Hyperglycaemia and insulin inhibition caused by drugs may be more common than hitherto believed, and studies both of structure-function relationships as well as mechanisms of insulin inhibition may throw light on a possible contributory cause of eventual insulin failure and the development of diabetes mellitus.

The relationship between chemical structure of a new dicarboxylic amino-acid derivative and antigastrin activity in the rat

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The antisecretory non-anticholinergic activity of a series of amino-acid derivatives (Rovati, Casula & Da Re, 1967a) has previously been investigated. The pharmacological properties of one of them N-benzoyl-N′,N′-di-*n*-propyl-DL-isoglutamine (CR 242*, xylamide†, Milid‡) (Rovati, Casula & Da Re, 1967b) was particularly studied.

Sixty rats were treated according to a technique modified from Lai (1964). The gastric secretion was stimulated by "Leo" gastrin tetrapeptide through continuous intravenous infusion at a dose of 25 mg/kg per hr. The infusion lasted 2 hr and secretion was collected every 10 min. An hour later, xylamide was injected intravenously at a dose of 500 mg/kg. A group of the animals was also injected with N-benzoyl glutamic acid which is xylamide less the amide group at equimolecular doses. Atropine at a dose of 30 mg/kg was also used. Histamine acid phosphate (5 mg/kg) and histamine and gastrin tetrapeptide at the doses indicated were also used as stimulating agents. The results obtained demonstrate that: (1) the stimulation induced by gastrin tetrapeptide gives a secretory response with a regression line of $y=0.096x+7.89$ ($F=29.3$) where $y=\mu$-equi H^+ and $x=$time in min; (2) xylamide produced a reduction of secretion that during the first 30 min diminished according to the regression line: $y=-0.466x+19.56$ ($F=22.90$); (3) N-benzoyl glutamic acid had no activity; (4) xylamide is also effective against histamine but ineffective against a combination of histamine and gastrin tetrapeptide. It seems important to emphasize the anti-gastrin activity of xylamide and the complete ineffectiveness of N-benzoyl glutamic acid. These compounds differ by an amide group. In the same way, gastrin lacks activity when the amide of the terminal amino-acid is missing (Gregory & Tracy, 1964).

* Laboratory denomination. † Common name. ‡ Trademark.

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Alloxan on islet cell membrane potentials

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The powerful diabetogenic action of alloxan may be explained by its ability to alter the permeability of pancreatic β-cells (Watkins, Cooperstein & Lazarow, 1964).

We now have evidence of a very rapid and sustained effect of alloxan on the electrical properties of islet cells.

Segments of mouse pancreas were placed in a Perspex tissue bath and maintained at 37° C in oxygenated Krebs–Henseleit solution containing glucose (2.7 mM). The islets of Langerhans were exposed by micro-dissection and potassium-citrate filled glass micro-electrodes used to record the cellular transmembrane potentials by methods described previously (Matthews, 1967).

Islet cells had normally a membrane potential of -19.9 mV $\pm$ S.E. 1.1 mV ($n=620$ impalements). In the presence of alloxan (5 mM) the islet cells rapidly depolarized. After about 15 min exposure the membrane potential had fallen to -10 mV; it was not restored after washing out the alloxan for 60 min. In contrast, the membrane potential recorded from pancreatic acinar cells was unaffected by alloxan (5 mM) and remained stable at -38.8 mV $\pm$ S.E. 2.1 mV ($n=79$) throughout.

It has been reported that glutathione protects islet cells against the action of alloxan (Watkins, Cooperstein & Lazarow, 1964). Preincubation of the pancreatic tissue with glutathione (10 mM) for 10 min did not, however, prevent the depolarization of islet cells by alloxan. On the other hand, if the islets were pretreated for 10 min with glucose (16.6 mM), alloxan (5 mM) no longer caused depolarization. Another stimulant of insulin secretion, L-leucine (15 mM), in these conditions did not prevent the depolarization by alloxan. Thus the protection by 16.6 mM glucose against alloxan induced depolarization may indicate an action of the glucose molecule at the alloxan "receptor" rather than an effect on the acceleration of the insulin secretion mechanism.

Maske & Weinges (1957) have shown that guinea-pigs are resistant to the diabetogenic effect of alloxan. Guinea-pig islet cells had a membrane potential of -20.6 mV $\pm$ S.E. 1.7 mV ($n=123$). and did not depolarize even when the concentration of alloxan was increased to 15 mM.

There appears, therefore, good correlation between the electro-pharmacological effects and the remarkable susceptibility of islet β-cells to alloxan.

P. M. D. is an M.R.C. Research Scholar. The work was supported by a grant from the Medical Research Council.

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Acemoquinazone, a new choleretic agent

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Acemoquinazone (1-morpholinoacetyl-3-phenyl-2,3-dihydro-4(1H)-quinazolinone), synthesized by Bonola, de Re, Massarani, Magistretti & Setnikar (1968) has a remarkable choleretic action, in rats, guinea-pigs, rabbits and dogs. This is a "true" choleretic activity, for the drug increases the excretion of dry residue and particularly of bilirubin and cholesterol. This activity was observed in all the species examined, at doses of 6–25 mg/kg, intraduodenally. In comparison with