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Hypoglycaemia and Temporary Hyperglycaemia in Infants of Low Birth Weight for Maturity

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The importance of hypoglycaemia in newborn infants who have suffered intrauterine malnutrition is now well established (Neligan, 1965). The number of reports on this subject is not yet extensive (Cornblath, Odell, and Levin, 1959; Brown and Wallis, 1963a; Neligan, Robson, and Watson, 1963; Tynan and Haas, 1963; Neligan, 1965), and gives the impression that the ultimate prognosis is often good, provided that treatment is early and adequate. Our experience has been different, and we are, therefore, reporting this further series of hypoglycaemic dysmature infants.

Neligan *et al.* (1963), Engleson and Zetterqvist (1957), and Hutchison, Keay, and Kerr (1962), commented upon the similarity in appearance between such infants and infants with temporary neonatal hyperglycaemia. One of our patients with symptomatic hypoglycaemia developed temporary neonatal hyperglycaemia and required insulin therapy. Because she possibly provides a link between the two conditions, we describe her case in detail.

Subjects

During the period June 1963, to September 1964, 460 infants below 2·5 kg. (5½ lb.) were admitted to Sorrento Premature Baby Unit. Blood sugar was estimated in all infants born to mothers with severe toxaemia, in those with obviously abnormal placentae, and in those who had the clinical features of dysmaturity (Clifford, 1954). The method used was that of Haslewood and Strookman (1939), which estimates blood 'true' sugar. In this way 20 infants with sugar levels below 20 mg./100 ml. were discovered. In common with Baens, Lundeen, and Cornblath (1963), and Neligan (1965), we regarded levels below this figure as indicative of significant hypoglycaemia.

The maturity and birth weights of the 20 infants are shown in Fig. 1. 16 fell below the 10th percentile of weight for gestation (Lubchenco, Hansman, Dressler, and Boyd, 1963); 7 were asymptomatic and, with one exception, were not treated; though not yet followed up beyond 12 months of age, they appear normal. Of the 18 placentae examined, 15 were macroscopically abnormal, with infarcted areas. Toxaemia had been present in 8 mothers; it was regarded as significant only in that it had resulted in placental insufficiency. There was no significant difference between the symptomatic and asymptomatic groups as regards placental state and history of maternal toxaemia (Table I).

The symptoms shown by 13 infants in the symptomatic group were non-specific (Table II). Hypotonicity, irritability, tremor, cyanosis, and apnoeic attacks were the most common. Of the 13 infants, 8 developed symptoms in the first 24 hours. Blood sugar levels were estimated twice in the first 24 hours following diagnosis and daily thereafter. With treatment clinical improvement was rapid. In only 6 patients, however, was a blood sugar reading over 20 mg./100 ml. obtained in the 24 hours after treatment was started. Yet, once the sugar had risen it remained normal in every case but one (Case 10).

Treatment

Treatment is summarized in Table III. All the treated infants were given either hydrocortisone (10 mg./kg. day) or prednisolone (2 mg./kg. day) for a minimum of three days. In addition they received either 10% dextrose or 20% laevulose, the majority of infants being fed by gastric tube. In one infant oral laevulose (20%) was accompanied by diarrhoea, and it was, therefore, not used again by this route. In 6 of the 9 children 10% glucose was given at a rate exceeding 80 ml./kg. day. The infant who relapsed (Case 10) had responded well to initial treatment at 43 hours, but, despite continued hydrocortisone, symptomatic hypoglycaemia recurred at 117 hours. A return of blood sugar to normal followed further laevulose, but she died after 24 hours as a result of multiple visceral haemorrhages.

Results

The results, shown in Table IV, indicate that despite what was at the time considered adequate treatment, symptomatic hypoglycaemia in this series had sinister significance. 4 infants died, and of the 9 survivors, only one is normal. The others show

