Diazoxide in Von Gierke's Disease

O. M. RENNERT and D. MUKHOPADHYAY

From the Department of Pediatrics, University of Chicago

The enzymatic defect in von Gierke's disease (glycogen storage disease, Type I), a deficiency of glucose-6-phosphatase, results in inability to utilize glycogen stores, periods of hypo-glycaemia, and chronic acidosis. Treatment hitherto has been only supportive. More recent attempts to modify the course of this disease have involved the use of thyroxine (Koulischer and Pickering, 1956) and glucagon (Lowe *et al.*, 1959) to influence the intermediary metabolism of glucose. Spergel and Bleicher (1966) studied the effect of the non-diuretic benzothiadiazine drug, diazoxide; their patients developed sensitivities to the drug, and its efficacy was not fully evaluated. Two patients with von Gierke's disease who have been receiving diazoxide are here presented.

Case Reports

Case 1. A Caucasian male child, born in 1960, birthweight 3232 g. (7 lb. 2 oz.), was first seen because of failure to gain weight. During the neonatal period there was hepatomegaly, hyperbilirubinaemia, and failure to gain weight, but no convulsions or episodes suggestive of hypoglycaemia or acidosis. At the age of 3 months when first seen he was cachectic and weighed 4082 g. (9 lb.). There was hepatomegaly to the level of the umbilicus; the spleen was not palpable.

The patient was the fourth child of healthy parents. The first child was a boy who was alive and well. The next two sibs were a brother and a sister, who died at 3 months and 2 days respectively; both were diagnosed as having von Gierke's disease at necropsy. A great grandmother was said to have had only 4 living children out of 12 pregnancies.

Laboratory data: at age 3 months. Serum CO_2, $7 \cdot 1$ mM/l.; glucose <20 mg./100 ml.; serum lipids, 3315 mg./100 ml.; serum cholesterol, 270 mg./100 ml.; cholesterol esters, 130 mg./100 ml. His urine showed acetone on many occasions.

He was given several injections of glucagon with no effect. At first he continued to have acidosis and hypoglycaemia, but was subsequently maintained on frequent feedings of a high-protein, low-fat, galactose-free diet which controlled his symptoms.

During the next 7 years he had to be readmitted to

hospital 57 times. His liver continued to enlarge and gradually his spleen became palpable. His weight, initially below the 16th centile, improved by 18 months of age, but from 5 years again declined. His height always remained well below the mean −1 SD. His numerous periods in hospital were usually precipitated by infections associated with acidosis, or epistaxis, and anaemia, which always responded well to supportive therapy.

Aged 7 years his weight was $18 \cdot 4$ kg. and height 100 cm. There was sparse hair on his scalp. His abdomen was distended, with circumference 70 cm. The liver edge was palpable 18 cm. and the spleen 15 cm. below the costal margins. Bone age was 3 years. Psycho-metric examination indicated that he functioned at a dull normal level of intelligence, IQ 80–90. Platelet count was 150,000–210,000 cu.mm. Hb $8 \cdot 8$–$9 \cdot 5$ g./100 ml. Red cell survival time was significantly shortened, 13 days as compared to a normal of greater than 25 days. Red cell osmotic fragility was increased. Clotting time, clot retraction, prothrombin time, prothrombin consumption, and thromboplastin generation time were normal, and other blood chemistry is shown in Table I. Glucose and galactose tolerance tests, and response to glucagon stimulation are shown in the Fig.

Diazoxide administration. He was initially placed on a daily dose of diazoxide of 4 mg./kg. 24 hr. in two divided doses. The platelet and leucocyte count remained stable. Random blood sugar determinations showed (Table II) a significant increase compared to pretreatment levels. After 10 days it was found that the patient could tolerate longer fasts between feedings and he was subsequently placed on three feedings per day, plus three snacks. Diazoxide was later increased to 8 mg./kg. daily given in three divided doses, when significant increases were found throughout the day in blood sugar values, with levels as high as 135 mg./100 ml. (Table II). He could now be successfully maintained on three meals a day with a single snack at bedtime. The degree of acidosis was much less, the level of lactic acid being reduced by 50% (Table I).

