INFANTILE HYPOGLYCAEMIA DUE TO INHERITED DEFICIENCY OF GLYCOCEN SYNTHETASE IN LIVER

BY

G. M. LEWIS, J. SPENCER-PEET* and K. M. STEWART

From the Departments of Paediatrics and Child Health and Chemical Pathology, The University of Leeds

(RECEIVED FOR PUBLICATION SEPTEMBER 24, 1962)

In 1909 Garrod introduced the concept of the metabolic block. Over 70 diseases are now thought to be due to inborn errors of metabolism, and of these some 20 have been shown to be due to a single enzyme defect. We now report the clinical condition resulting from the congenital absence of the liver enzyme glycogen synthetase. Our report is based on the study of identical twins who become hypoglycaemic after an overnight fast.

Hypoglycaemia is a feature of cretinism, hypopituitarism, adrenal insufficiency, galactosaemia, hereditary fructose intolerance, severe liver disease, glycogen storage disease and islet cell adenoma or hyperplasia. In many hypoglycaemic infants, however, no cause has been found. McQuarrie (1954) reporting on a large series of these cases proposed the term ‘idiopathic spontaneous hypoglycaemia’. Cochrane, Payne, Simpkiss and Wolff (1956) described patients in whom hypoglycaemia developed after protein meals, and after the administration of l-leucine. More recently Mabry, DiGeorge and Auerbach (1960) have shown that l-leucine is probably the only amino acid with this action. Broberger and Zetterström (1961) described a series of hypoglycaemic infants who did not increase adrenaline secretion in response to hypoglycaemia. Our investigations show that the twins to be described have a reduced capacity for the storage of glycogen in the liver. In a liver biopsy sample from one twin, complete absence of glycogen synthetase activity has been demonstrated.

Case Reports

Case 1. In April 1961 a male child aged 15 months was admitted to the General Infirmary at Leeds for investigation of mental retardation. He was the first-born of uniovular twins. Labour and delivery were uncomplicated, the estimated gestation period was 38 weeks, and birth weight 4 lb. 5 oz. (1·9 kg.). He had a prolonged attack of apnoea 46 hours after delivery, which was treated with intragastric oxygen and lobeline, and there were further attacks of apnoea during the next 12 hours. The first feed was given 48 hours after delivery, and the baby fed by tube for the first week.

The mother first became anxious when he was 2 months old because he was not showing interest or following objects with his eyes, and because he compared unfavourably with his twin. Head control was not acquired until the age of 6 months.

A late night feed was given regularly up to the age of 7 months, after which time feeds were sometimes omitted between 6 p.m. and 6 a.m. From the age of 8 months it was noticed that before the first feed of the day he was sometimes pale and showed transient internal strabismus, but that he improved rapidly after a feed. At 9 months of age an incident of this nature developed into a generalized convolution that lasted for 15 minutes and was followed by drowsiness for an hour. There were no further frank convulsions, but pallor associated with incoordinate eye movements continued to occur before the first feed of the day.

On admission he weighed 17 lb. 4 oz. (7·8 kg.), was 28 in. (70·9 cm.) in length and was apparently well nourished. There was no detectable enlargement of the liver or spleen. His head was small [circumference 17 in. (44·4 cm.)] and the anterior fontanelle was just palpable. The arms and legs were spastic. He could raise his head momentarily from the pillow when prone, but not when supine. Hearing and vision were normal, but mental development was grossly delayed.

Urine examined on admission contained a trace of sugar, but there was no acetone or other abnormality. After an overnight fast of 15 hours he was pale, disinterested in his environment, and subject to momentary stiffening of the arms and internal strabismus. A fasting blood sugar taken at this time was 7 mg./100 ml. blood (glucose oxidase method), and although he was hypoglycaemic the heel prick stimulated crying and the next feed was taken well. The following day the fasting blood sugar was 12 mg./100 ml.

Once fasting hypoglycaemia had been confirmed, we admitted his twin to hospital, since he also had convulsions.

