myocardium (in a developing infarct). Carbochromen (2 mg/kg intravenously) usually increased blood flow in the normal myocardium (myocardial thermal conductivity increment increased from $3{\cdot}3 \pm 0{\cdot}5 \times 10^{-4}$ cal.cm^{-1}.sec.$^{-1}$.°C^{-1} to $5{\cdot}5 \pm 0{\cdot}6$ units; a mean increase of 67%), decreased myocardial vascular resistance from 54 ± 6 arbitrary units to 31 ± 3 units (43%) and depressed myocardial "corrected temperature", an index of metabolic heat production, by $-0{\cdot}22 \pm 0{\cdot}03$° C. These myocardial effects lasted for about an hour. In this dose carbochromen did not influence either systemic arterial pressure or heart rate.

Effects on that part of myocardial energy lost as heat may be a mechanism by which organic nitrites and nitrates, and β-receptor blocking drugs, benefit the anginal patient (Grayson, Irvine & Parratt, 1967; Parratt, 1969). If this is so carbochromen might also be effective in this condition.

Acute ligation of the descending branch of the left coronary artery in dogs causes a marked reduction in local blood flow in the region of the myocardium (apex) supplied by this vessel. This is due to a progressive vasoconstriction leading to a total closure of the microcirculation in about six hours (Grayson & Lapin, 1966; Grayson, Irvine, Parratt & Cunningham, 1968). During this period injections of carbochromen decreased metabolic heat production in the myocardium and were still capable of dilating the vessels of the microcirculation (Fig. 1). We regard this as further evidence that the ischaemia that follows acute coronary occlusion is the result of an active vasoconstriction. The available evidence (Grayson *et al.*, 1968) suggests that this is due to activation of α-adrenotropic receptors in the myocardial microcirculation.

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The effect of "selective" beta-receptor blocking drugs on the myocardial circulation

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There is still some doubt as to the nature of the direct effect of the catecholamines on the vessels of the myocardial circulation. Sympathetic amines probably mainly

induce coronary vasodilatation through stimulation of myocardial metabolism, but part of this effect may be mediated through direct effects on myocardial vascular β-receptors (Parratt, 1967). We have used "selective" β_1 and β_2 adrenoreceptor blocking agents, that is I.C.I. 50172 (Dunlop & Shanks, 1968), which abolishes effects of catecholamines on heart rate and on contractility (β_1 effects) but not on vascular β_2-receptors and butoxamine (Wilkenfeld & Levy, 1968) and H 35/25 (1-(4'-methylphenyl)-2-isopropylamino-propanol; Levy & Wilkenfeld, 1969), which selectively block vascular β_2-receptors.

A heated thermocouple technique (Grayson & Parratt, 1966) was used to assess changes in blood flow in the muscle of the left ventricle in cats anaesthetized with pentobarbitone. The method measures myocardial thermal conductivity increment, Δ k (an index of local blood flow) and "corrected temperature" (an index of metabolic heat production) (McInnes & Parratt, 1969). Infusions of isoprenaline (0·25 μg/kg per min) were given before, and at various times after, I.C.I. 50172, butoxamine or H 35/25. I.C.I. 50172 (10 mg/kg intravenously) had little direct effect on myocardial blood flow (mean change +5%), myocardial vascular resistance, (—2%), "corrected temperature" (change $< -0{\cdot}01°$ C), diastolic arterial pressure (change $< +4$ mm Hg) or heart rate (—12%). It reduced the effects of isoprenaline on heart rate and myocardial blood flow without influencing the effect on diastolic pressure. It proved impossible completely to block β_1 effects without affecting β_2 (vascular) effects. Before I.C.I. 50172, isoprenaline increased heart rate by 50 ± 7 beats/min and Δk by $2{\cdot}1 \pm 0{\cdot}4 \times 10^{-4}$ cal.cm^{-1} sec^{-1} °C^{-1} and decreased diastolic pressure by $4{\cdot}3 \pm 2$ mm Hg. The corresponding figures after I.C.I. 50172 were 20 ± 1 beats/min, $0{\cdot}8 \pm 2 \times 10^{-4}$ cal.cm^{-1} sec^{-1} °C^{-1} and -10 ± 1 mm Hg.

