resorted to glyceryl trinitrate for every attack of angina pectoris. Even in those cases that had to be withdrawn from the trial the consumption of glyceryl trinitrate tablets in 24 hours was often of the order of one to three tablets. Patients limited their intake of glyceryl trinitrate for two reasons: they objected to "taking too many tablets" and the headache following glyceryl trinitrate was often extremely unpleasant. Relief from pain was obtained by a restriction of activity.

These findings differ markedly from those of many similar trials of drugs in the treatment of angina pectoris. Gillman and Prichard (1965) found a close correlation between glyceryl trinitrate consumption and angina attacks when working with propranolol.

Case 5 illustrates another aspect of the importance of the qualitative approach. When taking placebo this patient was confined to the house, physical activity was severely limited, and the slightest exertion precipitated his angina. On Trasacor therapy effort tolerance was greatly improved, so that pains were experienced and glyceryl trinitrate was taken only after severe exertion. Such marked improvement when on Trasacor therapy is not apparent from the Table, which depicts quantitative results only.

It is our opinion that in a trial of this nature more emphasis should be placed on qualitative results than has been customary in the past, as quantitative results can be misleading.

The abrupt replacement of Trasacor with placebo resulted in severe exacerbation of angina in seven patients, six of whom had to be withdrawn from the trial. This did not appear to be related to the dosage of the drug, which varied from 60 to 340 mg. daily in these cases. Perhaps the patients had become accustomed to a higher level of effort tolerance which could not be maintained once the Trasacor was discontinued. How-

ever, this does not appear to be the complete answer, as three patients suffered frequent angina attacks at rest and on effort for several days before reporting to the medical referee. Perhaps, in addition, there is some form of protracted "rebound" release of sympathetic drive when Trasacor is stopped abruptly. This finding suggests that caution should be exercised when stopping Trasacor in angina patients and that probably a count-down method should be used.

Patients who completed the trial commented on their sense of well-being and improved exercise tolerance during the Trasacor treatment periods. This contrasts with the mental depression reported following the use of propranolol (Waal, 1967). This may be explained by the difference in the haemodynamic effects of the two drugs (Wilson *et al.*, 1968).

We found that old age was no contraindication to Trasacor therapy and that large doses were well tolerated. One 76-year-old man had an optimum dosage of 340 mg. daily.

Conclusion.—This double-blind trial shows Trasacor to be non-toxic and a very useful drug for use in the treatment of angina pectoris.

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Preliminary Communications

Pituitary Polypeptide with Hypoglycaemic Action in Diabetes Mellitus

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Summary: A polypeptide isolated by the hydrolysis of growth hormone, studied in five patients with diabetes mellitus, has been shown able to produce hypoglycaemia, presumably by modifying the anti-insulin action of pituitary growth hormone. Possibly this substance may be suitable for treating cases of insulin resistance or when a circulating inhibitor of glucose uptake is present.

INTRODUCTION

Previously reported work (Bornstein *et al.*, 1968a) showed that hydrolysis of growth hormone yielded two ultrafilterable polypeptides, which by virtue of their specific action on the triose-phosphate dehydrogenases appeared capable of accounting for the early hypoglycaemic action of growth hormone (polypeptide ACG) and later the hyperglycaemic action of the hormone (polypeptide ING).

Further investigations (Bornstein *et al.*, 1969a) have shown that all actions of growth hormone on carbohydrate and fat metabolism may be accounted for by the actions of these two

polypeptides, since polypeptide ING inhibits glycolysis and fat synthesis while accelerating lipolysis, and polypeptide ACG is hypoglycaemic and able to reverse all inhibitions produced by ING.

All this previous work had been carried out in animals, but in view of these findings we decided to investigate the effect of polypeptide ACG on the hyperglycaemia of patients suffering from diabetes mellitus.

PRESENT INVESTIGATION

Techniques.—Polypeptide ACG was prepared from ovine growth hormone according to the technique previously described (Bornstein *et al.*, 1968b) and sterilized for use by ultrafiltration. The yield was 5 mg. from 2 g. of growth hormone, representing 500 g. wet weight of ovine pituitaries. The activity of each preparation was assayed by its ability to reverse the inhibition of glyceraldehyde-3-phosphate dehydrogenase produced by a standard concentration of ING. Blood glucose estimations were done by Dr. J. Owen, of the Biochemistry Department, Alfred Hospital, using the standard AutoAnalyzer technique. Plasma insulin estimations were done by using a modification of the double antibody immunoassay technique of Morgan and Lazarow (1963). The coefficient of variation of the method of a plasma pool containing 24 μ u./ml. was 8%.