Case 2. He was the second-born of the twins and was delivered by assisted breech, his birth weight being

* Present address: Department of Chemical Pathology, Charing Cross Hospital, London W.C.2.
INFANTILE HYPOGLYCAEMIA

TABLE 1

THE FAMILY: SUMMARY OF THE MAIN FINDINGS

<table>
<thead>
<tr>
<th>Age</th>
<th>Mental Development</th>
<th>Fasting Blood Sugar</th>
<th>Glucose Tolerance</th>
<th>Adrenaline Response</th>
<th>Glucagon Response</th>
<th>Fasting</th>
<th>Three Hours After Meal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father</td>
<td>40 yrs</td>
<td>Normal</td>
<td>Normal</td>
<td>Reduced</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mother</td>
<td>39 yrs</td>
<td>Normal</td>
<td>Normal</td>
<td>Reduced</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>June</td>
<td>5 yrs</td>
<td>Normal</td>
<td>Normal</td>
<td>Reduced</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>John*</td>
<td>3 yrs</td>
<td>Normal</td>
<td>Normal</td>
<td>Reduced</td>
<td>No response</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Case 1</td>
<td>26 mths</td>
<td>Severe</td>
<td>Hypoglycaemic</td>
<td>Reduced</td>
<td>Normal</td>
<td>Poor</td>
<td>Normal</td>
</tr>
<tr>
<td>Case 2</td>
<td>26 mths</td>
<td>Retarded</td>
<td>Hypoglycaemic</td>
<td>Reduced</td>
<td>—</td>
<td>Poor</td>
<td>Normal</td>
</tr>
<tr>
<td>Catherine</td>
<td>9 mths</td>
<td>Normal</td>
<td>Hypoglycaemic</td>
<td>Reduced</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* Note added in proof: Since writing this paper, John has sometimes been hypoglycaemic after an overnight fast, and on these occasions there is no response to glucagon.

3 lb. 8 oz. (1·6 kg.). Immediately after birth his breathing was gasping and irregular and he had short apnoeic attacks at the age of 40 hours. He was nursed in an incubator and not fed for 48 hours after delivery, after which he was tube fed for the first week. When regular night feeds were stopped at the age of 7 months, the mother noticed a resemblance to his twin in that he was sometimes pale and 'squinting' in the early morning.

When 8½ months old he had a convulsion in the early morning and was admitted to hospital. The convulsion lasted three hours and stopped immediately after a lumbar puncture, which was performed to exclude meningitis. In hospital his mental development was assessed as approximately that of a 5-month-old infant. He was discharged but readmitted three weeks later after a similar convulsion when the cerebrospinal fluid sugar was 35 mg./100 ml. Convulsions in the early morning recurred at approximately three-week intervals, and the infant was frequently seen to be pale and 'squinting' before the first feed of the day.

On admission to hospital at the age of 15 months he weighed 19 lb. 4 oz. (8·7 kg.), was 29 in. (73·6 cm.) in length with a head circumference of 18 in. (45·7 cm.). He was well nourished and had a similar facial appearance to his twin (Case 1), but had no evidence of any neurological abnormality. The liver was palpable 0·5 in. (1·3 cm.) below the costal margin, and the spleen was soft and palpable on inspiration. He sat up well, stood with support and his mental development was approximately that of a 10-month-old child. The blood groups of the twins were found to be identical, as follows:

ABO Rh MN S Pt Lu* K Le* Le Fy*
Al CcDee N — — — — — — —

Skin biopsy cultures showed no abnormality in the number or gross morphology of the chromosomes.

Family History. A brief summary of the clinical and laboratory findings in the parents and other siblings is set out in Table 1. The parents and two eldest siblings have no history of fits or other features of hypoglycaemia and are not mentally retarded.