He was followed at regular intervals on an outpatient basis, remaining symptom free, and after 4 months was readmitted for evaluation. Physical examination at this time revealed increased amounts of hair on the scalp but no other side-effects attributable to diazoxide. Abdominal circumference was now only 65 cm., both the liver (15 cm.) and the spleen (11 cm. below costal

TABLE I

Blood Chemistry* of 2 Brothers with Von Gierke's Disease Treated with Diazoxide

	Case 1		Case 2	
	Before Diazoxide	Diazoxide Therapy	Before Diazoxide	Diazoxide Therapy
Alkaline phosphatase (units %)	53	54	15	13
SGOT (units %)	68	98	40	—
SGPT (units %)	114	55	—	—
Cholesterol (mg./100 ml.)	305	220	285	325
Total lipids (mg./100 ml.)	1790	1105	1300	1220
Uric acid (mg./100 ml.)..	13·2	10	5·9	5·6
Lactic acid (mg./100 ml.)†	121	53	67·7	43
Pyruvic acid (mg./100 ml.)‡	3·65	2·9	3·6	2·6
Urinary norepinephrine (mg./24 hr.)	62·2	—	18·6	31·5

* Mean values of several determinations.
† Normal lactic acid = 6–16 mg./100 ml.
‡ Normal pyruvic acid = 0·4–0·9 mg./100 ml.

margin) being less enlarged. Laboratory determinations were repeated (Table I).

Case 2. The younger brother of Case 1. He was well until 3 months of age when he had a convulsion 2 hours after being fed. A blood sugar of 8 mg./100 ml. was recorded immediately after the convulsion, when he was admitted to hospital. Hypoglycaemia, and the acidosis found, were corrected. A liver biopsy showed increased glycogen stores, and no measurable glucose-6-phosphatase activity. Diazoxide was administered in a regimen similar to that of Case 1. A more striking improvement in glucose homeostasis was seen in this patient, blood glucose values ranging from 60–193 mg./100 ml. throughout the day (Table II) after 3 months of treatment.

Discussion

In man the glycogen content of liver normally varies between 0 and 5% of the wet weight of this organ. The homeostatic mechanisms for the degradation and release of glucose from glycogen involve the action of the enzymes phosphorylase, amylo-1,6-glucosidase, and glucose-6-phosphatase. The net reaction of phosphorylase and amylo-1, 6-glucosidase on glycogen is:

glycogen + $nHPO_4$ + mH_2O ⟶
nglucose-1-phosphate + mglucose + oligosaccharide.

Without involving the activity of glucose-6-phos-

o IV Glucose tolerance
▲ Oral galactose tolerance
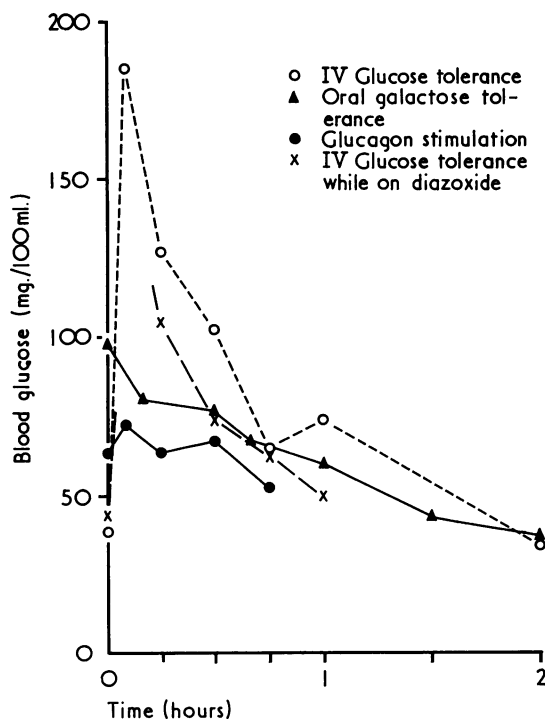● Glucagon stimulation
x IV Glucose tolerance while on diazoxide

FIG.—*Case 1. Blood glucose response to various agents.*

TABLE II

Effect of Diazoxide on Blood Glucose (mg./100 ml.)

