IDIOPATHIC INFANTILE HYPOGLYCAEMIA

BY

M. KINSBOURNE* and L. I. WOOLF†
From The Hospital for Sick Children, Great Ormond Street, London

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Occasionally an infant presents with the sudden onset of frequent epileptic seizures in whom the only finding of diagnostic significance is a persistently low blood sugar level.

The many causes of hypoglycaemia are discussed by Conn and Seltzer (1955), but in practice the possibilities in such a case are:

(1) Syndrome of 'idiopathic infantile hypoglycemosis' (McQuarrie, 1954), divisible in the first instance into 'leucine sensitive' and 'leucine insensitive' types (Cochrane, Payne, Simpkiss and Woolf, 1956). In the leucine sensitive type the hypoglycaemia is sharply aggravated by the oral ingestion of leucine, or of protein containing this amino acid. (2) 'Hyperinsulinism', pancreatic islet cell adenoma (Sherman, 1947) or hyperplasia, either macroscopic (Bickerstaff, Dodge, Gourevitch and Hearn, 1955), or microscopic (Engelhardt, Kraayenbrink and Villeneuve, 1955). (3) A rare presentation of some other endocrine defect, e.g. of pituitary, adrenal or thyroid function, or of a disorder of carbohydrate metabolism such as glycogen storage disease or galactosaemia.

The clinical and biochemical features of Group 3 are well known. The differential diagnosis of Groups 1 and 2 is less familiar, and the pathogenesis of Group 1 has hardly been explored.

The present paper describes a severe case of leucine insensitive idiopathic infantile hypoglycaemia. Biochemical findings, some of which seem not previously to have been described, are discussed in relation to pathogenesis.

Case History

A female infant, aged 4 months, was admitted to The Hospital for Sick Children, Great Ormond Street, on December 2, 1957, having become suddenly subject to frequent, uncontrollable, generalized fits without focal features three weeks earlier. The fits, which occurred at any time of day or night, were accompanied by a progressive deterioration of her previously normal mental function. Her family history was of no significance, except perhaps that her brother's rate of weight gain had been high: 8 lb. 1 oz. at birth, 23 lb. at 5 months and 79 lb. at 7 years. After a normal birth (birth weight: 7 lb. 8 oz.) the patient was breast fed for three weeks, then bottle fed, gaining weight very rapidly all the time.

On examination, she was obese (weight 17 lb.) with extreme hypotonia of the limbs and depressed reflexes. She sucked well, but seemed unaware of her environment, and responded only to pain with a high pitched cry. The head circumference was 16½ inches; there were no other abnormal signs.

There was no protein, reducing substance or ketone bodies in the urine. Blood examination showed Hb. 82%, W.B.C. and differential count were normal. Serum electrolytes were normal, except serum potassium 3·1 mEq./l. Blood sugar, during a fit was 35 mg./100 ml. (Folin and Wu estimation). Cerebrospinal fluid showed protein, 120 mg./100 ml.; sugar, 16 mg./100 ml.; chloride, 720 mg./100 ml. A W.R. was negative. Liver function tests were normal. There was no excess of blood galactose.

An E.E.G. (Dr. Pampiglione) showed 'An excess of slow activity over the two hemispheres with occasional paroxysmal changes. Isolated sharp waves suggest the presence of discharging areas.' A radiograph of the skull was normal.

Further blood sugar estimations confirmed a severe fasting hypoglycaemia.

Oral and intragastric glucose had failed to abolish the hypoglycaemia at a time when the infant suddenly developed diarrhoea and became acutely dehydrated. A rapid intravenous infusion of 5% dextrose restored normal hydration; three hours after the infusion was started the blood sugar had risen to 470 mg./100 ml.; and in another one and a half hours to 700 mg./100 ml., although very little glucose was given in the meantime.

