treatment restarted in this group were taking an average dose of 15 tablets (3·75 mg.) weekly when toxic effects were noted and were discharged subsequently on an average of 10 tablets (2·5 mg.) weekly. All patients were given potassium supplements to take whether diuretic treatment was envisaged or not.

In all, 59 elderly patients have been taken off digoxin. It would appear from the cases in group A that where treatment is instituted in the light of known cardiac disease, coronary artery disease, or hypertension it may have to be continued on a maintenance basis, even if the patient is symptomless, but that where treatment is started without a known primary cardiac lesion an opportunity should be taken to withdraw treatment after the heart is compensated before committing the patient to a maintenance regimen.

REFERENCES

British Medical Journal, 1964, **1**, 681.
Caird, F. I. (1963). *Postgraduate Medical Journal*, **39**, 408.
Dall, J. L. C. (1965). *Lancet*, **1**, 194.
Hurwitz, N., and Wade, O. L. (1969). *British Medical Journal*, **1**, 539.
Soffer, A. (1961). *Archives of Internal Medicine*, **107**, 681.
Von Capeller, D., Copeland, G. D., and Stern, T. N. (1959). *Annals of Internal Medicine*, **50**, 869.

Preliminary Communications

Increased Release of Gut Glucagon in Reactive Hypoglycaemia

British Medical Journal, 1970, **2**, 706–707

Summary: A patient with reactive hypoglycaemia showed hypersecretion of insulin in response to enteral beta-cell stimulation. Increased levels of gut glucagon-like immunoreactivity in serum were demonstrated by use of specific antisera. Other measurable hormones influencing carbohydrate metabolism were within normal limits. It is suggested that gut glucagon-like immunoreactivity may be of pathogenetic significance in reactive hypoglycaemia.

INTRODUCTION

Essential reactive hypoglycaemia forms about 70% of spontaneous hypoglycaemia (Conn and Seltzer, 1955). As hyperinsulinaemia alone cannot be responsible for reactive hypoglycaemia (Sussman *et al.*, 1966; Holdsworth *et al.*, 1969), the pathogenesis has remained obscure. Unger (1968) suggested that postprandial hypoglycaemia might be a consequence of pancreas glucagon deficiency. To investigate this possibility in a patient with severe reactive hypoglycaemia, serum levels of pancreas and gut glucagon-like immunoreactivity were measured with specific antisera (Heding, 1969).

One picogram equivalent of glucagon per ml. is defined as the amount of gut or pancreas glucagon-like immunoreactivity per ml. which can displace the same quantity of ^{125}I-glucagon from the antibodies as 1 picogram of crystalline pancreas glucagon per ml. It should be stressed that the dilution curve for gut glucagon-like immunoreactivity is linear in the assay.

CASE REPORT

A 55-year-old woman complained of weakness, dizziness, sweating, and anxiety three to five hours after larger meals. The symptoms had occurred four to six times a month for seven years. They were relieved by food or barley sugar. She had never become unconscious. On 23 October, 1968, she was admitted to hospital with a blood sugar of 22 mg./100 ml. and hypoglycaemic signs which were aborted by intravenous glucose. She was a thin middle-aged woman, height 5ft. 3in. (160 cm.) and weighing 42 kg. Retinopathy, palpable thyroid, enlarged liver, or surgical scars were not present. Neurological examination showed only a slightly increased patellar reflex.

Laboratory Data and Investigations. — Haemoglobin 12·7 g./100 ml., erythrocyte sedimentation rate 8 mm. per hour, white blood count 6,700/cu. mm. with a normal differential and normal red cell morphology. Urine analysis was normal. Serum creatinine, amylase, sodium, potassium, chloride, bicarbonate, calcium, and phosphate were normal. The basal metabolic rate was 113%, protein-bound iodine 4·5 μg./100 ml., and T3 test 2·8%—all within normal limits. The adrenocortical function was normal, as shown by repeated determinations of plasma hydrocortisone level, 24-hour urinary ketosteroid, and 17-ketogenic steroid excretion. *X*-ray examination of sella turcica was normal. Hypophysial function was found to be normal after the following tests: 24-hour urinary hypophysial gonadotropin excretion, metyrapone test, and serum growth hormone (Yde, 1968) levels after insulin stimulation. Serum alkaline phosphatase, aspartate aminotransferase, serum protein, and bromsulphthalein retention were all normal. Gastrointestinal function was tested, with the following results: gastric peak output of acid was 19·4 mEq/hr. after stimulation with 10 μg. of gastrin-tetrapeptide per kg. body weight; barium meal with nutritional contrast medium showed normal emptying of stomach and intestines and no evidence of ulceration; and urinary D-xylose excretion after administration of 25 g. of xylose was normal.

