

gap between the two curves tends to be abnormally wide.) The changes in alkali reserve are also part of an abnormal overall response. 'Normal' hypoglycæmia, if the term can be accepted, is an alkalotic condition. Both the hypoglycæmia and the metabolic alkalosis may be abnormal; but the two abnormalities 'fit'. In adults they are probably both normal responses to a metabolic abnormality which may have nothing to do with carbohydrate metabolism. In babies they may not be abnormal at all. The relationship shown in Fig 3 is abnormal at any age. It still leaves us to identify the biochemical lesion. But it tells us that there is a biochemical lesion to identify.

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Hypoglycæmia in the Newborn

The core of the problem of hypoglycæmia in the neonatal period, from the clinician's point of view, was summarized by Hartmann & Jaudon in 1937: '... the frequent occurrence in the newborn infants of cyanosis, irritability, listlessness and muscular disorders... might very well be due sometimes to hypoglycæmia which is almost a "normal" occurrence during the first few days of life.'

If hypoglycæmia in the adult is defined as a blood glucose level below 50 mg/100 ml, this has long been recognized as a physiological condition in the first few days of life, in that it occurs in the great majority of babies without appearing to do them any harm. For instance, in a group of 69 infants of a mean gestational age of 38 weeks, a single blood sugar estimation was made at a mean age of 31 hours, just before their first feed: 47 of the results fell below 50 mg/100 ml, and the mean for all the babies was 35 mg/100 ml. All the babies appeared perfectly well at the time they were bled, and throughout their stay in hospital.

Disturbances of cerebral function, manifest as neuromuscular inco-ordination and disorders of

respiration, culminating in convulsion, coma or death, are common in the newborn. It has been difficult to accept hypoglycæmia as their cause in the individual baby, however low his blood glucose level, when one knew that the well-looking baby in the next cot might have an equally low level. Real progress has been made in resolving this dilemma during the past five or six years by the systematic application of the therapeutic test of intravenous glucose in a number of centres: on the assumption that a neurological disturbance can properly be attributed to hypoglycæmia if it is associated with a low blood sugar level and is promptly reversed by intravenous glucose in a dose of 1 or 2 g. Cornblath *et al.* reported a series of 8 such cases in 1959, and about 50 more have been reported since then. In the Princess Mary Maternity Hospital, Newcastle upon Tyne, we think we see one such case among every 600-700 babies. This makes it a fairly rare condition, lurking among the far larger number of asymptomatic babies with low blood sugar levels, neurologically disturbed babies with normal blood sugar levels, and babies who have neurological disturbances due to other causes but associated with hypoglycæmia, either coincidentally or secondarily. But its importance is disproportionately great if it is one of those conditions which we are always on the look-out for in the newborn, in which early diagnosis and effective treatment can stave off disaster, and offer the possibility of a complete cure. Dr Vallance-Owen has suggested various possible effects upon the carbohydrate metabolism of the baby, which could result from one or other parent being a constituted diabetic. I do not wish to pursue this question further, since we have no direct observations on this subject. Nor do I wish to discuss the problems of hypoglycæmia in the offspring of mothers suffering from frank diabetes. I shall confine my attention to what could be called idiopathic hypoglycæmia in the newborn, in the sense that its cause is not clearly understood.

The clinical history of one of our first cases is typical in many respects. The baby weighed 2,700 g at 38 weeks' gestation. Apnoeic attacks began just after 24 hours, and the baby appeared dazed: the attacks rapidly became more frequent and by the age of 48 hours the baby was comatose. There had been no response to six doses of anticonvulsants and two injections of intravenous calcium during this time. At 48 hours blood was taken for sugar estimation and 1 g glucose was injected by scalp vein: there was a prompt improvement in the baby's condition to within normal limits, with a corresponding rise in the blood sugar level from less than 20 mg/100 ml. The glucose administration was continued at a

rate of 1 g hourly in a 10% solution: but when the drip stopped and administration by oesophageal tube was attempted the blood sugar fell below 20 mg/100 ml again and a clinical relapse occurred. Again the symptoms responded to intravenous glucose. Treatment was stopped during the fifth day of life and the baby remained well thereafter.