The blood sugar dropped back to hypoglycaemic levels in the next 24 hours, and then could not be raised even by further intravenous 5% dextrose. Therefore ACTH gel was given intramuscularly, 8 units 12-hourly, with an immediate dramatic rise in blood sugar concentration, and complete cessation of fits. After one month it was possible to reduce the ACTH to 8 units daily, and after another month prednisolone 2 mg. eight-hourly was successfully substituted.

The hypotonia soon disappeared. The rate of weight

* Present address: Bellevue Hospital, 550 1st Avenue, New York16, N.Y., U.S.A.
† Present address: M.R.C. Population Genetics Research Unit, Warneford Hospital, Oxford.

gain diminished almost to zero in the early months of treatment; then was resumed at a more normal level (Fig. 1).

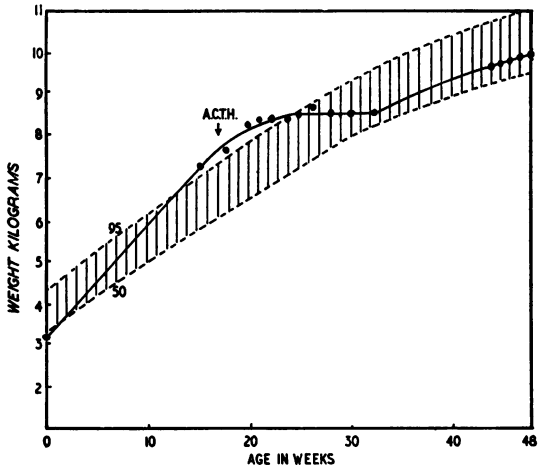

FIG. 1.—The patients' weight at different ages. The time of starting ACTH (and, later, steroid) therapy is indicated. The 50th and 95th percentiles for the weight of girls at different ages are shown and the area between shaded (Sundal, 1957; Tanner, 1958).

At 10 months of age and six months after starting treatment she was more alert than before, but was still grossly retarded (G.Q. 22, Griffiths scale), with a head circumference of 17¼ inches.

Methods of Investigation

Blood was collected, by heel prick, in bottles containing fluoride and oxalate. True blood sugar and non-sugar reducing substances were determined as described by Cochrane *et al.* (1956). Glucose was determined using glucose oxidase (Huggett and Nixon, 1957) and the biodeminrolit-treated tungstic acid blood filtrate. Urine for adrenaline estimation was collected over timed intervals in bottles containing 6N HCl. Adrenaline in urine was determined by a modification of the method of Euler and Orwen (1955); Snaith and Woolf (in preparation). In two specimens of urine catecholamines were also determined by Dr. M. Mann using a biological method.

Phenolic acids in urine were also analysed by a paper chromatographic method (cf. Armstrong, Shaw and Wall, 1956).

Results

Leucine Tolerance Test. The true blood sugar, initially 105 mg./100 ml., did not drop within 90 minutes of feeding leucine (0·15 g./kg. body weight). The non-sugar reducing substances (Cochrane *et al.*, 1956) were ≡13 mg. glucose per 100 ml. blood, which is normal.

This test was carried out under ACTH cover since it would have been potentially dangerous to feed leucine if the blood sugar were below about 30 mg. per 100 ml., and the results would have been difficult to interpret; there is no evidence that ACTH modifies sensitivity to leucine.

Serial Blood Sugars. (Before treatment with ACTH or steroids.) After being fed at 2.0 p.m. her blood sugar concentrations (Folin-Wu method) were:

Time (p.m.)	2.40	3.0	4.0	5.0	6.0
Blood sugar (mg./100 ml.)	42	37	31	26	24

Glucose Tolerance Test. The results are shown in Fig. 2.

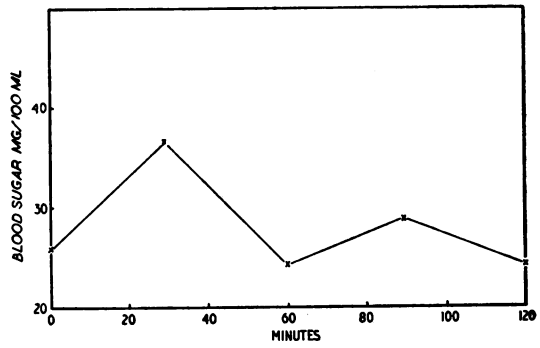

FIG. 2.—Glucose tolerance curve. 13 g. of glucose was fed at time 0.

