Assessment of Effects of Neonatal Hypoglycaemia

A Study of 41 Cases with Matched Controls

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Griffiths, A. D., and Bryant, G. M. (1971). *Archives of Disease in Childhood*, 46, 819. **Assessment of effects of neonatal hypoglycaemia.** 41 infants who had experienced neonatal hypoglycaemia (blood glucose less than 20 mg/100 ml) were reviewed at a mean age of 51 months and compared to a group of matched controls. Symptomatic and asymptomatic infants were represented in the hypoglycaemic group in a similar ratio to that found during a previous study of the incidence of hypoglycaemia in a special care unit.

Evidence of cerebral damage was found in 6 of the children who had been hypoglycaemic (14.6%) and in 5 of the controls (12.2%). This difference is not significant. The mean IQ and locomotor scores of the two groups were identical, and there was no difference in the incidence of behaviour disorders or convulsions.

It is concluded that, while it is important to identify and treat cases of 'true' symptomatic hypoglycaemia, the large majority of infants tolerate low blood glucose levels without sequelae. The prognosis for infants with asymptomatic hypoglycaemia is particularly good, none of the 12 infants in this series showing any evidence of cerebral damage.

The ability of newborn infants to remain apparently symptomless in the presence of low blood sugar levels has been known for many years (Hartmann and Jaudon, 1937; McKittrick, 1940; Norval, Kennedy, and Berkson, 1949; Haworth and Ford, 1960; Baird and Farquhar, 1962; Yu *et al.*, 1965), and even when symptoms occur they are usually coincidental (Griffiths, 1968). True symptomatic hypoglycaemia is rare with an incidence variously quoted as 2 per 1000 total births (Neligan, Robson, and Watson, 1963), 2.9 per 1000 total births (Cornblath, Segal, and Smith, 1967), and 1.3 per 1000 term births (Zetterström, 1963).

Despite the apparent lack of symptoms at the time, the possibility exists that low blood glucose levels might conceivably result in cerebral damage which only becomes manifest clinically later in childhood.

This paper presents the results of an investigation into the neurological status of a group of children who were hypoglycaemic during the neonatal period and compares them with matched controls.

Material and Methods

During the 2½ years from January 1964 to July 1966, 900 infants were admitted to the Special Care Unit. The reason for admission was either because they weighed less than 2 kg at birth, were ill, or were at risk. 112 of the infants were born at home or in other hospitals, the remainder being among the 6507 live births which occurred at the Cardiff Maternity Hospital during that period.

All infants were fed within 6 hours of birth. The average calorie intake increased from approximately 17 cal/kg on the first day of life, to approximately 90 cal/kg on the 7th day.

The infants were recorded as showing symptoms suggestive of hypoglycaemia if there were apnoeic attacks, irritability, 'juddery' movements, fits, or alterations of muscle tone.

Blood samples for glucose estimation were obtained by heel stab from all infants within 24 hours of admission to the Unit, irrespective of the presence of symptoms. The postnatal age of the infants at the time of initial sampling varied, but in the majority this was performed during the first day of life. Subsequent estimations were usually performed if the initial glucose value was less than 20 mg/100 ml or if the suggestive symptoms developed later. The heel was rubbed, but not other-

TABLE IA

Comparison of 41 Hypoglycaemic and 41 Control Infants to Illustrate Compatibility with Regard to Birthweight, Length of Gestation, and Age at Time of Examination

Factor Compared	No. of Hypoglycaemic Infants	Mean ($\pm$ SD)	No. of Control Infants	Mean ($\pm$ SD)	t	P
Birthweight (kg)						
1.0-1.5	6		1			
1.6-2.0	12	2.570	13	2.466	0.946	<0.4
2.1-2.5	7	(0.861)	11	(0.647)		>0.3
2.6-3.0	7		6			
>3	9		10			
Gestation (wk)						
<30	0		1			
30-32	2		2			
33-34	7	37.415	5	37.732	0.425	<0.7
35-36	9	(3.200)	6	(3.472)		>0.6
37-38	6		8			
39-40	9		9			
>40	8		10			
Age at examination (mth)						
<24	2		1			
24-35	0	51.122	1	52.659	0.636	<0.6
36-47	15	(11.431)	10	(10.137)		>0.5
48-59	11		18			
60 and over	13		11			

(For significance at $P = 0.05$, t lies between 1.980 and 2.000.)

