Ventricular extrasystoles were produced by the intravenous injection of increasing doses of adrenaline in dogs anaesthetized with morphine and pentobarbitone and respired with 1% halothane and room air (Allen *et al.*, 1970). The adrenaline challenge was repeated after increasing doses of the test compound. Kö 1173 was given to five dogs and phenytoin and procainamide to four dogs each. The arrhythmia was abolished in all dogs. The mean dose required to abolish the arrhythmia was 0·65 mg/kg for Kö 1173; 1·12 mg/kg for phenytoin and 4·12 mg/kg for procainamide.

These studies indicate that Kö 1173 is as effective as phenytoin in experimental cardiac arrhythmias. As Kö 1173 does not possess local anaesthetic activity or block β-adrenoceptors (Danneberg & Giesemann, personal communication) its action on cardiac arrhythmias may be similar to phenytoin (Bernstein, Gold, Lang, Pappelbaum, Bazika & Corday, 1965; Bigger, Bassett & Hoffman, 1968).

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Observations on the sub-division of β-adrenoceptors in the circulation of the dog

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The concept that β-adrenoceptors can be divided into β_1, exemplified by those which stimulate the heart, and β_2, which lower vascular resistance in skeletal muscle, is gaining wider acceptance (Lands, Arnold, McAuliff, Luduena & Brown, 1967). This paper describes a study of various drugs reputed to have a predominant effect on one or other of these receptors, in order to see whether this concept of two distinct types of β-adrenoceptor is justified.

Observations were made in dogs anaesthetized with morphine sulphate and pentobarbitone. The effects of the intravenous injection of isoprenaline, orciprenaline, isoetharine and salbutamol on heart rate were compared. The effects of the injection into the femoral artery of these four drugs on blood flow to the hind limb, measured by an electromagnetic flow probe around the artery, were also compared. All four drugs increased heart rate and femoral blood flow. The order of activity for increasing heart rate was isoprenaline>orciprenaline>isoetharine=salbutamol. The order for increasing femoral blood flow was isoprenaline>isoetharine=salbutamol>orciprenaline.

The effects of the intravenous injection of isoprenaline on heart rate and of the injection of isoprenaline into the femoral artery on hind limb blood flow were recorded before and after the intravenous injection of increasing doses of I.C.I. 50172 (practolol) and butoxamine which block the responses produced by β_1- and β_2-adrenoceptors respectively (Dunlop & Shanks, 1968; Levy, 1966). Large doses of both drugs reduced cardiac and peripheral vascular effects of isoprenaline but practolol produced

marked reduction in the isoprenaline tachycardia without affecting the increase in hind limb blood flow on intra-arterial injection of isoprenaline. The effects of butoxamine were not as clearly defined.

These results are compatible with the concept of β_1- and β_2-adrenoceptors.

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The potentiation of the cardiovascular responses of the dog to noradrenaline by desmethylimipramine

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The systemic pressor effects of noradrenaline injected intravenously are potentiated by desmethylimipramine (DMI). The mechanism of potentiation may be one or more of several, including an action on the heart, or increases in the effective concentration of noradrenaline either in the circulating blood or at a local level.

Dogs were anaesthetized with pentobarbitone sodium (32 mg/kg intravenously) and one hind leg was perfused at a constant rate by a Sigmamotor pump. Arterial blood was supplied to the pump from a cannula in the lower aorta and delivered to the leg through a cannula in the femoral artery. The femoral and sciatic nerves were cut and mass ligatures tied around the leg passing under the femoral artery and vein.

DMI (3 mg/kg intravenously) potentiated the blood pressure and perfusion pressure responses to noradrenaline. However, the increases in hind leg resistance induced by intravenous noradrenaline (0·5–2 μg/kg) were potentiated to a much greater degree than were the increases induced by noradrenaline injected directly into the leg. These experiments suggested that the potentiation was not simply due to an increase in noradrenaline concentration locally in vessels of the perfused hind leg or to a change in receptor sensitivity.

In other anaesthetized dogs, arterial blood concentrations of noradrenaline were estimated by the blood-bathed organ technique (Vane, 1964). Rat stomach strips were superfused with arterial blood at 10 ml/min. Noradrenaline, which relaxed the strips, was injected either directly into the bathing blood to calibrate the assay tissues or intravenously into the dog. DMI did not substantially alter the relaxations of the rat stomach strips induced by direct injections of noradrenaline, either in degree or duration. The peak concentrations of noradrenaline in the arterial blood following intravenous injections (0·5–2 μg/kg) were no greater after treatment with DMI (3 mg/kg intravenously) than before. However, the relaxation of the rat stomach strip after intravenously injected noradrenaline was prolonged.