Catherine was born in May 1961, one month after the discovery of hypoglycaemia in the twins. Pregnancy and labour were normal and she weighed 5 lb. 12 oz. (2·6 kg.) at birth; the estimated gestation period was 40 weeks. Random blood sugar levels performed in the neonatal period revealed several values below 40 mg. glucose/100 ml. blood. Fasting hypoglycaemia has been confirmed at intervals during infancy; 36 mg. at 5 months; 22 mg. at 10 months; 36 mg. at 13 months, each after a 10-hour fast. A glucose tolerance test performed at the age of 5 months revealed a degree of reduced tolerance similar to that found in the twins.

From birth, frequent feeds (at intervals of not more than six hours) have satisfactorily prevented hypoglycaemia, and the child's development has been normal.

The father was investigated for glycosuria when 8 years old, when a glucose tolerance test revealed a 'lag curve'. Fig. 1 shows the three siblings.

Methods

The blood sugar was estimated on capillary blood by the method of Hagedorn and Jensen (1923). The glucose oxidase method of Marks (1959) was also used and this is indicated where appropriate.

Plasma insulin was determined by the rat diaphragm assay of Vallance-Owen and Hurlock (1954), blood glycogen by van Creveld's method (1934), urinary catecholamines by a modification of the trihydroxyindole method of von Euler and Flodin (1935), 17-ketosteroids by the method of Gibson and Norymberski (1954) and 17-hydroxycorticosteroids by the method of Appleby, Gibson, Norymberski and Stubbins (1955). Glucose uptake of red cells was measured by the technique of Pennington and Leyburn (1960), the glucose being estimated by the glucose oxidase method.

Histological specimens were fixed in absolute alcohol and in formol calcium solution (Baker, 1958). The biopsy specimen for enzyme studies was placed immediately in ice-cold oxygenated Krebs-Ringer solution. Within 20 minutes of biopsy, homogenates were prepared in ice-cold 0·25 M sucrose containing 0·001 M ethylenediamine tetra-acetate with the aid of a Potter-Elvehjem homogenizer. Control liver biopsy specimens, obtained during abdominal surgery on fasting adults free from disease of the liver and biliary tract, were treated in the same way.
A 4% homogenate was used in most of the enzyme determinations. Phosphorylase was determined by the method of Sutherland and Wosilait (1956), on the basis of the inorganic phosphate released from glucose-1-phosphate and estimated by the method of Fiske and Subbarow (1925). Glucose-6-phosphatase was measured by a modification (T. R. Ricketts, 1962, personal communication) of the method of Hers (1959). Glycogen synthetase was determined by the method of Leloir and Goldberg (1960) based on the measurement of uridine diphosphate released from uridine diphosphoglucose.

Uridine diphosphoglucone pyrophosphorylase was measured according to Kalckar and Anderson (1957) by estimating the uridine diphosphoglucone formed from glucose-1-phosphate and uridine triphosphate. Uridine diphosphoglucone was estimated with its specific dehydrogenase. Glycogen was determined in specimens taken into warm 30% potassium hydroxide according to Good, Kramer and Somogyi (1933), the precipitated glycogen being hydrolysed in 0-6 N hydrochloric acid and estimated by the glucose oxidase method (Marks, 1959). Total lipids were extracted by (2:1) alcohol ether and measured gravimetrically (T. R. Ricketts, 1962, personal communication).

Clinical Laboratory Studies

During their stay in hospital both twins consistently developed severe hypoglycaemia (19-30 mg./100 ml. of blood by the method of Hagedorn and Jensen) when fasted for 12 hours overnight. The slow fall during the night is shown in Fig. 2. Prolonged glucose tolerance tests (Fig. 3) (2.5 g. glucose/kg. body weight) demonstrated that hypoglycaemia did not occur within six hours of the feed, revealed a somewhat reduced glucose tolerance and a moderate lowering of the renal threshold. Glucosuria occurred occasionally during the day. The only sugar in the urine was glucose.