	Diazoxide Dosage per Day					
			4 mg./kg.		8 mg./kg.	
Case No.	Range	Mean	Range	Mean	Range	Mean
1	20–75	60	20–110	75	30–140	85
2	30–70	55	35–108	64	60–193	110

phatase, this reaction results in the liberation of as much as 8% of the glucose of the glycogen moiety.

The deficiency of glucose-6-phosphatase in liver and kidney from patients with von Gierke's disease was elegantly demonstrated by Cori and Cori (1952) and Illingworth and Cori (1952). The demonstration (Langdon and Weakley, 1955; Ashmore, Cahill, and Hastings, 1956; Freedland and Harper, 1958; Segal and Washko, 1959) that various metabolites, hormones, and drugs may influence the assayable activity of glucose-6-phosphatase in normal liver suggests alternative explanations for the deficiency of this enzyme in hepatorenal glycogenosis, other than its absence. The biochemical situation seen in this disease might result if there existed two forms of glucose-6-phosphatase, inactive and active; under these circumstances the disease would result if the organism were unable to convert the inactive form to the active form (Field, 1966). A defect in this enzyme might also be explained by the absence of an inducer or presence of a repressor with resultant low or non-measurable levels of the enzyme (Nemeth, 1954).

In 1962 Dollery, Pentecost, and Samaan reported that the drug diazoxide, when used in the treatment of hypertension, induced diabetic ketoacidosis in a number of patients. This observation was confirmed by a number of other workers (Wilson et al., 1964; Hutcheon and Barthalmus, 1962; Okun, Russell, and Wilson, 1963). The hyperglycaemic effect of diazoxide was exploited to treat various forms of childhood hypoglycaemia with much success (Drash and Wolff, 1964). Three general mechanisms have been suggested to explain the hyperglycaemic effect of diazoxide (Spergel and Bleicher, 1966): (a) increased glycogenolysis—induced by catecholamine release; (b) depression of insulin release; and (c) inhibition of glucose uptake by liver. Diazoxide should, therefore, result in inhibition of glycogen production, increased glycogen breakdown, and hyperglycaemia—these factors suggested its possible value in the treatment of von Gierke's disease. Two patients with von Gierke's disease following diazoxide therapy were found to have higher fasting blood sugar levels, improved oral glucose tolerance, and lower levels of circulating insulin following this treatment. Drug sensitivity, as manifest by facial erythema and pruritus, developed after a short period, and no other conclusions could be drawn (Spergel and Bleicher, 1966).

In our patients no untoward effects from diazoxide therapy other than hirsutism have been noted. The initial daily dose of 4 mg./kg. resulted in a greater fluctuation of blood sugar values, with an increase in mean values as well (Table II). Random blood

sugar determinations obtained before therapy under similar dietary conditions never exceeded 75 mg./100 ml. in either patient, Increasing the daily diazoxide dose to 8 mg./kg. resulted in higher minimal and maximal blood glucose levels (Table II). It was in fact found that the patients no longer required feeds every 2 hours but could be satisfactorily maintained on three feeds per day plus two small snacks. In addition to the improved glucose homeostasis, acidosis lessened considerably (Table I). Case 1 has been followed for over 6 months while receiving diazoxide; in addition to maintenance of improved glucose and acid homeostasis, a marked reduction in his hepatomegaly has been noted.

Diazoxide exerts its effect on glucose metabolism by three major mechanisms. Fajans et al. (1965) and Seltzer and Allen (1965) demonstrated that circulating levels of insulin were depressed in all patients with β-cell insulinomas and in normal patients treated with diazoxide. Whether this depression of insulin levels is due to inhibition of release or interference with insulin productions is unknown at present. The second mode of action was delineated by Tabachnick, Gulbenkian, and Seidman (1964) who showed that diazoxide would produce hyperglycaemia in de-pancreatectomized or alloxanized dogs. Further, this effect could be abolished by pre-treatment of the experimental animal with adrenergic blocking agents. Senft (1965) demonstrated that the level of active phosphorylase in rat liver was increased by diazoxide: it was suggested that increased level of active phosphorylase was a consequence of inhibition of cyclic adenylic phosphodiesterase, with a resultant increase in available cyclic adenylic acid. On the basis of these considerations, the improved carbohydrate metabolism seen in these patients would be explained.