Plasma Insulin-like Activity. This was determined twice by Dr. J. Vallance-Owen. Before treatment with ACTH he found 120 micro-units of insulin-like activity per ml. of plasma, the blood glucose concentration being 6 mg./100 ml. This is near the upper limit of the normal range. After ACTH therapy was instituted he found 45 micro-units of insulin-like activity per ml. of plasma, the blood glucose concentration being 106 mg. per 100 ml.

Insulin Tolerance Test. The results of four tests, all carried out under cover of ACTH or prednisolone, are shown in Fig. 3.

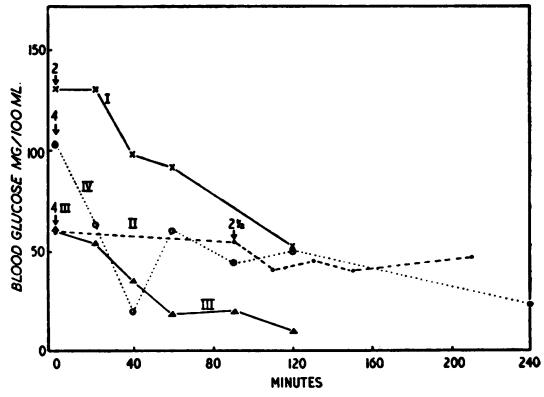

FIG. 3.—Insulin tolerance tests. Test I: 30.12.57. Test II: 20.6.58. Test III: 13.3.58. Test IV: 7.3.58. The indicated number (2, 2.5, 5 and 4 respectively) of units of insulin was injected intradermally at the time marked by the arrow.

Adrenaline Tolerance Tests. The results of four tests are shown in Fig. 4.

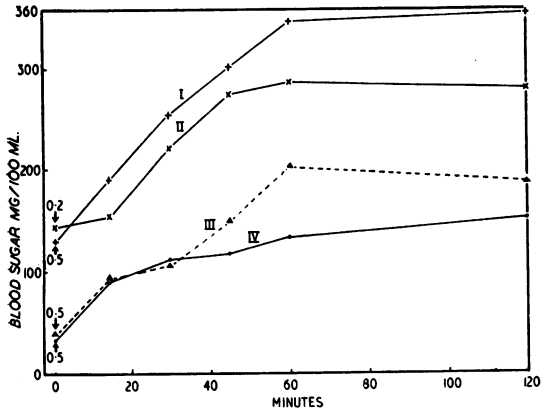

FIG. 4.—Adrenaline tolerance tests. Test I: 3.1.58. Test II: 20.1.58. Test III: 10.1.58. Test IV: 18.6.58. The indicated number of ml. of 1:1,000 adrenaline was injected subcutaneously at the time marked by the arrow (0·2 ml. for curve II, 0·5 ml. for the rest).

Glucagon Tolerance Test. The results of two tests are shown in Fig. 5.

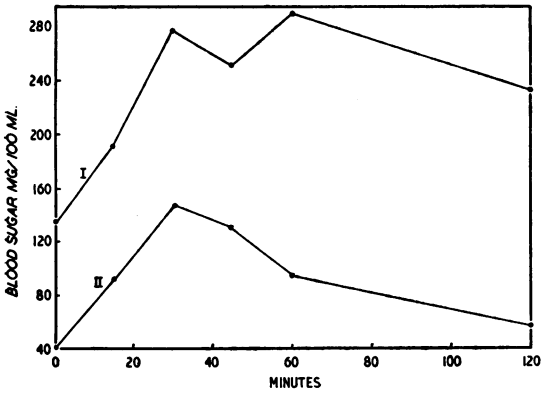

FIG. 5.—Glucagon tolerance tests. Test I: 21.1.58. Test II: 21.7.58. 0·2 mg. of glucagon was injected at time 0 in each case.