Common experience appears to agree with the report of Cornblath *et al.* (1961) that the blood glucose has to fall below 20 mg/100 ml before symptoms result. They also stated that if the level stays so low for a long time (which they did not define) symptoms almost invariably occur. Perhaps the time has come when we should consider accepting this as a definition of a hypoglycaemic blood level in the newborn.

Since administration of glucose through the gastro-intestinal tract cannot control this condition, we prefer to continue the diagnostic intravenous injection of 10% glucose solution into a scalp vein as a continuous drip at a rate of about 100 ml per kg per twenty-four hours. Oral administration combined with parenteral adrenal glucocorticoids may also be effective (Creery 1963). Treatment can normally be stopped after two or three days, but a careful clinical and biochemical watch needs to be kept for the possibility of an early relapse during the next day or two. Long-term follow-up is indicated because some of these babies have further hypoglycaemic attacks in later infancy or early childhood. This has happened in 2 of our first 12 cases.

Three further points should be mentioned: The first is the fact, for which there is plenty of evidence, that babies of inappropriately low birth weight for their period of gestation are especially liable to develop hypoglycaemia, with or without symptoms. The 30 cases of symptomatic hypoglycaemia in the neonatal period reported by Cornblath *et al.* (1959), Brown & Wallis (1963) and Neligan *et al.* (1963) all fall below the mean growth curve *in utero* from 32 weeks' to 40 weeks' gestation derived from the 13,000 or so single legitimate live births included in the community study of maternity in Newcastle upon Tyne (Russell *et al.* 1963) and all but 5 fall more than one standard deviation below the mean. The 24 further cases recently reported by Cornblath *et al.* (1964) bear the same sort of relationship to the intrauterine growth curve of Lubchenco. It was reported by Neligan *et al.* (1963) that, among asymptomatic babies, significantly lower blood sugar levels are found in those whose birth weight is disproportionately low for their estimated gestational age than in those whose weight is normal or high.

This fact might be explained on the basis of inadequate stores of liver glycogen at the time of birth in babies of poor intrauterine nutrition: because Shelley (1964) has confirmed that the postnatal critical depletion of liver glycogen stores which has long been known in animals also occurs in human babies, and that lower than normal concentrations are found in livers from babies whose birth weight is inappropriately low. This would accord well with the conclusion of Cornblath *et al.* (1963) that the tendency to neonatal hypoglycaemia is explained by the metabolic needs of the relatively large brain exceeding the capacity of the liver of the newborn baby to produce enough glucose to maintain a 'normal' blood level – by adult standards. But it would not explain either the tendency for some of these children to develop hypoglycaemic attacks in later infancy, or the findings of Broberger & Zetterström (1961) that babies of this type appear unable to increase their adrenaline output in the normal way in response to induced hypoglycaemia. The important fact remains, that babies who show clinical evidence of malnutrition at the time of birth, and who develop neurological symptoms during the second or third, rarely the first, day of life are especially likely to be suffering from hypoglycaemia and require urgent investigation from this point of view.

The second point is much more speculative. We know that the onset of neurological symptoms does not coincide in time with the fall in the blood sugar level. This occurs soon after birth, and it may remain below 10 mg/100 ml for up to forty-eight hours before symptoms begin. It is tempting to speculate whether some other metabolic fuel may be available to the brain during this time, and it is exhaustion of this too which precipitates the clinical trouble. A hint of the possible nature of such a fuel is given by the report of Edwards (1964) that induced hypoglycaemia in calves does not produce neurological symptoms so long as they have a sufficiently high level of lactate in their blood. Suggestive evidence that a high level of lactic acid in the blood and cerebrospinal fluid may protect the baby's brain against the ill-effects of hypoglycaemia has already been obtained in one case by the Nuffield Neonatal Research Unit at Hammersmith Hospital.