Summary

In two sibs with von Gierke's disease, the drug diazoxide resulted in improved glucose homeostasis.

REFERENCES

Ashmore, J., Cahill, G. F., Jr., and Hastings, A. B. (1956). Inhibition of glucose-6-phosphatase by hypoglycemic sulfonylureas. Metabolism, 5, 774.

Cori, G., and Cori, C. F. (1952). Glucose-6-phosphatase of the liver in glycogen storage disease. *J. biol. Chem.*, **199**, 661.

Dollery, C. T., Pentecost, B., and Samaan, N. A. (1962). Drug-induced diabetes. *Lancet*, **2**, 735.

Drash, A., and Wolff, F. (1964). Drug therapy in leucine-sensitive hypoglycemia. *Metabolism*, **13**, 487.

Fajans, S., Floyd, J., Knoph, R., and Rull, J. (1965). Evidence that decreased insulin secretion contributes to the benzothia-diazine-induced hyperglycemia. *Abstracts 47th Meeting of the Endocrine Soc., June 1965*.

Field, R. A. (1966). Glycogen deposition diseases. In *The Metabolic Basis of Inherited Disease*, 2nd ed., p. 141. Ed. by J. B. Stanbury, J. B. Wyngaarden, and D. Frederickson. McGraw-Hill, New York.

Freedland, R. A., and Harper, A. E. (1958). Metabolic adaptations in higher animals. III. Quantitative study of dietary factors causing response in liver glucose-6-phosphatase. *J. biol. Chem.*, **233**, 1.

Hutcheon, D. E., and Barthalmus, K. S. (1962). Antihypertensive action of diazoxide. A new benzothiadiazine with antidiuretic properties. *Brit. med. J.*, **2**, 159.

Illingworth, B., and Cori, G. T. (1952). Structures of glycogens and amylopectins. III. Normal and abnormal human glycogen. *J. biol. Chem.*, **199**, 653.

Koulischer, N., and Pickering, D. E. (1956). Glycogen-storage disease: a study on the effect of sodium 1-thyroxine and glucagon. *Amer. J. Dis. Child.*, **91**, 103.

Langdon, R. G., and Weakley, D. R. (1955). The influence of hormonal factors and of diet upon hepatic glucose-6-phosphatase activity. *J. biol. Chem.*, **214**, 167.

Lowe, C. U., Sokal, J. E., Doray, B. H., and Sarcione, E. J. (1959). Biochemical studies and specific therapy in hepatic glycogen storage disease. (Abstract.) *J. clin. Invest.*, **38**, 1021.

Nemeth, A. M. (1954). Glucose-6-phosphatase in the liver of the fetal guinea pig. *J. biol. Chem.*, **208**, 773.

Okun, R., Russell, R. P., and Wilson, W. R. (1963). Use of diazoxide with trichlormethiazide for hypertension. *Arch. intern. Med.*, **112**, 882.

Segal, H. L., and Washko, M. E. (1959). Studies of liver glucose-6-phosphatase. III. Solubilization and properties of the enzyme from normal and diabetic rats. *J. biol. Chem.*, **234**, 1937.

Seltzer, J., and Allen, E. (1965). Inhibition of insulin secretion in 'diazoxide-diabetes'. *American Diabetes Association Meeting, June 1965*.

Senft, A. (1965). Effect of diazoxide on liver phosphorylase. *Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak.*, **251**, 2.

Spergel, G., and Bleicher, S. J. (1966). Effects of diazoxide administration in Von Gierke's disease. *Diabetes*, **15**, 406.

Tabachnick, I. I. A., Gulbenkian, A., and Seidman, F. (1964). The effect of a benzothiadiazine, diazoxide, on carbohydrate metabolism. *ibid.*, **13**, 408.

Wilson, W. R., Stone, D. B., Okun, R., and Russell, R. P. (1964). Metabolic effects of diuretic and non-diuretic benzothiadiazines. (Abstract.) *Ann. intern. Med.*, **60**, 317.