There was a significant increase in mean heart rate after isoprenaline inhalation following ingestion of placebo (17·7 beats/min, S.E.M. 3·9, $t=4·53$, $P<0·01$) but not after propranolol. There was a small increase in heart rate following I.C.I. 50,172 (6·0 beats/min, S.E.M. 1·2, $t=5·0$, $P<0·01$) but this was significantly less than that following placebo ($P<0·05$).

Oral administration of I.C.I. 50,172 (200 mg) therefore significantly reduces the tachycardia but not the increase in skin temperature produced by isoprenaline inhalation. Propranolol (80 mg) abolishes both responses.

I.C.I. Laboratories kindly supplied the tablets of propranolol, I.C.I. 50,172 and placebo, and Riker Laboratories the " Medihaler " dispensers used in this study. J.H. is supported by a research grant from the Board of Governors of St. Bartholomew's Hospital.

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The effect of some catecholamine β-receptor blocking compounds on the toxicity to the heart of ouabain

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Data concerning the relevance of blockade of catecholamine β-receptors to the anti-digitalis effect of β-receptor blocking agents are rather contradictory. Several authors claim that the protective action of these compounds against digitalis-induced arrhythmias results only from their " non-specific " (local anaesthetic, quinidine-like) activity (Lucchesi, 1965; Somani & Lum, 1965), while others suggest that an anti-adrenergic mechanism might also be involved (Dohadwalla, Freedberg & Vaughan Williams, unpublished; Barrett & Cullum, 1968; Raper & Wale, 1968). It was therefore of interest to study the anti-digitalis and " non-specific " anti-arrhythmic effects of some recently introduced β-receptor blocking agents such as oxprenolol, I.C.I. 50,172 and (−)-propranolol.

Oxprenolol has recently been reported to be a potent β-receptor blocking agent with some local anaesthetic activity (Brunner, Hedwall & Meier, 1968). I.C.I. 50,172 was also found to possess β-receptor blocking potency with marked cardio-selectivity, but without local anaesthetic properties (Barrett, Crowther, Dunlop, Shanks & Smith, 1967; Dunlop & Shanks, 1968). The β-receptor blocking activity of oxprenolol is in the range of that of (±)-propranolol, whereas I.C.I. 50,172 proved to be 2–4 times (*in vivo*) or about 60–70 times (*in vitro*) less potent than (±)-propranolol (Barrett, unpublished; Dunlop & Shanks, 1968; Jackson, 1968).

The anti-digitalis effect was studied in urethane-anaesthetized guinea-pigs, as described by Vaughan Williams & Sekiya (1963). The local anaesthetic potency was determined in desheathed sciatic nerves of the frog, and the direct cardiac actions were studied in isolated rabbit atria. Oxprenolol (0·75–6 mg/kg intravenously) greatly increased the dose of ouabain required to produce extrasystoles and completely prevented the appearance of ventricular fibrillation. I.C.I. 50,172 protected against ouabain-induced fibrillation; the dose required, however, was about 2–3

times higher than that of oxprenolol. (—)-Propranolol showed marked protective action in a dose range of 0·375–3 mg/kg intravenously. The doses required to exhibit 50% protection against ouabain-induced ventricular fibrillation ((—)-propranolol : oxprenolol : I.C.I. 50,172) were 2·7 : 3·3 : 6·8 μ-moles/kg, the relative molar activities to procaine for local anaesthesia 3·5 : 1·4 : 0·04. All the three compounds exhibited quinidine-like actions on the parameters of atrial function. They decreased the maximum driving frequency, conduction velocity and the rate of rise of the intracellularly recorded atrial potentials.

Since the protective effect of I.C.I. 50,172 against ouabain-induced ventricular fibrillation correlates much better with its *in vivo* β-receptor blocking potency than with its local anaesthetic and quinidine-like activity, our observations support the view that " specific " blockade of β-receptors might contribute to the anti-digitalis effect of the β-receptor blocking agents.

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Sodium fluxes in cultured cells in the presence of ouabain

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L cells (fibroblasts) were explanted and cloned from mouse subcutaneous tissue (Sanford, Earle & Likely, 1948) and where they have been selected to grow in suspension (Earle, Bryant, Schilling & Evans, 1956) they are called L suspension or L.S. cells. Lamb & MacKinnon (1967) showed that 10^{-3}M ouabain caused an immediate reduction in the K^+ influx in L.S. cells. However, after 4 hr in the presence of ouabain, K^+ influx had recovered to a value slightly greater than the control. Both Na^+ removal and the addition of 10^{-3}M di-nitrophenol and 10^{-4}M iodo-acetic acid reduced the K^+ influx in cells treated with ouabain for 4 hr to about 20%. These results indicated the existence of an ouabain-insensitive Na^+–K^+ pump.

In the present experiments we measured the Na^+ fluxes in the presence of ouabain. For this, L cells grown in plastic Petri dishes at 37° C were used. The cells were loaded with $^{24}Na^+$ and then washed with five changes of inactive Krebs solution