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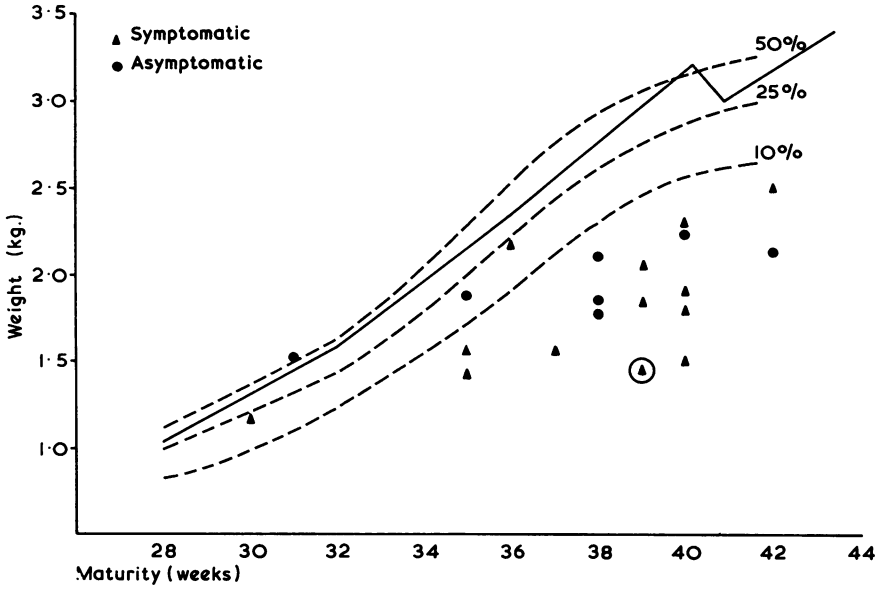

FIG. 1.—*Weight and maturity at birth of 20 hypoglycaemic infants. Broken lines, standards of Lubchenco* et al. *(1963): continuous line, mean birth weights, Sorrento Hospital.* Ⓐ = *infant developing hyperglycaemia.*

TABLE I

Evidence of Abnormal Placenta and/or Maternal Toxaemia

	Symptomatic Group	Asymptomatic Group	Total
Total cases	13	7	20
Placenta: macroscopical appearance			
Normal	3	—	3
Infarcted	9	6	15
Not examined	1	1	2
Maternal toxaemia			
Present	4 (2 severe)	4 (2 severe)	8
Absent	9	3	12
Percentage	30	57	40

TABLE II

Symptoms, Pre-treatment Blood Sugar, and Age at Which Blood Sugar became Normal

Case No.	Hypotonicity	Tremor	Irritability	Pallor	Apnoea	Convulsions	Cyanosis	Blood True Sugar		Blood Sugar > 20 mg./100 ml. at Age
								mg./100 ml.	Age (hr.)	
1	+	+	+	+	+	+	+	9	53	90 hr.
2	–	+	+	–	+	–	+	3	5	31 hr.
3	+	+	–	–	–	+	+	10	72	96 hr.
4	+	+	+	–	+	–	+	0	7	24 hr.
5		+	+	–	–	+	–	4	56	108 hr.
6	+	+	–	–	+	+	–	14	76	114 hr.
7	+	–	+	–	–	–	+	0	13	36 hr.
8	+	+	+	–	+	+	–	0	16	30 hr.
9	+	–	+	–	+	–	+	3	21	34 hr.
10	+	–	+	–	+	+	+	17	24	67 hr.*
11	+	–	–	–	+	–	+	19	16	8 dy.
12	+	+	+	+	+	–	+	8	44	68 hr.
13	+	+	+	–	+	–	+	0	67	–
Total	11	9	10	2	10	6	10			

* Hypoglycaemia recurred at 122 hours.

TABLE III

Treatment

Case No.	Duration (days)		Rate (ml./kg. day)	Route	Duration of Steroids (days)
	10% Dextrose	20% Laevulose			
1	2	—	90	Intravenous (scalp)	3
2	1	—	50	Gavage	1
3	2	—	80	Gavage	6
4	2	—	40	Gavage	7
5	2	—	100	Gavage	9
6	2	—	90	Gavage	7
7	1	—	80	Gavage	1½
8	—	2	90	Intravenous (umbilicus)	7
9	—	2	50	Intravenous (umbilicus)	5
10	—	3	95	Oral	5½
	—	6th day	80	Intravenous (umbilicus)	
11	1½	—	40	Oral	nil
12	2	—	100	Intravenous (scalp)	8
13	Breast fed until collapse: died before treatment possible				

