24 h). In the control group there were fifteen deaths, of which only three were sudden unexpected deaths.

All the amitriptyline patients who died apparently received conventional dose regimes and none received any drugs known to interact with tricyclic antidepressants. Thus the association between administration of amitriptyline and sudden death in patients with cardiac disease has been confirmed. No increased incidence of sudden death was found in patients receiving amitriptyline without a diagnosis of cardiac disease or in cardiac patients whose amitriptyline was discontinued at least 2 weeks before death or discharge. The position regarding other tricyclic antidepressants is currently being examined.

We have considered two of the possible factors which might be contributing, alone or in combination, to this cardiotoxicity: (1) interaction with concomitantly administered drugs—we have found that in rats, administration of tricyclic antidepressants for 2 weeks increases the toxicity of digoxin; (2) a decreased rate of drug

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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