significantly different from control at 10 mg/kg ($P < 0.01$ Student t). It was significantly less potent than ICI 63197 ($P < 0.01$ analysis of variance) and a 10 mg/kg dose of diazepam was equipotent with a 5 mg/kg dose of ICI 63197. The theophylline effect also increased with dose ($P < 0.01$ analysis of variance). It was less potent than ICI 63197 ($P < 0.01$ analysis of variance), both 20 mg/kg and 40 mg/kg giving the same difference from control values as 10 mg/kg of ICI 63197.

Desipramine (3.75, 7.5 and 15 mg/kg i.p.) and trifluoperazine (1.25, 2.5 and 5 mg/kg, i.p.) both of which have been shown to have phosphodiesterase inhibiting properties *in vitro* (Janiec, Korczak-Dziuba & Herman, 1974) showed the same potency as the lowest dose used of ICI 63197 but showed no dose response relationship.

The model appears to be a convenient one to evaluate the *in vivo* potency of potential central phosphodiesterase inhibition.

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The effect of chronic administration of D-penicillamine on the rat pancreas

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In response to secretin the exocrine pancreas secretes a watery juice rich in bicarbonate. There is evidence to suggest that this secretion is produced by ductular elements (Bencosme & Lechago, 1971) which comprise less than five per cent of the mass of the gland (Bolender, 1974).

Feeding rats a copper deficient diet containing D-penicillamine (2 g/kg) selectively destroys pancreatic acinar tissue whilst leaving ductular elements functionally intact (Folsch & Creutzfeldt, 1976). After six weeks on this diet weaning rats exhibited a reduced rate of growth and a much reduced pancreas. Light microscopy indicated a non-inflammatory atrophy and fatty infiltration of pancreatic acinar tissue. Ductular elements were unaffected.

Amylase activity was markedly decreased in pancreatic homogenates from penicillamine treated animals whereas the activities of Mg^{2+} and Ca^{2+} stimulated adenosine triphosphatases (ATPases) together with succinic dehydrogenase (SDH) increased (Table 1). The ratio of the mean enzyme activities in penicillamine treated and control animals was about the same for Mg^{2+}-ATPase (2.7), Ca^{2+}-ATPase (3.2) and the mitochondrial marker SDH (2.6), suggesting that the elevated ATPase activities could have resulted from a relative increase in the concentration of mitochondria in the tissue.

The hormone responsiveness of the duct cells was investigated by determining the effects of secretin on cyclic AMP levels *in vitro*. In unstimulated glands the cyclic AMP levels for control and penicillamine treated animals were 4.7 ± 0.6 (24) and 23.8 ± 6.0 (24) μmoles cyclic AMP/kg protein ($P < 0.004$) and in the presence of secretin (0.25 C.U./ml) 10.9 ± 1.2 (24) and 77.8 ± 10.1 (24) μmoles cyclic AMP/kg protein ($P < 0.0005$). The magnitude of this stimulation was 2.3 and 3.3 times in control and penicillamine treated animals respectively, indicating that the sensitivity of the gland to secretin is not decreased by penicillamine treatment.

Table 1 Enzyme activities in pancreatic homogenates from control and penicillamine treated rats. The values indicated are the mean ± s.e. mean (no. of animals). For all enzymes the control and treated activities are significantly different, $P \leqslant 0.005$ (Mann-Whitney U test)

Enzyme	*Control*	*Penicillamine treated*
Amylase (i.u./mg DNA)	35,258.6 ± 5361.7 (7)	118.9 ± 43.6 (23)
Succinic Dehydrogenase (μmoles Formazan min^{-1} mg DNA^{-1})	162.4 ± 32.5 (7)	415.3 ± 60.4 (23)
ATPases (μmoles Pi min^{-1} mg DNA^{-1})		
(1) Mg^{2+}-ATPase	19.3 ± 2.2 (7)	51.5 ± 7.7 (23)
(2) Ca^{2+}-ATPase	19.5 ± 2.4 (7)	62.2 ± 8.5 (23)

It is concluded that this preparation may prove a useful model for the study of pancreatic duct cells.

Financed by the Cystic Fibrosis Research Trust.

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Inhibition of rabbit muscle pyruvate kinase by lithium

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Lithium is of importance in the prophylactic treatment of manic-depressive psychoses but its exact mode of action is not known. It has been suggested that an important aspect of its action is via interaction with magnesium dependent enzymes (Birch, 1974). Lithium was originally shown to inhibit pyruvate kinase by Kachmar & Boyer (1953) though the level of lithium used was very high (100 mM). A preliminary report of lithium's action on a number of magnesium dependent enzymes has been made (Birch, Hullin, Inie & Leaf, 1974).

The present work was undertaken to provide a detailed investigation of the inhibition of pyruvate kinase by lithium. The interaction of lithium with all the substrates of the enzyme was examined and the results indicate that lithium was competitive with respect to ADP binding to the enzyme and non-competitive with respect to all other substrates. Under the normal assay conditions (85 mM Tris.HCl buffer, pH 7.5, 0.5 mM phosphoenolpyruvate, 10 mM magnesium chloride, 5 mM ADP, 20 mM potassium chloride, 0.25 mM NADH and excess lactate dehydrogenase) 10 mM lithium produced a 16–24% inhibition of the maximum pyruvate kinase activity. This is a lower level of inhibition than indicated by the previous preliminary study (Birch *et al.*, 1974) but is still at a significant level. At the intracellular ADP concentrations of approximately 1.2 mM the level of inhibition is markedly increased. Further work to discriminate between a specific lithium, general ion, or ionic strength phenomena showed that it was not a general ion nor ionic strength effect but that inhibition was also found with calcium and sodium, the order of inhibition being calcium > lithium > sodium. Kinetic investigation showed that the calcium inhibition was of a similar type to lithium, i.e. competitive to ADP binding. However calcium levels unlike lithium levels are rigidly controlled by the body and so the inhibition of pyruvate kinase by calcium is unlikely to be of physiological significance.

The prophylactic dose of lithium gives a plasma lithium level of 0.6–1.4 mM (Hullin, McDonald & Allsopp, 1972) and at this level the inhibition of pyruvate kinase is insignificant. There is still the possibility however of accumulation of lithium in certain body tissues. Should the level be raised to 4 or 5 mM the level of inhibition would be significant especially at the intracellular ADP level. Whether these conditions of 4–5 mM lithium are likely is open to question.