TABLE IV

Results in 13 Symptomatic Cases

Case No.		Follow-up (mth.)	Deaths	Survivors	
				Damaged	Normal
1	Spastic cerebral palsy	17		1	
2	Died (31 hours): intrauterine pneumonia	—	1		
3	Spastic cerebral palsy	17		1	
4	Mentally retarded	12		1	
5	Spastic cerebral palsy	10		1	
6	Normal	12			1
7	Died (48 hours): intrauterine pneumonia	—	1		
8	Spastic cerebral palsy: retarded	10		1	
9	'Delayed': not seen since	5		1	
10	Died (6½ days): pulmonary haemorrhage	—	1		
11	'Delayed'	8		1	
12	'Temporary diabetes', ? cerebral palsy	8		1	
13	Died (68 hours): pulmonary haemorrhage	—	1		
Total			4	8	1

cerebral damage of variable severity. The normal infant was the oldest of the group to develop symptoms, and treatment differed from the rest in that a higher dose of hydrocortisone was given (20 mg./kg. day). Necropsy in the 4 infants who died showed that 2 had bacterial pneumonia, which was presumably of intrauterine origin, and the other 2 had extensive pulmonary haemorrhage. One of the latter was admitted moribund 14 hours after the onset of symptoms and died before treatment could be started. In this patient an additional finding was the presence of prominent pancreatic islet tissue.

One patient (Case 12) is of especial interest as she developed transient hyperglycaemia necessitating insulin therapy, and details of this infant are discussed later.

Discussion

This series resembles other reports of hypoglycaemic dysmature newborn infants in several aspects. Maternal toxaemia was present in 40%, macroscopical placental disease was present in the majority, and all symptomatic infants were of low weight for gestational age.

Our results contrast with other series in two respects. First, our mortality is higher, and secondly, the majority of our survivors show brain damage, whereas other series have a low mortality and the majority of survivors are normal.

The reasons for these differences are not obvious. Selection of cases in other series may account for some of the differences. Our patients resemble those of Tynan and Haas (1963), in that more than half showed symptoms in the first 24 hours of life; similarly there was a high mortality. Neligan *et al.* (1963) and Brown and Wallis (1963a) excluded cases in the first 24 hours of life, and the latter authors (Brown and Wallis, 1963b) agreed that prognosis was less favourable at this time. One of the fatal cases of Tynan and Haas had intracranial haemorrhage. In our patients birth injury appears to be an unlikely explanation of the brain damage, as 7 of the 9 infants were in good condition after delivery. Is it possible that the brain damage occurred within the

first few hours of life? Most of the infants were transferred from other hospitals, some up to 50 miles away, and several had deteriorated by the time they had reached this unit. There may well have been apnoeic episodes during the journey due to hypoglycaemia or other factors. Apnoeic episodes can probably cause brain damage in the newborn infant (McDonald, 1964). However, we have no positive evidence that such attacks did occur.

Could the low capillary blood sugar levels be misleading as evidence of general hypoglycaemia? MacGregor and Robinson (1965) have suggested that as a result of capillary stasis, blood sugar levels obtained by heel-prick may not necessarily reflect levels in the general circulation in sick infants. A considerable number of the estimations in our patients were performed on specimens obtained by heel-prick, and it could be argued that some of the low levels were results of capillary stasis in infants ill from other conditions causing metabolic disturbances, or from cerebral damage. However, the rapid clinical response to treatment in the infants in our series seems adequate evidence that their symptoms were due to cerebral deficiency of glucose. Another possible explanation for the poor results in our patients is that therapy was less energetic than in other series. Neligan (1965) recommends 10% glucose at the rate of 80 to 100 ml./kg. day for intravenous therapy. Only 4 of our patients were given amounts less than this, but the route varied. In addition, all our patients received steroid therapy. Is the route of administration of glucose crucial? Neligan (1965) prefers intravenous to oral glucose and states that by itself oral glucose is inadequate to raise blood sugar and maintain a level above 20 mg./100 ml. Nevertheless, the oral route of glucose administration was reported by Creery (1963) as giving satisfactory increases in blood sugar, and in most of his cases hydrocortisone was not necessary. It is not clear whether oral glucose combined with steroid therapy is adequate. If it is agreed that the high incidence of cerebral damage in the survivors in our series was due to persistent hypoglycaemia, then it must be assumed that it is not. It would also follow that clinical improvement alone is an insufficient indication of successful therapy.

Prevention. We must conclude that not one of the possibilities considered is, by itself, an adequate explanation of the poor results in our patients.