There was a satisfactory rise of blood sugar after the subcutaneous administration of adrenaline following an overnight fast (Case 1, 40 mg.; Case 2, 50 mg.). The fasting blood glycogen levels were low (Case 2, 2-3 mg. 100 ml. blood; Case 1, 2-8 mg./100 ml., compared with a normal range of 10-15 mg.). Plasma phospholipids, esterified fatty acids and cholesterol were normal.
INFANTILE HYPOGLYCAEMIA

Frequent determination of blood sugar throughout 24 hours did not suggest excessive secretion of insulin following a meal. Fasting plasma insulin levels were below normal adult values (Case 1, 37 μu units/ml; Case 2, 44 μu units/ml), but of the same order as a control of the same age (34 μu units/ml). The twins were hypersensitive to insulin (0-1 units of soluble insulin intravenously per kg. body weight) as shown by the fall of blood sugar from 56 to 7 mg./100 ml. in 75 minutes. Hypoglycaemia persisted following the intravenous administration of glucose. These findings do not suggest hyperinsulinism. The oral administration of l-leucine (0-13 g. per kg. body weight given three hours after a meal) had no effect on the blood sugar level.

During a three-and-a-half-hour period, before and after the administration of insulin, urine was collected for determination of catecholamine excretion. This was not increased during insulin-induced hypoglycaemia. Clinically this hypoglycaemia was associated with incoordinate eye movements, yawning, a moderate rise in pulse rate, but unaltered blood pressure. These findings are similar to those made by Broberger and Zetterström (1961) in five of 11 cases of idiopathic hypoglycaemia. In order to distinguish between a failure of the nerve phase of adrenal stimulation, and a lack of intrinsic adrenal medullary response, the latter was tested with histamine (D. R. Wood, 1962, personal communication). There was no increased secretion of catecholamine following histamine (0-2 mg. subcutaneously).

Adrenocortical function was assessed by the 24-hour urine excretion of 17-hydroxycorticosteroids (Case 1, 1·2 mg.; Case 2, 0·64 mg.) and 17-ketosteroids (Case 1, 0·8 mg.; Case 2, 0·33 mg.), and by the response to ACTH given over a four-day period to Case 1. For a control period of two days before the administration of ACTH, fasting blood sugars, urinary steroids and absolute eosinophil counts were determined. For four days ACTH was given subcutaneously in a dosage of five units six hourly. On this régime the fasting blood sugar rose from 20-70 mg./100 ml., the 24-hour excretion of 17-hydroxycorticosteroids rose from 2·2 to 13·2 mg., and the eosinophil count fell from 240 to 16/c.mm. These results show that the adrenal cortex is capable of responding to ACTH.

The twins had normal serum sodium, potassium, chloride, bicarbonate, urea, alkaline phosphatase, thymol turbidity, bilirubin and transaminases. The urine amino acid pattern was normal. Occasionally small amounts of ketones were present in the urine when fasting.

In order to determine whether the storage or mobilization of glycogen was impaired, glucagon (0·02 mg./kg. body weight) was administered intramuscularly in the fasted state and three hours after a meal. The results (Fig. 4) revealed no significant response to glucagon when fasting, but a normal response three hours after a meal. As glucagon mobilizes liver glycogen but does not affect muscle, the good response to glucagon after a meal supports the view that the enzymes concerned in hepatic glycogenolysis are intact. The insignificant response to glucagon in the fasted, as compared with the fed state, suggested a depletion of glycogen stores during the night fast, and a reduced, but not complete, inability to form liver glycogen. Attention was thus turned to the metabolic stages of glycogen formation.

The initial step in glycogen formation from blood glucose involves phosphorylation by glucokinase. Galactose and fructose are phosphorylated by their own specific hexokinases. Should glucokinase be the defective step the substitution of either of these sugars should by-pass the defect. However, neither of these sugars (40-50 g.), when added to the evening meal, altered the fasting blood sugar next morning, thus suggesting that glucokinase was not the limiting factor. This is further supported by the finding that the in vitro glucose uptake of erythrocytes was normal (42 mg./100 ml. packed cells hour). The other enzymes leading to glycogen synthesis could only be examined directly in a sample of liver obtained at biopsy.