CARBOHYDRATE TOLERANCE TESTS

The immunoreactive insulin and glucagon-like immunoreactivity were studied (see Table). The patient was maintained on a diet containing 250 g. of carbohydrate daily, and at least three days elapsed between tests, which were all made in the morning, after the patient had fasted for 12 hours. Blood was drawn from the antecubital vein without stasis. For the glucagon assay the blood was heparinized and 1 ml. of aprotinin (Trasylol) (5,000 kallikrein inactivating units per ml.) was added per 10 ml. of blood. The blood was then shaken, immediately centrifuged, and deep-frozen at −30° C. Blood glucose was measured by a glucose oxidase method (Christensen, 1967). Plasma insulin levels were determined by the immunoassay of Ørskov (1967) and pancreas and gut glucagon-like immunoreactivity by the method of Heding (1969), using two different anti-glucagon sera—one specific for pancreatic glucagon, the other reacting with both pancreatic and gut glucagon-like immunoreactivity.

Carbohydrate Tolerance Tests

Test	Agent	Route of Administration	Dose
Prolonged glucose (6 hours)	Glucose	Oral	100 g.
Tolbutamide ..	Sodium tolbutamide	Intravenous	1 g.
Glucagon ..	Insulin-free glucagon	Intramuscular	1 mg.
Leucine	L-Leucine	Oral	250 mg./kg.
Gastrin	Gastrin-tetrapeptide	Subcutaneous	10 μg./kg.
Prolonged fasting (72 hours)			

The plasma insulin and blood glucose levels after enteral glucose-loading and parenteral stimulation with pancreatic glucagon, tolbutamide, and tetragastrin are shown in Fig. 1. Enteral stimulation produced a significantly higher insulin response than did the varied parenteral stimulation.

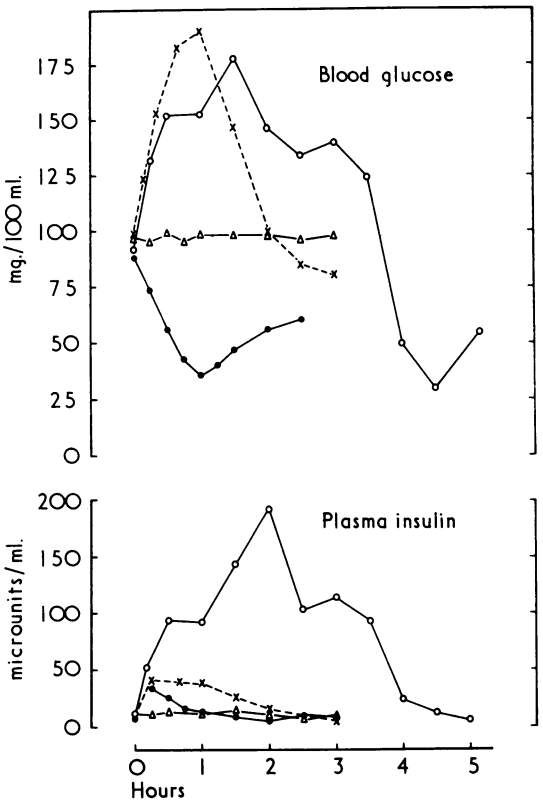

FIG. 1.—Blood glucose concentration and plasma insulin levels during loadings with 100 g. glucose per os (o————o), 1 mg. glucagon intramuscularly (x————x), 0·42 mg. gastrin-tetrapeptide subcutaneously (△————△), and 1 g. tolbutamide (Rastinon) intravenously (●————●).

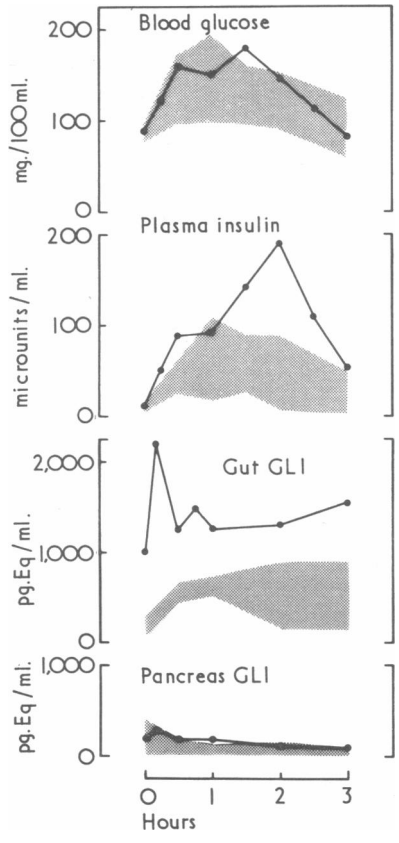

FIG. 2.—Blood glucose, plasma insulin, and pancreas and gut glucagon-like immunoreactivity (GLI) during an oral glucose loading (100 g.) in the patient (●————●) and seven normal subjects (shaded area) (mean ± 2 S.D.),