In view of the report of Smallpeice and Davies (1964), that an early high calorie intake may prevent hypoglycaemia, our symptomatic and asymptomatic groups were compared with regard to milk intake. In Fig. 2 the two groups are compared by case number in ml. milk/kg. for the first three days of life. There is a striking difference. This is due to the very different admission state of the patients in the two groups. Infants who were ill on admission were either given nothing in the first 24 hours, or were fed towards the end of this time with small quantities of 5% glucose. The diagnosis of hypoglycaemia led to further delay in feeding milk, or to discontinuation of milk feeds. In the asymptomatic group, because of the dysmature appearance, the nursing staff had started feeding earlier and/or had fed for expected weight. This striking difference appears to support the hypothesis of Smallpeice and Davies, though an alternative explanation would be that those ill on admission, who received smaller amounts, had already sustained brain damage. Further suggestive evidence is provided by the results of a controlled trial of immediate and later feeding recently completed at Sorrento (Wharton and Bower, 1965). Whereas none of the 118 premature babies fed early showed symptomatic hypoglycaemia, it occurred in 4 of the 121 fed later, though in every case the first feed was given before 18 hours of age. Unfortunately, the mortality rate in the immediate-fed group was significantly higher than in the later-fed group.

Mechanism. The mechanism of the disorder is still little understood. Shelley (1964) and Dawkins (1964) have commented upon the poor glycogen reserves of the newborn infant, and Cornblath, Wybregt, and Baens (1963) noted the great deviation from normal in brain/liver weight ratio in dysmature infants. The weight of the brain is almost normal for gestation, and as it can apparently utilize only glucose and lactate it is at a special disadvantage in a state of glycogen depletion. The explanation for the absence of symptoms in the asymptomatic group, even though the blood sugar levels were low, may lie in the higher fat intake in this group. Novák, Melichar, Hahn, and Koldovsky (1965) have shown that fatty acid levels rise to a maximum in the first 24 hours of life in the normal full-term infant, and the low RQ of the newborn indicates that fat is utilized for energy. Fat, by supplying an adequate energy reserve in the normal infant, appears to spare glucose for its essential cerebral function. Moreover, free fatty acids could, through their influence on the glucose fatty acid cycle (Randle, Garland, Hales, and Newsholme, 1963), counteract the sensitive insulin release mechanism which Cornblath, Wybregt, Baens, and Klein (1964) propose as a cause of hypoglycaemia in these infants. Early feeding of the dysmature infant with milk may provide the fatty acids essential for non-cerebral metabolism.

