of magnesium was increased, the degree of potentiation of sympathomimetic responses compared to controls was decreased. Similar procedures in which the Ca^{2+} was used in Mg^{2+}-free solution showed that increasing the Ca^{2+} concentration also inhibited the degree of potentiation of the responses. However, at equimolar concentrations, the degree of potentiation of the sympathomimetic responses was less with the reduced Mg^{2+} than with the reduced Ca^{2+} solution.

Perfusion with either Ca^{2+}- and Mg^{2+}-free Krebs or with normal Krebs containing cocaine (50 ng/ml) antagonized the response to tyramine and had no effect on the response to octopamine, but potentiated the responses to metaraminol and noradrenaline. Perfusion with normal Krebs solution in the presence of ouabain 10^{-5} M, potentiated the responses to metaraminol and noradrenaline, but abolished the responses to tyramine and octopamine. Substitution with Ca^{2+}- and Mg^{2+}-free solution showed that ouabain had no effect on the tyramine response or on the responses to the other three amines. In the presence of a Krebs solution containing half the normal Mg^{2+} and no calcium, ouabain again had no effect. However, in the presence of solutions containing half the normal calcium and no magnesium, ouabain reduced the response to tyramine. Perfusion with 12 mM K^+ Krebs abolished the ouabain action indicating that ouabain was probably affecting the sodium-potassium ionic transfer system, possibly at the neuronal level.

Assuming that all the sympathomimetic amines, to which an indirect action is attributable, must enter, that is be taken up into, the adrenergic neurone before they effect a release of noradrenaline (Iversen, 1966), it would seem that there is probably more than one transport mechanism involved. These results may indicate the nature of the mechanism by which noradrenaline is released by the indirectly acting sympathomimetics.

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Myocardial effects of indoramin hydrochloride, a new hypotensive agent

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Indoramin, (3-(2-(4-benzamidopiperid-1-yl)ethyl)indole hydrochloride, Wy 21901), is a new potent hypotensive agent which combines α-adrenoreceptor blocking and cardio-inhibitory properties (Alps, Hill, Johnson & Wilson, 1970) and appears to provide a new mechanism of action for the treatment of hypertension in man. Like propranolol, indoramin causes bradycardia, reduced myocardial contractile force and decreased cardiac output in anaesthetized cats (Alps, Johnson & Wilson, 1970). It reduced the force and rate of contraction of the isolated rabbit heart and showed a potent local anaesthetic action (Alps, Hill, Johnson & Wilson, 1970). Because of these findings it seemed important to examine the electrophysiological effects of indoramin on the heart. Isolated canine myocardial strips were used in these experiments since in

previous studies canine myocardium has been shown to be as sensitive as human myocardium to the isomers of propranolol (Coltart & Meldrum, 1971).

The effect of varying concentrations of indoramin was studied on the action potential and contractile response of strips of canine ventricular muscle *in vitro*. Electrophysiological parameters were measured by conventional microelectrode techniques and contractile responses were assessed simultaneously by a strain gauge. At a concentration which occurs in human plasma after oral hypotensive doses of indoramin ($2{\cdot}6\times10^{-7}$ M), there was a statistically significant ($P=<0{\cdot}001$) decrease in V_{max} of depolarization, whereas resting potential, action potential amplitude, repolarization time and the contractile response were unchanged. Only with much higher concentrations of indoramin ($2{\cdot}6\times10^{-5}$ M–$4{\cdot}16\times10^{-4}$ M) was a reduction of contractile response demonstrated. In this respect, indoramin differed from (±)-propranolol which showed a clear dissociation between the concentration of the drug producing maximal β-blockade in man and that demonstrating a quinidine-like decrease of the V_{max} of depolarization on the human myocardial action potential (Coltart, 1971; Coltart & Meldrum, 1971).

Indoramin is of interest because it has a membrane stabilizing effect *in vitro* at a concentration which occurs in human plasma after administration of effective hypotensive doses of the drug, but the electrophysiological change is not accompanied by direct depression of the myocardial contractile response. Thus the alteration in myocardial contractility caused by indoramin would seem to be due to other properties, possibly including blockade of cardiac α-adrenoreceptors (Govier, 1968). Unlike propranolol, therapeutic concentrations of indoramin produce a decrease in the depolarization rate of the myocardium which may prove beneficial in the suppression of cardiac arrhythmias.

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Relative potency of intravenous prinodolol and propranolol in man

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Prinodolol (LB 46) a β-adrenoceptor blocking drug, is 4·6 times more potent than propranolol on isolated tissues (Saameli, 1967) and 20–40 times more potent than propranolol when administered orally to man (Hill & Turner, 1969).

This communication compares the effects of intravenous administration of prino-