Urinary Adrenaline. The first two specimens of urine examined apparently contained large amounts of adrenaline:

Specimen	1	2
Cat assay of urine	14·7	30 µg./12 hr.
Cat assay of urine concentrate ..	29·4	90 ,, ,,
Chromatography urine concentrate	200-300	170 ,, ,,

Unfortunately the techniques of adsorbing the catecholamines on alumina and of chromatography had not at that time been perfected and these two results must be considered doubtful. ACTH was withheld during the 24 hours of this test, but at the end the blood sugar concentration was 94 mg./100 ml.

In all subsequent urine specimens examined, no trace of adrenaline could be found. This in spite of the fact that hypoglycaemia was induced (*a*) by twice withholding prednisolone for up to 25 hours and (*b*) by giving insulin on two occasions, when blood sugar levels dropped to 35, 22, 20, 10 mg./100 ml. respectively.

3-Methoxy-4-hydroxymandelic acid, probably the major urinary metabolite of adrenaline (Armstrong, McMillan and Shaw, 1957) was not increased in amount in any of these specimens of urine as compared with control specimens passed before the onset of hypoglycaemia.

Discussion

Diagnosis. There was no evidence of pituitary dwarfism, Addisonian pigmentation or cretinism in this case. There was no hepatomegaly or ketonuria, and there was a good glycaemic response to adrenaline which excluded glycogen storage disease. Blood and urine examination excluded galactosaemia. The great rarity of hyperinsulinism in infancy and the normal plasma insulin level justified treating the case in the first instance as idiopathic without resorting to laparotomy and pancreatic biopsy.

Thus the present case resembles the cases described by McQuarrie as infantile idiopathic hypoglycaemia in which there was a severe hypoglycaemia causing convulsions uncontrolled by dietary measures, but responding to ACTH or gluco-corticoids. The result of the leucine tolerance test puts the infant into the leucine insensitive group.

Treatment. McQuarrie (1954) found ACTH superior to cortisone. In the present case prednisolone which can be given orally proved effective at a reasonably low dose. The response to ACTH or prednisolone is not only far greater than that normally elicited, but exceeds that found in infantile hypoglycaemia of various causation (Sherman, 1947; Geppert, Spencer and Richmond, 1950; Ulstrom, Ziegler, Doeden and McQuarrie, 1952; Engelhardt *et al.*, 1955; Cochrane *et al.*, 1956).

When the glucose supply to cells exceeds their oxidative requirements, the excess enters other metabolic pools involving fat formation in particular. This effect is inhibited by adrenal cortical steroids (Boutwell and Chiang, 1954). This may be the basis of the infant's very rapid weight gain, and its striking suppression by ACTH.

The very high blood glucose levels when the infant was first given intravenous fluid are difficult to explain. The continued rise in blood sugar level from 470 to 700 mg./100 ml., while little more dextrose was given, suggests an outpouring of glucose from depots into the blood, which could possibly be due to gluco-corticoids released in

response to the stress of acute dehydration and of cutting down on a vein for infusion.

Judging by her present backwardness and the microcephaly, presumably secondary to brain damage, this infant, though she had fits for less than four weeks, has suffered some irreversible mental impairment. This illustrates the urgency in diagnosing and treating this condition.

Investigations. The rapid drop in the blood sugar level during the fasting state suggests too rapid a loss of glucose from the blood to the tissues. The oral glucose tolerance test supports this impression which is confirmed by the failure even of intravenous glucose to produce normal sugar levels.

The value of plasma insulin-like activity, obtained before treatment, was a high normal, as found in an adult after a carbohydrate meal and was far less than that found in organic hyperinsulinism in infancy (Engelhardt *et al.*, 1955; Cochrane *et al*, 1956). In normal adults the plasma insulin-like activity varies inversely with the blood sugar level (Vallance-Owen and Hurlock, 1954); at so low a level of blood glucose as 6 mg. % it is surprising to find any insulin-like activity at all. The 'low normal' figure after treatment is further evidence against hyperinsulinism, but is difficult to interpret, since ACTH may raise the plasma level of insulin antagonist (Vallance-Owen and Lukens, 1957).