TABLE IB

Comparison of 41 Hypoglycaemic and 41 Control Infants to Illustrate Compatibility with Regard to Apgar Score, Social Class, Position in Family, and Birthweight Related to Gestational Age

Factor Compared	No. of Hypoglycaemic Infants	No. of Control Infants	χ^2 (value for sig $P = 0.05$)	P
Apgar Score				
1-3	14	15		
4-6	12	9	0.587	<0.8
7-10	15	17	(5.991)	>0.7
Social Class				
I	4 }	3 }		
II	3 }	7 }	0.501	<0.8
III	23 }	22 }	(5.991)	>0.7
IV	7 }	5 }	The unclassified cases were not included in the analysis of χ^2	
V	2 }	4 }		
Unclassified	2	0		
Position in Family				
1st	25	24		
2nd	8	10		
3rd	6 }	3 }	0.308	<0.9
4th	1 }	3 }	(5.991)	>0.8
5th or subsequent	1 }	1 }		
Birthweight in relation to gestation (centiles)				
<10	13	11		
10-24	7	6		
25-49	4	9	2.389	<0.7
50-74	8	6	(9.488)	>0.5
75 and over	9	9		

(Those subgroups bracketed together in the Table were aggregated when χ^2 was calculated, in order to obtain sufficiently large numbers of infants in each group.)

wise warmed, and the interval between sampling and feeding varied. Blood glucose was estimated by a modification of the method of Watson (1962) and hypoglycaemia was diagnosed if the level was less than 20 mg/100 ml.

Blood glucose values of less than 20 mg/100 ml on one or more occasions were detected in 115 of the infants. 13 of these infants died during the neonatal period and the necropsy findings have been reported previously (Griffiths, 1968). In every case there were gross pathological changes unrelated to hypoglycaemia which appeared to be the cause of death. A further 23 infants either moved away from the area subsequently or had neonatal records which could not be traced.

Normoglycaemic control infants matched exactly for sex and as closely as possible for birthweight, gestational length, Apgar score, social class (Registrar General's Classification), and position in family, were chosen from infants admitted if possible within three months of the index case. An acceptable match was made for 75 of the 79 hypoglycaemic infants.

For the purpose of assessment the infants were divided into groups of 6, each group containing 3 index cases with their respective controls. The order of examination of the infants within any group of 6 was randomized by means of previously allotted numbers, and the infant's neonatal blood glucose level was unknown to the examiner at the time of the test.

The children were seen in their homes where possible, but a number were seen at the clinic. The examinations, which were carried out between September 1968 and March 1970, embraced the following procedures:

- (1) A detailed medical history, particular attention being paid to milestones of development and to a history of convulsions.
- (2) A complete physical and neurological examination.
- (3) A cover test to detect a squint, and a Stycar screening test of vision.
- (4) Hearing was tested using the Stycar method, and followed up by audiometry if necessary.
- (5) An assessment of locomotor status was made, by observation and by completing the Ruth Griffiths locomotor scale with its extensions, which gave a locomotor quotient.
- (6) Intelligence testing was carried out, where practicable, using the Terman Merrill adaptation of the Stanford Binet test, and this also gave an opportunity to study the child's fine movements and hand-eye co-ordination. Some of the children were too young for this test, and therefore a General Quotient was obtained using the Ruth Griffiths test.
- (7) Behaviour was assessed using the Behaviour Section of the Stott Systemic interview guide (from birth to 5 years).

Results

Out of a possible 150 infants (75 pairs), 99 were actually examined, the remainder being lost to follow-up as a result of moving away from the district (14), unrecorded changes of address (14),

being persistently away from home (19), unwillingness to co-operate (3), or death (1). 17 of the 99 infants examined were excluded from analysis as they were single members of a matched pair (11 index cases and 6 controls). The following results apply to the 82 remaining infants who constitute 41 matched pairs.

(1) **Compatibility of hypoglycaemic and control groups.** Tables I A and B illustrate the compatibility of the two groups with regard to birthweight, gestational length, age at time of examination, Apgar score, social class, position in family, and birthweight in relation to gestational age (expressed by the centile ratings of Lubchenco *et al.*, 1963).

Application of the 't' test reveals no significant difference between the groups with regard to birthweight, gestational length, or age at time of examination, while the χ^2 test shows that the groups are also similar in regard to the other factors.

Twenty-nine of the hypoglycaemic infants and 30 of the controls were examined in their homes and the remainder in the clinic.

(2) **History of convulsions.** 10 of the 82 children had had one or more convulsions, 4 in the hypoglycaemic group and 6 among the controls (Table II). However, the 2 who could be regarded as epileptic (Cases 30 and 48) were both in the hypoglycaemic group, and these were the 2 children who were also grossly handicapped in other ways (Table III).

(3) **Vision.** One of the hypoglycaemic infants

TABLE II
Infants with History of Convulsions

	Index No.	History
Hypoglycaemic Infants	30	Epilepsy
	48	Epilepsy
	50	Occasional attacks between 3 and 4 years thought to be <i>petit mal</i>
	76	One fit which occurred 2 weeks after mumps
Control Infants	19 c	4 attacks between 3 and 4 years; normal EEG
	32 c	4 fits between 3 and 4 years, thought to be 'febrile convulsions'
	50 c	4-6 attacks; some possibility that they were breath-holding rather than epileptic; EEG refused
	51 c	One fit only
	60 c	Admitted twice in status epilepticus at 12 months and has a residual mild hemiplegia
	72 c	One convulsion associated with tonsillitis