The plasma insulin, blood glucose, and pancreas and gut glucagon-like immunoreactivity during oral glucose loading compared with the response in seven normal persons are shown in Fig. 2. While pancreas glucagon-like immunoreactivity levels are not significantly different from normal, gut glucagon-like immunoreactivity concentrations are above the normal mean + 2 S.D.

DISCUSSION

The hypoglycaemic attacks in this patient were classed as reactive since other causes of spontaneous hypoglycaemia could be excluded. In this patient an oral glucose load produced hypoglycaemia after four and a half hours, preceded by a significant insulin hypersecretion. In contrast to the moderate insulin response to parenteral beta-cell stimulation, the intestinal insulinogenic mechanism (McIntyre *et al.*, 1965) appears to have been overactive.

What constitutes the humoral intestinal insulin stimulation is not exactly known. "Gut glucagon," however, causes a significant release of insulin and lowers the blood glucose concentration (Unger *et al.*, 1968). The increased gut glucagon-like immunoreactivity secretion in our patient might therefore be responsible for the hyperinsulinaemia and reactive hypoglycaemia after oral glucose loading. Pancreozymin-cholecystokinin, secretin, and probably gastrin may also increase the beta-cell secretion (Chrisholm *et al.*, 1969; Dupre *et al.*, 1969). In the present case we found that gastrin was without effect, as the biologically active carboxyterminal gastrin-tetrapeptide did not produce any insulin response on parenteral administration (Fig. 1). The part played by pancreozymin-cholecystokinin and secretin in our patients is not known.

Our study suggests that gut glucagon-like immunoreactivity may be a pathogenetic factor in reactive hypoglycaemia. The hypothesis of Unger (1968) that postprandial hypoglycaemia may be caused by deficiency in pancreas glucagon is not supported by our study.

We thank Miss Ulla Søegaard Pedersen for technical assistance, and Dr. Aage Prange Hansen, who performed the growth hormone analysis.

ADDENDUM: Another patient with severe reactive hypoglycaemia was recently studied. He also demonstrated a significantly increased release of gut glucagon-like immunoreactivity.

JENS F. REHFELD, M.D.
LISE G. HEDING, LIC. TECHN.

Department of Clinical Chemistry, Medical Department B, Bispebjerg Hospital, and the Novo Research Institute, Copenhagen.

REFERENCES

Chrisholm, D. J., Young, J. D., and Lazarus, L. (1969). *Journal of Clinical Investigation*, **48**, 1453.
Christensen, N. J. (1967). *Scandinavian Journal of Clinical and Laboratory Investigation*, **19**, 379.
Conn, J. W., and Seltzer, H. S. (1955). *American Journal of Medicine*, **19**, 460.
Dupre, J., Curtis, J. D., Unger, R. H., Waddell, R. W., and Beck, J. C. (1969). *Journal of Clinical Investigation*, **48**, 745.
Heding, L. G. (1969). Paper presented at 5th Annual Meeting of the European Association of the Study of Diabetes, Montpellier, 1969.
Holdsworth, C. D., Turner, D., and McIntyre, N. (1969). *British Medical Journal*, **4**, 257.
McIntyre, N., Holdsworth. C. D., and Turner, D. S. (1965). *Journal of Clinical Endocrinology and Metabolism*, **25**, 1317.
Ørskov, H. (1967). *Scandinavian Journal of Clinical and Laboratory Investigation*, **20**, 297.
Sussman, K. E., Stimmler, L., and Birenboim, H. (1966). *Diabetes*, **15**, 1.
Unger, R. H. (1968). *American Journal of the Medical Sciences*, **255**, 273.
Unger, R. H., Ohneda, A., Valverde, I., Eisentraut, A. M., and Exton, J. (1968). *Journal of Clinical Investigation*, **47**, 48.
Yde, H. (1968). *Acta Endocrinologica*, **57**, 557.