dolol and propranolol. The plasma half life of prinodolol was found to be 3·34 h (S.D.±0·24). This compares with a value of 2·34 h (S.D.±0·22) for propranolol (Shand, Nuckolls & Oates, 1970).

Preliminary double blind studies in four volunteers showed that intravenous prinodolol (0·25 and 0·5 mg) produced a dose-response inhibition of tachycardia induced by isoprenaline aerosol and that the effect of propranolol (5 mg) was intermediate between the two doses of prinodolol.

In a double blind definitive study, prinodolol (0·1 and 0·5 mg) and propranolol (2 and 10 mg) were administered intravenously to four normal male subjects (20–40 years) and the inhibition of exercise tachycardia measured at 15, 60 and 240 min after injection, using a bicycle ergometer, and an electrocardiograph for recording heart rate. At rest the dose-response relationship for the two drugs was in opposite directions, propranolol producing a fall and prinodolol a rise in resting heart rate. Both drugs produced a significant dose-dependent inhibition of exercise tachycardia throughout the experimental period. The potency ratio of prinodolol to propranolol was between 5 and 10 to 1.

Measurement of plasma concentrations of both drugs (propranolol by the method of Shand, Nuckolls & Oates (1970) and prinodolol by a slight modification of that used by Pacha (1969)) showed that the mean concentration of prinodolol 15 min after the administration of 0·5 mg was 6·2 ng/ml (S.D.±1·6) and that of propranolol 15 min after administration of 10 mg was 88·5 ng/ml (S.D.±15·6). There was a linear fall in heart rate with increasing log plasma drug concentration and this was similar for both compounds in all subjects. The common slope was b=−12·6, indicating that a 10-fold increase in plasma concentration of either drug would produce a mean decrease in heart rate of 12·6 beats/minute.

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Interaction between phosphodiesterase inhibitors and catecholamines on contractions of the cat soleus muscle

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β-Adrenoceptor agonists produce a decrease in peak tension and an increase in the rate of relaxation of the maximal twitch of the slow-contracting cat soleus muscle (Bowman & Zaimis, 1958). The effect is consistent with an enhanced rate of decline of the active state of the stimulated muscle. The changes produced in the unit of contraction result in a marked decrease in fusion and in tension when subtetanic contractions are elicited by frequencies of stimulation that include the physiological range (5–15 Hz). This effect of β-adrenoceptor agonists also occurs in slow-contracting

units in human muscles (Marsden & Meadows, 1968) and probably underlies the muscle tremor that often occurs as an unwanted effect of sympathomimetic bronchodilators. Figure 1 illustrates such an effect on the cat soleus muscle. (—)-Adrenaline (1 μg/kg i.v.) caused a marked reduction in the tension of the clonus evoked by indirect stimulation. This was associated with an increase in the speed of relaxation of each contractile component of the clonus. Gross muscle action potentials were not reduced.

The compounds ICI 58, 301 (3-acetamido-6-methyl-8-n-propyl-*syn*-triazolo [4,3-a] pyrazine), ICI 61, 129(3-acetamido-5-methyl-8-n-propyl-*syn*-triazolo [4,3-a] pyrazine) and ICI 63, 197 (2-amino-6-methyl-7-oxo-8-n-propyl-*syn*-triazolo [4,3-a] pyrazine) are inhibitors of cyclic AMP phosphodiesterase (Somerville, Rabouhans & Smith, 1970). In intravenous doses that by themselves were without effect on contraction, ICI 58, 301 (0·5 mg/kg) and ICI 63, 197 (50 μg/kg) potentiated (—)-adrenaline and (—)-isoprenaline in their actions on the soleus muscle. ICI 61, 129 was without effect in doses of up to 10 mg/kg. The effect of the catecholamines (before or after the phosphodiesterase inhibitors) was blocked by propranolol (100 μg/kg) or sotalol (5 mg/kg).

The rank order of potency of the compounds in potentiating catecholamines was

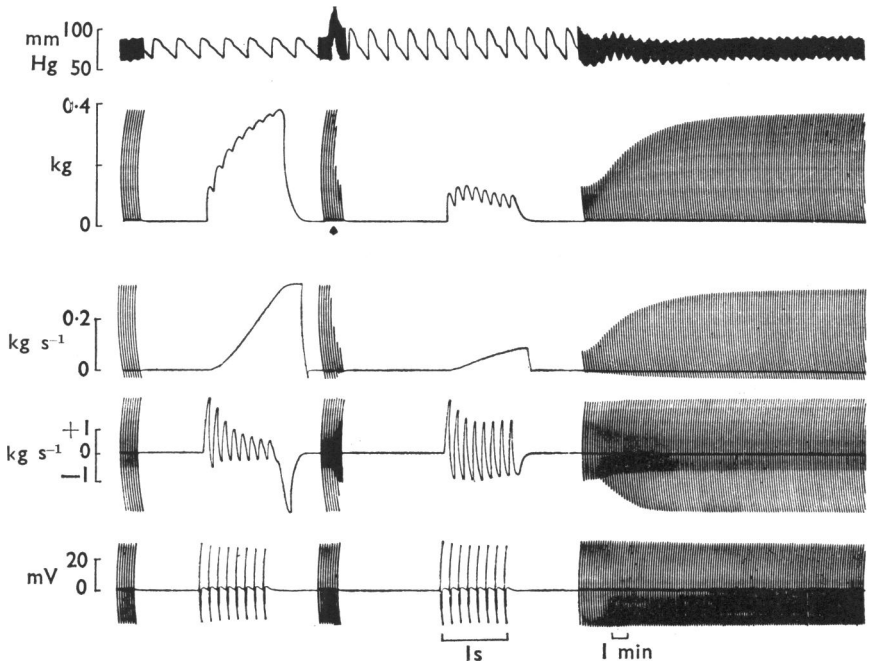

FIG. 1. Cat 2·2 kg. Effect of (—)-adrenaline (1 μg/kg i.v. at the arrow) on the contractions of the soleus muscle evoked by stimulating the motor nerve at a frequency of 8 Hz for 1 s every 10 seconds. The pen recording includes two contractions recorded on fast moving paper. The successive records from the top downwards are general arterial blood pressure, soleus muscle tension, tension time integral, rate of development of tension and gross muscle action potential respectively.

the same as that determined by Somerville, Rabouhans & Smith (1970) (and personal communication) for their phosphodiesterase inhibiting activity. The results are therefore compatible with the hypothesis of Sutherland & Robison (1966) that effects evoked via β-receptors are mediated by cyclic AMP.

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α-Adrenoceptor mediation of central hyperthermic responses to noradrenaline in rabbits (T)

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