Liver Biopsy. Biopsy was performed on Case 1, six hours after a meal, the blood sugar being maintained by an intravenous glucose infusion. Enzyme studies on the biopsy, and on adult biopsy controls, are recorded

**Table 2**

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Case 1 (μmol g/min.)</th>
<th>Controls (μmol g/min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycogen synthetase</td>
<td>0·00</td>
<td>1·40—3·10</td>
</tr>
<tr>
<td>UDPG—pyrophosphorylase</td>
<td>0·68</td>
<td>0·66—1·62</td>
</tr>
<tr>
<td>Phosphorylase</td>
<td>17·00</td>
<td>13·00—22·00</td>
</tr>
<tr>
<td>Glucose-6-phosphatase</td>
<td>11·20</td>
<td>6·60—11·00</td>
</tr>
</tbody>
</table>

Results expressed as micromoles of product per g. liver per minute. Values given are the mean of three determinations.
in Table 2. No glycogen synthetase activity was detected. Absence of activity was confirmed by a repeat determination with three times the amount of liver, and with control determinations on normal rat liver being done simultaneously. The glycogen content of the biopsy was 0·45% and total lipids were 9.8% of wet weight. Biopsy samples of liver from normal young men, 14 hours after a meal, contain 4·04-6·11% glycogen (Bergström, Findor and Hultman, 1961).

The histological report (Dr. T. W. Sutherland) on the liver biopsy was as follows:

'The general pattern of the lobules and portal tracts appears normal. There is no necrosis, abnormal pigmentation or cirrhosis. Sections stained for glycogen (periodic acid-Schiff method and Best's carmine) show scanty granular material in the hepatic epithelium (Fig. 5). More abundant glycogen is present in the control section. Sections stained for fat (Oil-red O)
INFANTILE HYPOGLYCAEMIA

show that most of the epithelial cells contain globules of fat, some of which are large, causing distension of the cells. The appearances indicate glycogen depletion and pronounced fatty change of the liver.

Clinical Progress and Dietary Management

The periods of hypoglycaemia before breakfast are readily abolished by giving a milk and cereal feed at 11 p.m. and an early breakfast at 6 a.m. Attempts were made to discover a diet that would prevent hypoglycaemia in the early morning without resorting to a régime which the mother would find difficult to carry out in the home. A high fat diet was badly tolerated and did not prevent fasting hypoglycaemia. During a three-day period a high protein diet with the last feed given at 9 p.m. resulted in fasting sugar levels 12 hours later of 5C-60 mg./100 ml. On their discharge from hospital, it was felt unwise to rely on a high protein diet to prevent fasting hypoglycaemia. The mother was requested to give a meal at 11 p.m. which we knew to be effective. At home the twins sometimes refused this extra feed and on one occasion both infants had to be readmitted to hospital because hypoglycaemic symptoms and convulsions recurred in the early morning.

Treatment with ephedrine was tried in view of the twin's apparent inability to produce adrenaline in response to hypoglycaemia, and because good results had been obtained by Broberger and Zetterström (1961) in similar infants. Ephedrine (10 mg. daily) had no effect on the fasting blood sugar levels.

With consistently regular feeding at 11 p.m. the twins are no longer subject to hypoglycaemia. Recent determinations of blood sugar during the night (Fig. 2) suggests that there has been some improvement. This may be due to either increasing age or to the dietary régime.

Discussion

The outstanding clinical features of the identical twins are retarded mental development, and the occurrence of convulsions and hypoglycaemic manifestations when fasted overnight.

The salient biochemical findings are hypoglycaemia following a 12-hour fast, reduced glucose tolerance, a low blood glycogen, and a failure of glucagon to raise significantly the blood sugar in the fasted state. With the exception of the fasting hypoglycaemia, these findings can be explained by a reduced capacity to store glycogen in the liver, and suggest the possibility of an enzyme defect in the synthesis of glycogen.