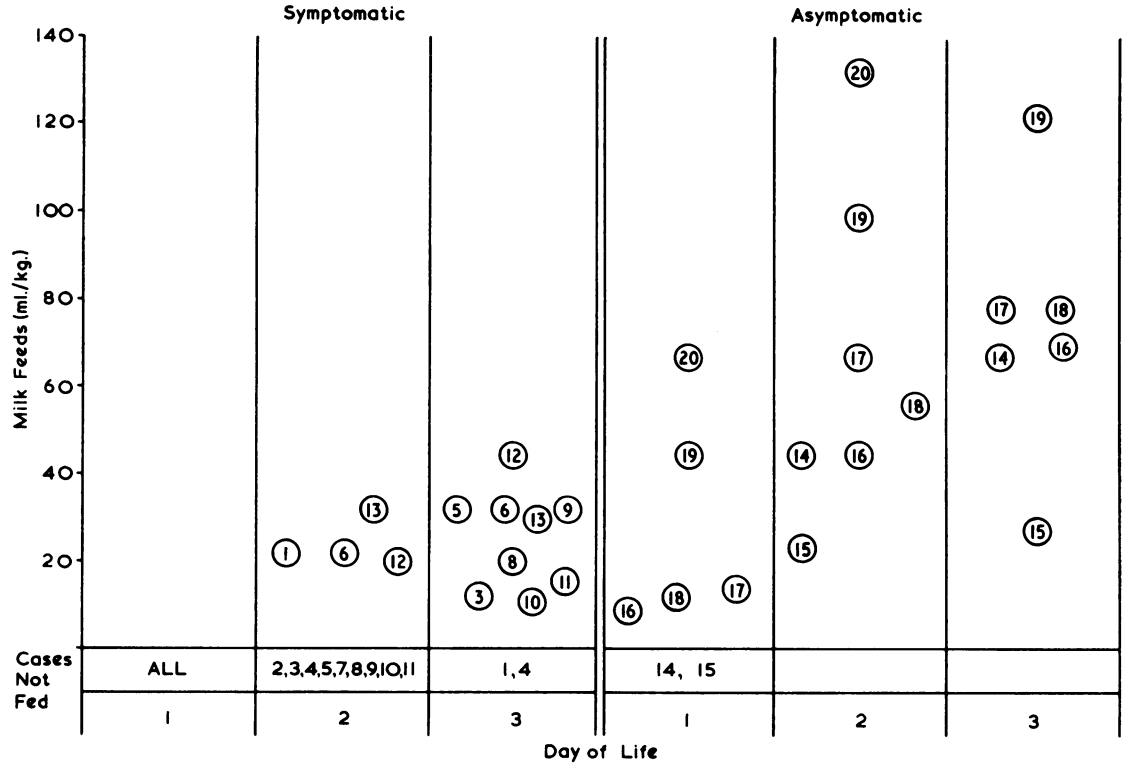

FIG. 2.—*Quantities of milk feeds given in the first three days of life in 20 hypoglycaemic newborn infants with and without symptoms. Numbers refer to individual cases.*

Recommendations. In view of the fact that neonatal hypoglycaemia may be one of the preventable causes of cerebral damage, and in the light of our experience, we suggest that oral milk feeds, if necessary by intragastric drip, should be given early to dysmature infants. Should this preventive measure be unsuccessful and symptomatic hypoglycaemia develop, intravenous glucose should probably be given in addition to steroids.

The Patient Showing Hyperglycaemia

This infant (Case 12) resembled most of the 17 cases of idiopathic neonatal hyperglycaemia which have been reported, except that her insulin requirements were somewhat higher. As there was proven hypoglycaemia preceding the hyperglycaemia, her case is described in detail (Fig. 3).

She was born at 39 weeks maturity, birth weight 1·5 kg. (3 lb. 3 oz.). The maternal grandfather has late-onset diabetes mellitus. In addition to an extremely dysmature appearance she was pallid, extraordinarily alert, and active. She started 10% glucose feeds at 16 hours followed by diluted breast milk. Despite this, when 41 hours old, she suddenly collapsed after slight premonitory twitching. The venous blood sugar level was 8 mg./100 ml. She responded immediately to 2·5 g. glucose intravenously. Treatment was continued with 10% glucose intravenously and hydrocortisone (later prednisolone). Twelve hours later she took breast milk avidly from a bottle. Her early hospital course is seen in Fig. 3. On the fifth day the blood sugar rose to 860 mg./100 ml. but no keto-acidosis developed. Because of polyuria, glycosuria amounting to 20 g./100 ml. urine, and weight loss, prednisolone was withdrawn. Lumbar puncture showed the CSF to be normal apart from a sugar of 225 mg./100 ml. The symptoms persisted and the blood sugar remained above 400 mg./100 ml. Soluble insulin was therefore started. The dosage was deliberately kept low because of the danger of hypoglycaemic brain damage. Plasma insulin, measured immunochemically 16 hours after the first dose (1 unit) of soluble insulin, was 40 μU/ml. At the same time the plasma cortisol was 4·5 μg./100 ml., the cholesterol 48 mg./100 ml., and total lipid 320 mg./100 ml. Soluble insulin was given 8-hourly according to the results of urine testing, some glycosuria being permitted as a safeguard. A steady weight gain was achieved and only on one occasion did she develop any symptoms. She became pallid but remained active and fed well. Blood