Results of Injection of Polypeptide ACG into Patients Suffering from Diabetes Mellitus

	Case 1†		Case 2		Case 3		Case 4		Case 5		Mean change BG from Control
Age and sex . . .	46 M		44 M		41 M		32 M		28 M		
Duration (in years) . .	11		8		8		4		2/52		
Treatment* . . .	D		SU		SU		SU and BI		Nil		
Dose of ACG (in mg.)	0.25		1.0		1.0		2.0		1.0		
Time	BG	PI	BG	PI	BG	PI	BG	PI	BG	PI	
-30 minutes . .	260	18	240	13	350		310	20	285		
-15 minutes . .	270		245		365		320		285		
0 minutes . .	270	18	240	19	365	18	315	18	290	20	0
+20 minutes . .	235	24	235	16	340	19	315	21	265	4	-17 (P < 0.05)
+40 minutes . .	230	23	225		340		295		260		-25 (P < 0.01)
+60 minutes . .	260	20	215		325	8	295	21	250		-25 (P < 0.05)
+80 minutes . .	—		220		295		260		230		-51 (P < 0.02)
+100 minutes . .	—		210	22	315		255	20	240	3	-48 (P < 0.01)

* Treatment code: D=Diet only. SU=Sulphonylurea. BI=Biguanide. †Patient resistant to 100 units of insulin per day.

BG=Blood glucose levels, in mg./100 ml. PI=Plasma insulin levels, in μ u/ml.
Mean plasma insulin: 0 time = 18.6; 20 min. = 16.8.

Patients.—Five patients aged 28 to 46 years and with a history of diabetes varying from 2 weeks to 11 years were investigated. All gave informed consent to the studies. The details are given in the Table.

Experimental.—In all cases treatment was suspended for at least 48 hours before the experiment, the patient was fasted overnight, and a sample of blood was taken for glucose estimation and plasma insulin assay. The blood glucose level was then followed for 30 minutes, and at zero time a further sample of blood was taken for insulin assay and ACG injected intravenously. The blood glucose level was determined every 20 minutes for up to 100 minutes, samples for plasma insulin being taken at 20 minutes at least once again during the period of observation.

RESULTS

The Table shows the patients' histories, blood glucose levels, and plasma insulin levels during the experiment. The Chart shows the mean changes in blood glucose level in four of the patients, the fifth (Case 1) being excluded because of the low dose (0.25 mg.) of ACG given and the presence of insulin resistance.

A fall in blood glucose is observable at 20 minutes and except in Case 1 is progressive to 80 minutes and then sustained, all falls being statistically significant when compared with the mean blood glucose level of the control period. Further, this fall is not accompanied by any significant change in plasma insulin at 20 minutes.

DISCUSSION

The administration of ACG to patients in varying dosages consistently produced a fall in blood glucose, which in the dosage of 1 or 2 mg. was sustained for up to 100 minutes and possibly longer.

Change in blood glucose levels from starting value as a result of administration of ACG.

Thus the control of the blood glucose level may depend on the level of endogenous insulin, on the relative levels of ING and ACG, or on all three factors. It seems improbable that ACG alone would be sufficient to produce hypoglycaemia, but it is likely that ACG may have a very marked effect in increasing insulin sensitivity. Therefore ACG may have therapeutic possibilities in the treatment of cases of insulin resistance, particularly in ketoacidosis, since the polypeptide has been shown to inhibit lipolysis (Bornstein *et al.*, 1969b). Furthermore, there is the interesting possibility that patients who respond to ACG and who are capable of secreting insulin in response to variations in blood glucose level might possibly be stabilized without any requirement for dietary control, as their glucose metabolism would be controlled by endogenous insulin secretion.

Many investigators have found with some patients that hypophysectomy arrests the progress of vascular complications. Early in the current investigations it was shown that complicated cases of diabetes mellitus had a higher concentration of a circulating inhibitor of glucose uptake than uncomplicated cases (Bornstein and Hyde, 1959). It is conceivable that administration of ACG may have a prophylactic or therapeutic effect on these states.

Since the development of long-term clinical studies is hampered by the low yield of ACG (0.1% from growth hormone in the present technique) we are at present investigating methods of improving the yield, as well as studying the sequence of amino-acids in the ACG with a view to synthesis of the polypeptide.

The potentiating effect of ACG on insulin action is at present being tested and will be the subject of a later communication.

J. McD. ARMSTRONG, PH.D.,
Senior Lecturer in Biochemistry.

J. BORNSTEIN, M.D., D.S.C.,
Professor of Biochemistry.

F. M. NG, PH.D.,
Lecturer in Biochemistry.
Monash University, Victoria, Australia.

H. P. TAFT, M.D., F.R.A.C.P.,
Physician, Diabetic and Metabolic Unit, Alfred Hospital, Melbourne, Australia.

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