Site of Biochemical Block. The enzymes concerned with metabolism of glucose and glycogen are shown in Fig. 6, together with the sites of individual enzyme deficiencies which have previously been described.

In the twins (Cases 1 and 2), the biochemical block in the synthesis of glycogen is due to the absence of glycogen synthetase, which was demonstrated in the liver biopsy specimen. The other liver enzymes examined were normal (Table 2) and dietary studies indicated that the defect was not in hexokinase.

The demonstration of this enzyme defect would not have been possible until recently. The classical work on glycogenesis, carried out by Cori and Cori (1952), suggested that muscle and liver phosphorylase, acting in conjunction with the branching and debranching enzymes, catalysed the reversible reaction between glycogen and glucose-1-phosphate. Some modification of this concept was required, however, in the light of later work by Schmid and Mahler (1959), who showed that in McArdle's syndrome there is excess muscle glycogen, although the fundamental defect is an absence of muscle phosphorylase. This finding directed attention to the alternative route of glycogen synthesis via glycogen synthetase (Leloir and Cardini, 1957). In this pathway uridine diphosphoglucone is converted to glycogen by glycogen synthetase. The importance of the uridine diphosphoglucone pathway in liver, as well as in muscle, is emphasized in the recent report by Hers (1959) of defective liver phosphorylase in a new type of glycogen storage disease.

In our patients, who have no glycogen synthetase in the liver, some carbohydrate stores are deposited, as shown by the positive response to glucagon after meals, and by the direct analysis of liver. This small amount of glycogen may be produced via liver phosphorylase. The appreciable response to adrenaline after a 12-hour fast may result from the breakdown of muscle glycogen to lactic acid which is then reconverted to glucose in the liver. For this reason we regard the glucagon test as a more critical index of liver glycogen storage. We do not know whether the muscles lack glycogen synthetase.

The failure of Case 2 to increase catecholamine excretion during hypoglycaemia is similar to the findings in other cases of hypoglycaemia in infancy (Broberger and Zetterström, 1961; Kinsbourne and Woolf, 1959; Haworth and Coodin, 1960). Broberger and Zetterström suggest that, in children, failure of the adrenal medulla to secrete increased amounts of adrenaline results in hypoglycaemia. However, von Euler, Ikkos and Luft (1961) showed that blood sugar levels before and after administration of insulin were the same in adrenalectomized patients as in those of a normal control group provided that cortisone was given post-operatively to the former group. This suggests that in adults the adrenal medulla is not essential for maintenance of normal blood sugar.
The absence of glycogen synthetase in the liver does not, by itself, explain the occurrence of fasting hypoglycaemia. Healthy infants over 7 months of age maintain a normal blood sugar during a fast of 24 hours (Kaye, Davidson, Williams, Kumagai and Picou, 1961). During fasting the blood sugar is stabilized by the production of sugar from protein. Thus the occurrence of hypoglycaemia, when the twins are fasted overnight, probably involves the failure of gluconeogenesis as well as of liver glycogen storage.

Glycogen synthetase is not known to be involved in gluconeogenesis. The following explanation of the failure of gluconeogenesis is suggested. Long, Katzin and Fry (1940) showed that administration of adrenal steroids led to an increased formation of glucose from protein. The synthesis of glucocorticoids is in turn controlled by ACTH. The latter specifically activates the adrenal enzyme, phosphorylase, which breaks down glycogen to glucose-1-phosphate and finally to glucose-phosphate (Haynes and Berthet, 1957). Glucose-phosphate then enters the pentose phosphate pathway of Warburg and Dickens, making available in the adrenal cortex a supply of reduced coenzyme II, which is necessary for the 11- and 17-hydroxylations in the synthesis of cortisol (Pincus, 1959; Haynes and Berthet, 1957). Thus, if glycogen
INFANTILE HYPOGLYCAEMIA

47

Synthetase were absent from the adrenal as well as the liver, the synthesis of adrenal steroids during a prolonged fast would be limited and gluconeogenesis could not be maintained.