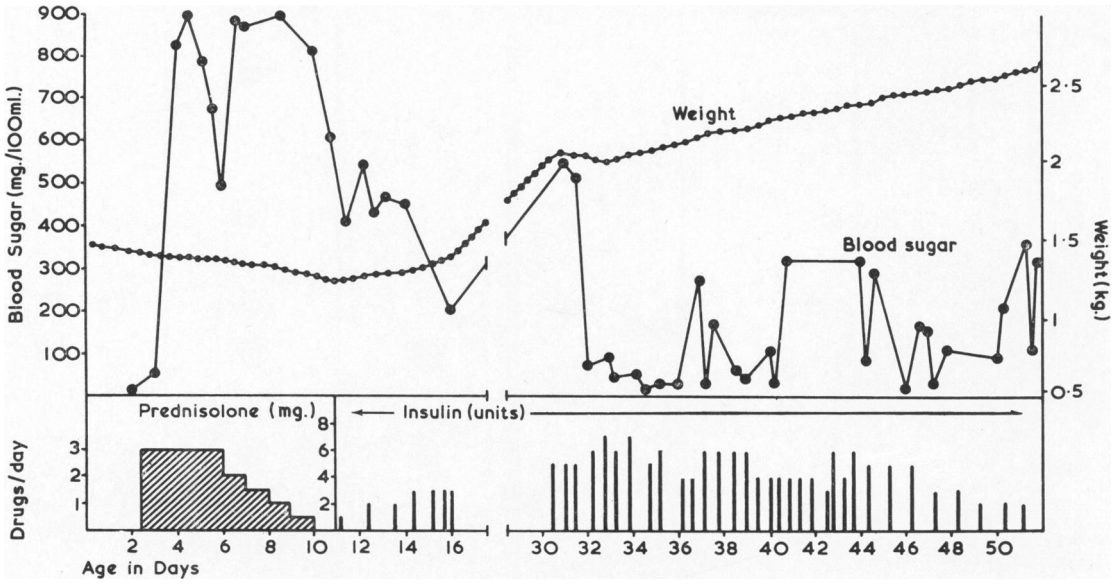

FIG. 3.—*Blood sugar, weight, and treatment in Case 12 during first weeks of life.*

sugar at this time was found to be zero. At 3 months she was discharged home on Lente insulin 4 units daily. Her insulin requirement gradually diminished until at 4 months of age it was no longer needed. When reviewed at 8 months she weighed 7·8 kg. (17 lb.) and mental development was normal. Apart from the presence of brisk tendon reflexes in the lower limbs, neurological examination was negative. Her glucose tolerance curve was normal, the fasting total lipid was 820 mg./100 ml., cholesterol 256 mg./100 ml., and paper electrophoresis showed a prominent pre-β fraction.

Lewis and Mortimer (1964) recently discussed the features of idiopathic neonatal hyperglycaemia, pointing out the absence of ketonuria, and the fact that it was an entity distinct from hyperglycaemia associated with neonatal infections and cerebral abnormalities. Lewis and Mortimer, in common with previous authors, also noted the low birth weight and dysmature appearance of the majority of the reported cases. Despite these features, there has been no other report of proven hypoglycaemia in these children, though the infant reported by Osborne (1965) was thought to be hypoglycaemic before the onset of hyperglycaemia which proved fatal. Lewis and Mortimer reported blood insulin studies in their two cases. Their findings were suggestive either of defective insulin production or of the presence of antagonists. It appears unlikely that the level of plasma insulin in our patient was due to the one unit given 16 hours earlier, and the fact that she was conspicuously hyperglycaemic at that time suggests the presence of insulin antagonism. In this respect it is of considerable interest that Osborne noted unusually large numbers of islets of Langerhans in his case. The relatively high insulin requirements in our patient may have been related to her steroid therapy; however, in view of the family history of diabetes it could be argued that the hypoglycaemia was a 'prediabetic' phenomenon, as described by Lloyd (1964), and that her hyperglycaemia was steroid provoked. A fact in favour of this explanation is the more recent finding of a high cholesterol and fasting 'pre-β' lipoprotein fraction in the serum. However, in view of her neonatal appearance and the apparently complete remission we favour the former explanation. The recent glucose tolerance test was normal in the absence of steroid provocation.

Summary

Data are presented on 20 infants of low birth weight for maturity who were found to be hypoglycaemic. Of these, 13 developed symptoms; despite apparently adequate treatment 4 died and only 1 of the 9 survivors is normal. Possible explanations for the disparity between these results and those of others are discussed, in particular the influence of intravenous therapy, case selection, and capillary stasis. No single explanation is considered to be satisfactory. Comparing the symptomatic and asymptomatic groups, one factor of probable importance is the higher milk intake in the asymptomatic group. Only when hypoglycaemia has been either prevented by diet, or treated urgently at the earliest suspicion, will it be possible to assess its importance in the aetiology of cerebral damage in the newborn.

One patient with symptomatic hypoglycaemia

developed temporary hyperglycaemia which necessitated insulin therapy. Possible explanations for this are suggested.

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