there is also present the antigenicity of the histocompatibility loci. This was done by transplanting the L1210 leukaemia in mice (F_3) obtained from the mating of the backcrosses (C57BL/6 female × DBA/2 male)F_1 × DBA/2 male. In these animals the proportion of C57BL/6 homozygosis is 1/16 and that of the mice susceptible to the L1210 is therefore $(15/16)^n$ (n = number of histocompatibility loci admitting independent antigenicities).

The results (Table 1) first indicate that treatment with methotrexate (0.65 mg/kg per day for 4 days) or with arabinosyl cytosine, although prolonging the average survival time, does not elicit any increase in the percentage of the 50-day survivors. In mice treated with a higher, but non-toxic, dose of methotrexate (0.65 mg/kg per day for 12 days) the proportion of 50-day survivors was markedly reduced. In both treated and control groups, all the 50-day survivors were resistant to the intraperitoneal reinoculation of 2×10^3 L1210 ascites cells, thus demonstrating that the regression of the leukaemia was brought about by immunological mechanisms.

The results also show that the number of histocompatibility loci which is able to hinder the development of the lymphoma depends on the size of inoculum, being of about two loci in the mice transplanted with 2×10^6 leukaemic spleen cells and of three to four in those inoculated with 2×10^3 L1210 ascites cells.

These results strongly suggest that the immunosuppressive activity of antineoplastic agents can reduce the ultimate therapeutic effects of antitumour treatments.

Structure activity of diuretics as hyperglycaemic agents

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We have investigated structural changes in the chlorthalidone (1-oxo-3-(3′-sulphamyl-4′-chlorophenyl)-3-hydroxyisoindoline) molecule and have prepared a compound C3/76 (1-oxo-3-(4′-chlorophenyl)-3-hydroxyisoindoline). This is anti-diuretic in the water-loaded rat and shows prolonged and marked hyperglycaemic and insulin inhibiting effects, being in this respect several times more potent than chlorthalidone. Removal of the sulphamyl group led to loss of diuretic activity, and caused anti-diuresis as well as hyperglycaemia associated with insulin inhibition, similar to that found in the development of diazoxide from chlorothiazide.

In our laboratory we have prepared demethylated diazoxide (3-methyl-7-chloro-1,2,4-benzothiadiazine-1,1-dioxide) (AO25), which shows good hyperglycaemic activity and in contrast to diazoxide, little toxicity and no anti-diuretic activity in the rat, both orally and intraperitoneally. It also inhibits insulin secretion *in vitro*. Larger doses of AO25 intravenously in the Rhesus monkey produced hyperglycaemia, reduced plasma insulin level, and a moderate diuresis.

Tolbutamide in the anaesthetized as well as unanaesthetized dog interferes with all three parameters of diazoxide action, on pancreatic islet cells, kidneys, and blood vessels. It also interferes with the action of diazoxide on the isolated rat renal artery. Tolbutamide also interferes with the hyperglycaemic and hypotensive action of AO25. In view of the similarity of tolbutamide and the benzothiadiazines, a competitive inhibition is postulated.

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).