Three subjects received placebo, 100, 200, 400 or 800 mg I.C.I. 66082 or 80 mg propranolol randomized and double blind. I.C.I. 66082 200 mg produced maximum inhibition of heart rate (H.R.) on tilting, 61±9·3 (mean±S.E. mean), placebo 79±9·3, $p<0.05$. After 3 min cycling (100 W), almost maximum inhibition was observed following 100 mg I.C.I. 66082, H.R. 85±5·8, placebo H.R. 109±5·8 ($p<0.05$); 800 mg produced little further inhibition (H.R., 83±7·1). Increased sympathetic stimulation dissociated the effect of the various dose levels, e.g., after 150 W, placebo H.R. 133±8·7, 100 mg 103±6·7 $p<0.05$; 200 mg H.R. 100±4·0, then progressively falling until after 800 mg the H.R. was 92±6·0, after propranolol 80 mg the H.R. was 99±4·8. I.C.I. 66082 diminished the rise of exercise blood pressure e.g., 150 W placebo, mean pressure 100 mmHg±5·8 following 800 mg I.C.I. 66082 86 mmHg±8·7 ($p<0.05$).

Blood levels obtained between 1·25 mg and 40 mg I.V., 100 mg and 800 mg orally, were proportional to the dose. One minute blood levels after 10 mg I.V. (0·36 μg/ml) decreased initially with a $T\frac{1}{2}$ of 20–30 min, then $T\frac{1}{2}$ increased and at 1–2 h after injection reached a maximum 5–6 h. Red cell drug concentration is 20% higher than plasma. Orally, peak levels occur at about 3 h and are calculable from the equation: peak blood levels μg/ml=oral dose (mg/kg)×0·44. Most peak levels are close to these obtained 3 h after a similar I.V. dose. Then they appear to decrease with a $T\frac{1}{2}$ of 5–6 h. Usually the drug was well absorbed (>50%, similar to most laboratory animals), occasional doses were poorly absorbed as indicated by low blood levels and low urinary excretion.

I.C.I. 66082 is therefore an effective β-adrenoceptor blocking drug in man. Experiments examining cardioselectivity are in progress. Doses of I.C.I. 66082 producing equivalent inhibition of exercise tachycardia are only one-third as active as propranolol inhibiting isoprenaline, the pattern expected from a drug showing selectivity (see Table 1). Half-life measurements indicate twice or thrice daily dosage is appropriate.

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The influence of urine pH on the renal excretion of practolol and propranolol

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The absorption of four β-adrenoreceptor blocking drugs through the buccal mucous membrane has been studied by Hicks (1973) over a pH range of 5·5–9·5. The absorption of propranolol and Ro 3–3528 (6–7—dimethyl–α–isopropylamino-methyl–2–benzofuranmethanol) was pH dependent, while that of practolol and pindolol appeared to be almost independent of pH. It is known that practolol and propranolol have similar pKa values, 9·5 and 9·45 respectively, but different partition coefficients, 0·19 and 28·5 respectively. The possibility that reabsorption of these two drugs across the renal tubular epithelium is similarly pH dependent has been investigated.

Four normal, male volunteers each took propranolol (80 mg) or practolol (200 mg) on three separate occasions so that the excretion of each drug could be determined with the urine pH uncontrolled, or acidified by ammonium chloride ingestion, or alkalinized by sodium bicarbonate ingestion (Beckett & Rowland, 1965). The 24 h excretion of propanolol was measured fluorimetrically (Shand, Nuckolls & Oates, 1970), and practolol spectrophotometrically (Turner, Burnam, Hicks, Cherrington, MacKinnon, Waller & Woolnough, 1971).

The results are given in Table 1. The urinary excretion of propranolol markedly decreased in all four subjects as the pH of the urine rose, whereas with practolol the urine

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.