TABLE 1. *Urinary excretion of practolol and propranolol under different pH conditions*

Subject	Urine pH	Amount excreted in urine in 24 h Practolol (g)	Propranolol (mg)	Urine pH
S_1, 39 years	4·86	0·127	0·993	5·10
	6·56	0·119	0·050	6·54
	7·74	0·123	0·023	7·70
S_2, 28 years	4·68	0·160	1·932	4·72
	5·42	0·132	0·266	5·75
	8·04	0·155	0·003	8·11
S_3, 19 years	5·04	0·163	0·788	4·99
	6·32	0·166	0·245	6·00
	7·79	0·163	0·006	7·95
S_4, 28 years	5·31	0·152	0·765	5·30
	5·93	0·178	0·030	6·35
	7·90	0·171	0·017	7·36

pH did not modify its excretion. These results are not due to differences in gastrointestinal absorption, since both drugs are 70–100% absorbed (Paterson, Connolly, Dollery, Hayes & Cooper, 1970; Fitzgerald & Scales, 1968). They confirm the findings of Bodem & Chidsey (1973) that the urinary excretion of practolol was unaffected by changes in urine pH. The dependence of excretion of unchanged propranolol on urine pH indicates that pharmacokinetic studies on this drug should be performed under conditions in which the urine pH is strictly controlled.

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Changes in drug metabolizing ability in thyroid disease

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Animal studies have shown that the activity of the liver microsomal enzymes involved in drug metabolism changes markedly following thyroidectomy or administration of thyroxine (Conney & Garren, 1961; Kato & Takahashi, 1968). The present study was designed to investigate possible changes in drug metabolizing ability occurring in patients with abnormal thyroid states.

Drug metabolizing ability was assessed mainly by determination of plasma antipyrine half-life and clearance rate in female thyrotoxic and hypothyroid patients. Patients were also assessed throughout the period of their treatment. In addition, in some of the thyrotoxic patients, the plasma half-life of ^{35}S–methimazole was used as a further index of metabolism. The plasma antipyrine half-life in the untreated hyperthyroid patients was significantly lower, and the clearance rate significantly higher, than in normal females (Table 1), thus indicating that this group metabolized antipyrine more rapidly. Conversely, the antipyrine half-life in untreated hypothyroid patients was significantly higher than control values.

TABLE 1 *Antipyrine elimination in thyroid disease*

Thyroid state	No. of patients	Antipyrine Half-life (hr)	Volume of distribution (l)	Clearance (l/hr)
Hyperthyroid	18	7·9±0·6 p<0·001	28·2±0·8 p<0·001	2·6±0·2 p<0·05
Normal	36	10·8±0·4	33·1±0·8	2·2±0·1
Hypothyroid	20	16·2±2·3 p<0·005	36·5±2·1 N.S.	2·0±0·2 N.S.

Values shown as means ±S.E.M.
The probabilities shown relate to differences between the means for abnormal thyroid subjects and for the corresponding controls.

In thyrotoxic patients treated with the antithyroid drug carbimazole, the plasma antipyrine half-life increased from 8·9±1·0 h (mean±S.E.M.) after one week's treatment to 11·4±1·1 h after nine weeks. During the same period plasma ^{35}S–methimazole half-life values increased from 7·9±0·4 h to 11·2±1·2 h. To study the relative influence of carbimazole therapy and changing thyroid state on drug metabolizing ability, a further group of thyrotoxic patients was studied during treatment with carbimazole and triodothyronine. In this group, antipyrine half-life values increased much less rapidly than in the group treated with carbimazole alone.

These findings suggest that marked changes in drug metabolizing ability occur in abnormal thyroid states and during treatment. Evidence is provided that the level of circulating thyroid hormones is important in controlling the rate of drug metabolism in this condition. These human studies are in general supported by our animal studies on the effects of thyroxine administration to rats.

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Inhibition of phenytoin metabolism by sulthiame

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Sulthiame causes an elevation of serum phenytoin levels when added to existing phenytoin therapy (Hansen, Kristensen & Skovsted, 1968 ; Olesen & Jensen, 1969), and often produces phenytoin intoxication (Houghton & Richens, unpublished). The mechanism of this interaction has been disputed. Hansen *et al.* (1968) found an increase in the serum half-life of phenytoin when sulthiame treatment was begun, and suggested that hepatic hydroxylation of the drug was inhibited. However, Olesen & Jensen (1969) found no change in the 24 h urinary excretion of the major metabolite of phenytoin, 5–(p-hydroxyphenyl)–5–phenylhydantoin (HPPH), and considered that displacement of bound phenytoin from sites such as red cells might be the cause of increased serum levels. This question has been re-examined in a group of 6 epileptic patients who were receiving a combination of phenytoin and sulthiame and in most cases a variety of other anticonvulsant drugs. Serum and urinary phenytoin, and urinary HPPH, were estimated by gas chromatography (Houghton, Latham & Richens, 1973), and the serum half-life of phenytoin was measured by giving 10 μCi of ^{14}C-labelled phenytoin orally. These estimations were performed before, and one month after, stopping sulthiame treatment. In all 6 patients serum phenytoin levels fell, half-lives shortened and the ratio of urinary HPPH to phenytoin (HPPH : DPH ratio) changed in favour of the metabolite (Table 1). These results suggest that sulthiame interferes with the hepatic hydroxylation of phenytoin.