Turner, 1969), and AH 5158, a drug with some α-blocking effect as well as β-blocking action (Farmer, Kennedy, Levy & Marshall, 1972; Boakes, Knight & Prichard, 1971). Propranolol was also administered, as was a larger dose of its D-isomer. Small doses of D-propranolol have been found previously to be ineffective (Wilson, Brooke, Lloyd & Robinson, 1969).

Five volunteer patients exercised on a cycle ergometer at constant work load before (control) and after injection of drug or saline, at weekly intervals under standardized conditions. A second post-injection exercise was performed 5 min after pain from the first post-injection exercise subsided. Gradually increasing doses of each drug were administered in a run-in period, and patients were accustomed to the experimental procedure. The trial proper involved the randomized double blind administration of saline, D-propranolol 80 mg and graded doses of propranolol, 10 mg, 40 mg, 80 mg, pindolol, 1 mg, 4 mg, 16 mg, and AH 5158, average 30 mg and average 55 mg. Some

TABLE 1.
Duration of exercise (seconds, mean ±S.E.)

n=5 Drug:	Control (C)	Post injection	Increase on C
Saline	196 (26·3)	200 (23·0)	4 (7·0)
Propranolol (10 mg)	199 (32·6)	*263 (37·3)	*****64 (10·4)
Propranolol (40 mg)	171 (18·5)	**274 (28·3)	**104 (22·4)
Propranolol (80 mg)	180 (13·0)	*296 (28·4)	****116 (26·7)
Pindolol (1 mg)	211 (16·7)	****271 (26·6)	*60 (21·8)
Pindolol (4 mg)	198 (21·6)	****293 (28·2)	***96 (17·6)
Pindolol (16 mg)	184 (19·1)	*243 (18·9)	**59 (17·6)
AH 5158 (av 30 mg)	201 (26·6)	**283 (29·0)	***82 (23·7)
AH 5158 (av 55 mg)	229 (30·0)	***281 (36·7)	++52 (32·0)
D-propranolol (80 mg)	190 (15·5)	++207 (26·2)	++17 (16·6)

P with respect to saline
* < 0·05 ** < 0·025 *** < 0·01 **** < 0·005 ***** < 0·001 ++ > 0·10

of the results are given in Table 1. All drugs produced a significant increase in exercise tolerance with the exception of D-propranolol. There is a less clear dose response relationship with pindolol and AH 5158. This may be due in the latter instance to its increasing hypotensive action with larger doses. Pindolol although it has high potency, has a flat dose response curve (Boakes, Boeree & Prichard, to be published).

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Preliminary studies on the pharmacology of an antidysrhythmic, Kö 1173, in man

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Kö 1173 is a new antidysrhythmic drug (Singh & Vaughan Williams, 1972; Allen, Kofi, Ekue, Shanks & Zaidi, 1972) resembling lignocaine in structure. It can be administered intravenously and is well absorbed after oral dosage. Blood levels were measured

by gas-liquid chromatographic techniques. The pH of 2 ml samples of plasma was adjusted to 10 with sodium hydroxide (0·75 N) and the drug extracted into ether. 20 μl of acetone and acetic anhydride were added to the separated ether layer which was then evaporated to dryness, using a stream of nitrogen, on a sand bath. The residue was redissolved in 2 μl of acetone, 1 μl of which was injected into the gas chromatograph (Perkin Elmer F 11) equipped with a flame ionization detector. Methylamphetamine was used as an internal standard.

To determine the pharmacokinetics and clinical effects of the drug, 100 mg boluses of Kö 1173 were administered to six patients who had stable premature beats. The patients rested in a quiet room for 30 min after insertion of an indwelling catheter and were then given 10 ml of saline intravenously. Kö 1173 was injected over a 2 min period. Blood for drug level measurements was taken at 5 min intervals for 1 h together with 60 s e.c.g. rhythm strips. For all six patients under study, a semilogarithmic plot of blood level concentration against time suggested that the drug has a biphasic half-life. The first half-life was very similar in all cases with a mean of $12{\cdot}3 \pm 0{\cdot}53$ min (mean $\pm$ S.E.). The second half-life was more prolonged and variable for each study, the results ranging from 53 min to 170 minutes. In 4 patients the frequency of premature beats was significantly suppressed. One patient only had a transient suppression and another showed no response. The steady plasma levels after the initial fall were similar, irrespective of their clinical response. In one oral study of drug absorption, the patient received Kö 1173 in a dose of 7 mg/kg body weight. The peak blood level occurred at 3 h with a half-life of 160 min which was similar to that of the second phase half-life after intravenous administration.

Myocardial function was assessed using the duration of aortic ball valve travel time as an index of myocardial depression after increasing intravenous doses of Kö 1173. The measurements were repeated on a separate occasion using lignocaine. Kö 1173 caused minimal myocardial depression equal to that found with lignocaine. Depression of contractility was dose related and was apparent immediately following administration.

Kö 1173 is an effective antidysrhythmic drug with an apparent biphasic half-life within the duration of this investigation. Its action has a rapid onset and persists in spite of a rapid fall in blood levels during tissue distribution.

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Interaction between debrisoquine and phenylephrine in man

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Phenylephrine has been used to study human baroceptor reflexes; the intravenous method (Bristow, Honour, Pickering, Sleight & Smyth, 1969) was modified to enable oral phenylephrine and cuff blood pressure measurements to be used (Aminu, 1972). Some exaggerated blood pressure responses were then observed in hypertensive subjects taking debrisoquine (3,4-dihydro-2 (1H) isoquinoline carboxamidine sulphate) (Aminu, D'Mello & Vere, 1970).

Four normal subjects, two females and two males, took debrisoquine (0·5–0·75 [mg/kg]/day) in capsules as divided doses, increasing the dose until sufficient was taken to cause measurable changes in the cardiovascular response to a passive tilt of 80°. Syrup, with or without phenylephrine (0·75 mg/kg) was taken before debrisoquine, and