action. The following phenomena have been examined following the administration of insulin (0.15 units/kg) to normal volunteers: (1) pupillary size measured by intra-ved pupillography with unilateral ophthalmic sympathetic blockade; (2) heart rate during complete \( \beta \) and a/\( \beta \) blockade; (3) the rate of secretion of parotid saliva; (4) sweat production measured by a microhygrometer. The results indicate a selective cholinergic component in the hypoglycaemic reaction.

HORMONAL AND METABOLIC EFFECTS OF CHLOR-
PROPAMIDE AND GLIBENCLAMIDE IN A CROSS-OVER
STUDY IN PATIENTS WITH DIABETES MELLITUS
St Thomas' Hospital Medical School, London

Although sulphonylurea drugs are widely used in the treatment of 'maturity-onset' diabetes, their mechanism of action is disputed. We have compared the hormonal and metabolic effects of chlorpropamide and glibenclamide in a 16 month cross-over study of twenty diabetic patients. These patients' glucose tolerance had not responded to an average of 2 months diet treatment alone, even though their weights were then less than 115% of desirable. Each patient underwent 100g, 5 h oral glucose tolerance tests (OGTTs) after: (1) diet therapy alone; (2) diet plus one sulphonylurea (randomly allocated); (3) diet plus a placebo; (4) diet plus the other sulphonylurea; (5) diet plus a placebo. Glucose tolerance and insulin secretion, which had improved marginally in diet therapy alone, improved markedly after sulphonylurea treatment, only to relapse on placebo, as shown in Table 1. We found no significant differences between results after the different sulphonylureas and all twenty-values have been taken together.

**Table 1**

| Glucose area* (mmol/l) h 80±4 53±4 78±6 56±5 78±6 | OGTT No. 1 2 3 4 5 |
|---|---|---|---|---|---|
| Insulin area* (mU/l) h 55±9 88±9 60±11 99±12 67±11 | --- |

*Values are means±SEM for the total areas between response curves and abscissa.

Ketone body, free fatty acids (FFA) and glycerol concentrations were lowest after sulphonylurea treatments. Lactate, pyruvate and growth hormone concentrations throughout OGTTs and fasting cholesterol and triglyceride concentrations were lowest after sulphonylurea treatments. Lactate, pyruvate and growth hormone concentrations throughout OGTTs and fasting cholesterol and triglyceride concentrations did not relapse as far after OGTT 4.

These results suggest that the effects of both sulphonylureas studied are mediated by increased insulin secretion and there was some evidence of a progressive beneficial effect of treatment.

RELATIONSHIPS BETWEEN THE MOLECULAR STRUC-
TURE AND METABOLISM OF INSULIN
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Experiments with chemical analogues of neurotransmitters and hormones have been instrumental in increasing our understanding of the biological properties of such substances. Recent advances in protein chemistry have made this approach applicable to the study of the metabolism of insulin.

Metabolic clearance rate (MCR), half life (\( T_1/2 \)), apparent distribution space (DS) and urinary clearance (UC), of insulin, proinsulin and thirteen semisynthetic analogues of insulin have been measured by a priming-dose constant infusion technique in dogs.

Four analogues had modifications both at the N terminus of the A chain (\( A_1 \)) and near the C terminus of the B chain (\( B_{19} \)), and three of these had a synthetic crosslink between the two groups. Four analogues were modified solely at \( A_1 \), two at \( B_{19} \) and three at the N terminus of the B chain (\( B_1 \)).

At low plasma insulin concentrations MCR approached cardiac output (32 ml/minkg\(^{-1}\)) falling progressively to 15 ml/minkg\(^{-1}\) at concentrations of 200 \( \mu \)U/ml. Analogues modified at \( A_1 \) and \( B_{19} \), particularly the cross-linked materials, had markedly lower MCRs (4.5-8.8 ml/minkg\(^{-1}\)).

\( T_1/2 \) (4.6 min for insulin) was correspondingly prolonged for these analogues (10.6-13.5 min). There were no differences in DS.

\( A_1B_{19} \) modification increased urinary clearance fifteen-fold from 0.1 ml min\(^{-1}\) kg\(^{-1}\) for insulin to 1.5 ml min\(^{-1}\) kg\(^{-1}\).

\( B_1 \) modified analogues did not differ in any respect from insulin.

It is concluded that the mechanisms of insulin metabolism...