The final point, and probably the most important of all from the community's point of view, is that we do not appear to know the magnitude of the risk of permanent brain damage being produced by neonatal hypoglycaemia of any particular duration or degree, with or without symptoms. Until adequate controlled

follow-up studies have been done we will not know whether asymptomatic babies should be treated or not.

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Diabetes Mellitus Presenting as Spontaneous Hypoglycæmia in Childhood

The association of spontaneous hypoglycæmia and diabetes mellitus was first emphasized by Allen (1953). In the course of an investigation into the duration of the obesity which so often precedes the onset of classical symptoms, he found that many of his patients gave as a reason for their excessive food intake the fact that they had episodes of hunger, weakness, sweating, trembling and irritability which were relieved only by eating. He attributed these symptoms to hypoglycæmia and found them to be present in 55% of 1,207 diabetic patients. The duration of the hypoglycæmic phase was between one and twenty-five years with an average of twelve years. Seltzer *et al.* (1956) investigated 110 adults with mild untreated diabetes and found that in 69% hypoglycæmic symptoms had been the presenting feature. Glucose tolerance tests were characterized by a normal fasting blood sugar, an early hyperglycæmic plateau and a late drop to hypoglycæmic levels. They concluded that symptomatic spontaneous hypoglycæmia may be one of the earliest clinical manifestations of diabetes mellitus and that this should be ranked as one of the most common forms of spontaneous hypoglycæmia.

The occurrence of spontaneous hypoglycæmia in the earliest stages of the natural history of diabetes in childhood does not appear to be so widely reported. In the majority of children the

classical symptoms of thirst, polyuria and weight loss appear abruptly and within a few weeks the diagnosis is made. Although most parents say their children have been healthy up to the onset of these symptoms it is possible that minor manifestations of hypoglycæmia could be overlooked. Allen (1953) records the case of one boy diagnosed as having diabetes at the age of 11 years, who had had hypoglycæmic symptoms since the age of 4. Traisman *et al.* (1959) report hypoglycæmia as the presenting symptom in 2 out of 110 diabetic children and Bessman (1960) records 2 such cases presenting in one year. We have recently studied 2 children with spontaneous hypoglycæmia which we believe to be due to diabetes mellitus and report the findings in more detail:

Case 1 E O'R, a girl, is the third living child in the family. Her mother, who has two diabetic siblings, was found to have diabetes at the age of 18 years and has had 11 pregnancies. Seven children are living, one died from gastroenteritis at the age of 2 months, 2 died in the neonatal period and one was still-born after 28 weeks gestation. There is no history of diabetes in the father's family. Our patient was born at home and weighed 4.1 kg. At the age of 3 days she was admitted to hospital because she refused to feed. She showed the typical appearance of an infant of a diabetic mother and her blood sugar was 32 mg/100 ml. Subsequent progress was satisfactory and she was followed up in the out-patient department. An oral glucose tolerance test at the age of 5 years showed the rather unusual feature of a second peak at one and a half hours but was otherwise considered to be normal. Between the ages of 5 and 7 years there was an indefinite history of attacks of weakness and vomiting accompanied by pallor or flushing. These symptoms were attributed to tonsillitis and her tonsils and adenoids were removed at the age of 7 years.

She was next seen a year later when she had a generalized convulsion before breakfast. In the post-epileptic phase she vomited and remained drowsy and in this state she was admitted to hospital. On examination she was moderately obese (about 4.5 kg above the

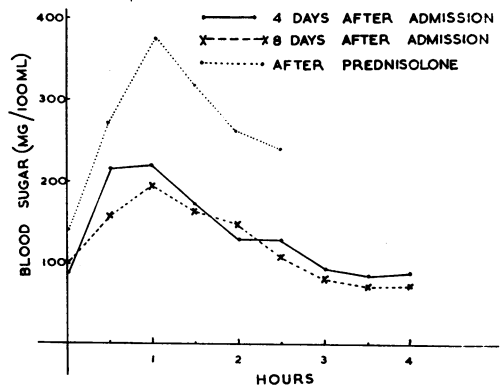


Fig 1 Case 1 Oral glucose tolerance tests at the age of 8 years