The studies of Case 1 show that the administration of ACTH stimulates the adrenal cortex, and that its prolonged use prevents fasting hypoglycaemia. These results may appear to be contrary to the above theory, but further investigations of adrenocortical function in the fasted state are being undertaken.

A Familial Disease. Absence of glycogen synthetase has been directly demonstrated in the liver of one twin. The clinical laboratory findings in the other twin are very similar, and an absence of the same enzyme seems highly probable. The youngest sibling, Catherine, becomes hypoglycaemic after an overnight fast and has reduced glucose tolerance. This suggests that Catherine has the same enzyme defect as the twins and that the condition is familial.

The difference in degree of mental retardation in the identical twins suggests that this has been influenced by the environmental conditions. Mental deficiency is known to follow frequent hypoglycaemia (McQuarrie, 1954) and associated microcephaly has also been described (Darrow, 1936). The infants were fasted for 48 hours after birth and suffered from attacks of apnoea, more severe in Case 1. Delayed development was first noted in Case 1 at 2 months, and in Case 2 at 8 months. Although in the latter case it may be related to the stopping of late night feeds at 7 months, the fact that mental retardation had already appeared in one child suggests a possible relation to the severe apnoeic episodes that may have been due to hypoglycaemia. Periods of apnoea and cyanosis in the first 48 hours of life have often been reported in hypoglycaemic children (Broberger and Zetterström, 1961; Hartmann, Wohltmann and Holowach, 1961; Conn and Seltzer, 1955). This suggests that neonatal hypoglycaemia is not without danger and should be looked for and treated at this time. The youngest sibling, Catherine, has been protected from hypoglycaemia by a midnight feed and is developing normally.

The father and two elder siblings (Table 1) do not develop hypoglycaemia, but show reduced glucose tolerance. In the event of an alternative method to liver biopsy being found to demonstrate deficiency of glycogen synthetase, it may prove possible to determine whether the hypoglycaemic infants represent the homozygous condition for absence of glycogen synthetase, while the parents and some of the siblings are heterozygous.

Summary

The clinical condition arising from the inherited deficiency of the liver enzyme glycogen synthetase is described in identical twins.

These infants consistently developed profound hypoglycaemia after an overnight fast. One twin is mentally defective, the other is below average mental development and both have had convulsions in the early morning.

Reduced glucose tolerance, a rise in blood sugar following the administration of glucagon after a meal, but not in the fasted state, suggested an impaired ability to store glycogen in the liver. This has been confirmed by liver biopsy in one twin, which showed a low glycogen content and complete absence of glycogen synthetase.

Hypoglycaemia can readily be prevented in the twins by giving an additional meal at midnight. A younger sibling also has fasting hypoglycaemia and reduced glucose tolerance which strongly suggests that the condition is familial. From birth this infant has consistently been given an additional feed at midnight and is developing normally.

Other members of the family, with the exception of the mother, exhibit abnormalities of carbohydrate metabolism, but do not have fasting hypoglycaemia.

Our thanks are due to Professor W. S. Craig, Department of Paediatrics and Child Health, and to Professor G. H. Lathe, Department of Chemical Pathology, for much advice and help in this investigation. We also wish to thank Mr. F. G. Smiddy, Department of Surgery, the General Infirmary at Leeds for performing the liver biopsy; Dr. T. W. Sutherland, Department of Pathology, University of Leeds, for the histological studies; Dr. C. A. Rank, Department of Genetics, Sheffield University, for chromosome analyses; Mr. D. J. Bilkus, Department of Medicine, Royal Free Hospital, London, for plasma insulin assays; Mr. G. Clough, Biochemistry Laboratory, Harrogate and District Hospital, for urinary catecholamine determinations; and the Blood Group Reference Laboratory for blood grouping. We are indebted also to Mr. J. B. Holton, Mr. T. R. Ricketts, Miss J. W. Summerscales and Dr. C. Toothill of the Department of Chemical Pathology, University of Leeds, for analytical assistance; and to Dr. R. Beaver, Dr. T. V. A. Jabbar, Dr. J. Mencher, Sister E. Barrass and Sister J. Wilson, for their willing co-operation. The Medical Research Council assisted by providing some of the materials.