It was more difficult selectively to block β_2-receptors with H 35/25 (5 mg/kg) or butoxamine (5 mg/kg). However, in three experiments with each substance, the effects of isoprenaline on heart rate were unaffected (mean increase +40 beats/min before the blocking agents and +37 beats/min after them) and yet the effect of isoprenaline on diastolic pressure was reversed (mean of —10 mm Hg before blockade and +2 mm Hg after). The isoprenaline-induced increase in myocardial blood flow was unaffected (mean increase in Δk, $+2{\cdot}6 \times 10^{-4}$ cal.cm^{-1} sec^{-1} °C^{-1} both before and after blockade). When H 35/25 blocked both β_1 and β_2 receptors the effect of isoprenaline on myocardial blood flow was much reduced.

These results suggest that, in the cat, the increase in myocardial blood flow produced by isoprenaline results from stimulation of β_1 (myocardial) receptors; the vasoactive substance presumably released through stimulation of myocardial metabolism does not increase blood flow by an action on myocardial vascular (β_2) receptors.

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A comparison of the effects of bretylium, lignocaine and propranolol on experimental cardiac arrhythmias

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Propranolol and lignocaine are widely used in the treatment of cardiac arrhythmias in man. On the basis of observations in animals it has been suggested that there are two ways in which propranolol may abolish experimental cardiac arrhythmias. Its effect on arrhythmias induced by a catecholamine has been attributed to blockade of beta receptors for catecholamines, while its effect on ouabain-induced arrhythmias has been attributed to a local anaesthetic effect similar to that of quinidine and procaine (Barrett & Cullum, 1968). Recently it has been suggested that bretylium has anti-arrhythmic properties (Bacaner, 1968). We have compared the effects of these three drugs on two types of experimental arrhythmias.

In dogs anaesthetized with morphine and pentobarbitone and respired with room air and 1% halothane increasing doses of adrenaline (0·2–6·4 μg/kg) were given by intravenous injection until a period of ventricular ectopic beats, lasting at least 10 sec, was produced. The adrenaline challenge was repeated after propranolol (0·05 μg/kg) and increasing doses of lignocaine (0·8 to 6·4 μg/kg), using four and five dogs respectively for each drug. Lignocaine was much less effective than propranolol in abolishing these arrhythmias. In seven dogs a fixed dose of bretylium tosylate was given and the adrenaline challenge repeated at hourly intervals. In two dogs the intravenous injection of bretylium (10 mg/kg) had no effect on the arrhythmia. In four out of five dogs bretylium (20 mg/kg) protected from the arrhythmia when tested two or more hours later. The adrenaline arrhythmias were potentiated during the first hour after bretylium administration.

Ventricular or nodal tachycardia was produced in dogs anaesthetized with morphine and pentobarbitone, by the intravenous injection of ouabain. After establishment of the arrhythmia the test compound was infused intravenously. In three dogs the mean dose of propranolol to abolish the arrhythmia was 1·9 mg/kg and in three given lignocaine, 3·0 mg/kg when infused at 0·2 mg/kg per min and 2·2 mg/kg when infused at 1·0 mg/kg per min. The intravenous infusion of bretylium at a rate of 0·2 mg/kg per min resulted in the restoration of sinus rhythm after 15·9 mg/kg and in three others intravenous infusion of bretylium (20 mg/kg) over twenty minutes resulted in the return of sinus rhythm, at 12, 41 and 52 min respectively after starting the infusion.

These studies indicate that lignocaine and bretylium can abolish experimental cardiac arrhythmias. The mode of action of bretylium on these arrhythmias is obscure as it does not appear to possess quinidine-like or local anaesthetic activities (Papp & Vaughan Williams, 1969).