The initial response to intradermally administered insulin was normal, thus excluding tissue hypersensitivity to the hormone. The continued drop in blood sugar concentration, over several hours after administration of insulin, is seen in some normal infants (Daniel, 1941).

Unlike older children (Snaith and Woolf, unpublished) and adults (von Euler and Luft, 1952), this infant did not excrete increased urinary adrenaline in response to hypoglycaemia, whether induced by administration of insulin or by withholding steroid. We have no way of deciding whether this was due to a failure to produce adrenaline or a failure to release it into the blood stream in response to hypoglycaemia. Each test was preceded by several days of adequate therapeutic control, which excluded the possibility of exhaustion of the adrenal medulla by over-stimulation. Cortico-steroid treatment as such has no effect on the secretion and release of adrenaline (Luft and von Euler, 1952).

The enormous rises in blood sugar level elicited by adrenaline and glucagon are unprecedented in 28 years' experience at Great Ormond Street (Payne, personal communication) and apparently also in the literature (Desmond, 1953, in normal neonates; Livingston and Bridge, 1942, in normal infants; McQuarrie, 1954, in idiopathic infantile hypoglycaemia; Cochrane *et al.*, 1956, in leucine sensitive hypoglycaemia). Although adrenaline is said to release ACTH from the anterior pituitary (Gershberg, Fry, Brobeck and Long, 1950) the initial response to adrenaline was in this case too rapid for this to make an important contribution, and there is no evidence that glucagon causes release of ACTH. This hypersensitivity is unlikely to be due to previous lack of circulating adrenaline since an adrenalectomized child had a normal response to injected adrenaline (Payne, personal communication). Nor does long-term treatment with ACTH or cortisone cause hypersensitivity to adrenaline.

Pathogenesis. In the normal subject, glucose is continuously transferred from the blood to the cells at a rate that depends, among other things, on the concentration of insulin in the plasma which is itself dependent on the blood sugar level. In the fasting state the blood sugar concentration is maintained from tissue stores under the control of a number of hormones: adrenaline, glucagon, gluco-corticoids and, hence, ACTH. Yet deficiency of each of these hormones is not alone sufficient to cause hypoglycaemia (Zucker and Berg, 1937; Goldner, Volk and Lazarus, 1952; Lazarus and Volk, 1953; Staehelin, Labhart, Froesch and Kägi, 1955; Ginsberg and Paton, 1956; von Euler, 1956).

The failure to maintain normal blood sugar levels on amounts of oral or intravenous glucose that should have been adequate in an infant of this size suggests that there is an excessive loss of glucose to the tissues. This is associated with a moderately high level of blood 'insulin', which cannot alone account for the hypoglycaemia, but suggests a failure to inhibit the secretion of insulin. It further appears that the body has lost the power to respond to hypoglycaemia, even though each hormone in turn, adrenaline, glucagon and ACTH, has been shown to produce an adequate glycaemic response. In other words, there was a failure in the mechanisms that limit the passage of glucose into the cell, and also a failure in the mechanism guiding the release of hormones homeostatic for blood sugar. The latter must itself be a cellular function and may be another aspect of the former.

Summary

A case of severe leucine insensitive idiopathic infantile hypoglycaemia is presented and biochemical tests are discussed in relation to its pathogenesis. A complex disturbance of hormonal and cellular factors controlling blood sugar level is

revealed, perhaps based on a single fundamental cellular defect.

We should like to thank Dr. G. H. Newns for permission to study and report this case, Dr. W. W. Payne for much helpful advice and for carrying out many of the estimations, Dr. J. Vallance-Owen for estimating plasma insulin-like activity, the nursing staff for their untiring care and assistance, and the Research Committee of The Hospital for Sick Children for a research fellowship awarded to one of us (L.I.W.).

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