References


ARCHIVES OF DISEASE IN CHILDHOOD

_Amer. J. Med._, 19, 460.

Cori, G. T. and Cori, C. F. (1952). Glucose-6-phosphatase of the 

Darrow, D. C. (1936). Mental deterioration associated with 

Fiske, C. H. and Subbarow, Y. (1925). The colorimetric determina-

Frowde, London.


Good, C. A., Kramer, H. and Somogyi, M. (1933). The determina-

Hagedorn, H. C. and Jensen, B. N. (1923). Zur Mikrobestimmung 
des Blutzuckers Mittels Ferricyanid. _Biochem. Z._, 135, 46.

Recognition and investigation of hypoglycemia. _J. Pediat._, 58, 864.

Haworth, J. C. and Coodin, F. J. (1960). Idiopathic spontane-

Haynes, R. C. and Berthet, L. (1957). Studies on the mechanism 

Hers, H. G. (1959). Études enzymatiques sur fragments hératriques: 
application à la classification des glycogénoises. _Rev. int. 
Hépat._, 9, 35.

Kalckar, H. M. and Anderson, E. P. (1957). Enzymatic deter-
mination of UTP. In Methods in Enzymology, ed. S. P. Colowick 

Kaye, R., Davidson, M. H., Williams, M. L., Kumagai, M. and 
Picou, D. M. (1961). The response of blood glucose, ketones, 
and plasma nonesterified fatty acids to fasting and epinephrine 

Kinsbourne, M. and Woolf, L. J. (1959). Idiopathic infantile hy-
pglycemia. _Arch. Dis. Childh._, 34, 166.

from uridine diphosphate glucose. _J. Amer. chem. Soc._, 79, 6340.


cortex and carbohydrate metabolism. _Endocrinology_, 26, 305.

Leucine-induced hypoglycemia. _J. Pediat._, 57, 539.

McQuarrie, I. (1954). Idiopathic spontaneously occurring hyp-

Marks, V. (1959). An improved glucose-oxidase method for deter-
mining blood, C.S.F., and urine glucose levels. _Clin. chim. 
Acta_, 4, 395.

Pennington, R. J. and Leyburn, P. (1960). Glucose utilization 
by erythrocytes from muscular dystrophy patients. ibid., 5, 766.

Pincus, G. (1959). Recent developments in the study of adrenal 
cortical steroid biosynthesis. 4th Int. Cong. Biochem., Vienna, 

with myoglobinuria: Demonstration of a glycolytic defect 
in the muscle. _J. clin. Invest._, 38, 2044.

Sutherland, E. W. and Wolslait, W. D. (1956). The relationship 
of epinephrine and glucagon to liver phosphorylase. I. Liver 
phosphorylase: preparation and properties. _J. biol. Chem._, 
218, 459.

Vallance-Owen, J. and Hurlock, B. (1954). Estimation of plasma-
insulin by the rat diaphragm method. _Lancet_, 1, 68.

Dis. Childh._, 9, 9.

of noradrenaline and adrenaline in urine. _Acta physiol. scand._, 33, suppl. 118, 57.

resting conditions and after insulin in adrenalectomized human 
subjects. _Acta endocr._ (Kbh.), 38, 441.
Infantile Hypoglycaemia due to Inherited Deficiency of Glycogen Synthetase in Liver
G. M. Lewis, J. Spencer-Peet and K. M. Stewart

Arch Dis Child 1963 38: 40-48
doi: 10.1136/adc.38.197.40

Updated information and services can be found at:
http://adc.bmj.com/content/38/197/40.citation

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/