Index No.	Sex	Social Class	Position in Family	Birthweight (kg)	Gestation (wk)	Centile	Maternal Age	Pregnancy	Delivery	Apgar Score	Blood Glucose (mg/100 ml)
30	M	V	1	3.0	36	75	24	APH PET	Normal vertex	8	87 hr 18 n 93 hr 20 n 6th day 47 n
48	M	III	3	2.23	42	<10	35	Anaemia	Rapid vertex delivery of meconium stained infant	2	1 hr 13 n 16 hr 50 n 23 hr 14 n 40 hr 12 n 64 hr 37 n 88 hr 56 n 122 hr 30 n
32	M	IV	1	1.9	37	<10	32	Twin; APH Prem. rupt. membranes	2nd twin; normal vertex	7	35 hr 35 n 60 hr 12 n 84 hr 12 n
50	M	III	1	1.45	37	<10	26	Low oestriol levels; small baby not growing	LSCS	10	0.5 hr 13 n 25 hr 19 n 72 hr 31 n
51	F	III	2	1.45	39	<10	27	Low oestriol levels; small baby; urinary infection	Assisted breech; fetal heart rate 70-90	7	10 hr 9 n 14 hr 18 n 34 hr 42 n 59 hr 33 n 82 hr 34 n 106 hr 39 n
76	M	I	1	3.25	41	50-75	24	Normal	Normal vertex	2	17 hr 19 n 40 hr 38 n 64 hr 36 n
32c	M	II	1	2.5	39	10-25	21	PET	Normal vertex	9	84 hr 20 n 5th day 52 n
60c	M	III	1	2.35	34	75-90	27	Twin (first)	Forceps vertex	10	43 hr 38 n
51c	F	III	7	2.03	41	<10	32	Normal	Normal vertex, 48 hr after ARM cord tight around neck	7	10 hr 60 n 34 hr 62 n
50c	M	III	1	2.0	35	25	23	APH	Prem. rupt. membranes; normal vertex	8	5 hr 45 r 30 hr 42 r 54 hr 34 r
48c	M	III	2	2.95	37	50-75	36	APH	Normal vertex	1-3	1.5 hr 41 r 25 hr 40 r 50 hr 40 r

FFP, fresh frozen plasma; RDS, respiratory distress syndrome; APH, antepartum haemorrhage, PET, pre-eclamptic toxemia, LSCS, lower segment caesarean section.

was blind, due to retrolental fibroplasia. There were no other children who were visually handicapped, but 7 had squints, 2 being in the hypoglycaemic group, and the remainder among the controls.

(4) **Children showing evidence of cerebral damage.** The relevant details are summarized in Table III.

The numbers are fairly evenly distributed be-

Cerebral Damage

Relevant Treatment	Relevant Symptoms	Other Details	Age at Examination (mth)	IQ	Locomotor Score	Evidence of Cerebral Damage	Comment
0% dextrose from 87 hr to 1 day	Convulsions and apnoeic attacks from 3rd day	Retroplacental clot; 'placental insufficiency'	59	—	—	Severe epilepsy and gross cerebral palsy	
0% dextrose from 91 hr begun	Twitching, juddery, frog position, 'cerebral signs,' abnormal movements	Aspiration pneumonia; FFP given for low thrombotest; urinary tract infection; 'boggy' anterior fontanelle; cerebral haemorrhage	53	—	—	Gross bilateral hemiplegia with severe subnormality and epilepsy	
fructose only	Cool and hypotonic	Jaundiced (max. bilirubin 7.5 mg/100 ml); thereafter good progress	62	110	90	Mild (R) hemiplegia with abnormal EEG	
0% dextrose from 12 to 6 hr	Hyperactive	Small placenta (250 g); idiopathic RDS; low thrombotest; diarrhoea (klebsiella infection); urinary infection	51	95	90	Slow general development; poor motor co-ordination; fits at 3½ yr	
7.5% dextrose from 12 to 64 hr	None while hypoglycaemic; cool and anxious later	Low thrombotest; diarrhoea— <i>Esch. coli</i> 055	51	81	82	Slow general development; poor speech; enuretic	IQ low for family
e	None while hypoglycaemic; convulsion on 7th day when glucose 83 mg	Perinatal asphyxia; intubated; suspicion of sutural diastasis	42	85	93	One fit at 3 yr, after mumps; hyperactive and distractable behaviour	IQ low for family
0% dextrose from 87 hr to 6 hr	Apnoeic attacks; boggy AF, limp; cerebral cry; head retraction	Placenta 368 g infarct covered ½ surface; ? cerebral haemorrhage or meningitis; CSF turbid but sterile; no increase in cells; protein 72 mg; glucose 4 mg (blood glucose 20 mg) at 60 hr	68	69	82	Slow speech, squint, 4 fits between 18 and 30 mth	
	Juddery only	Jaundiced (maximum bilirubin 15 mg/100 ml, oedema	58	107	86	Mild (L) hemiplegia; status epilepticus twice at 12 mth	
0% dextrose from 12 hr to 1 day	Cerebral signs	Initial signs of respiratory distress and cerebral irritation with boggy anterior fontanelle and abnormal movements; pathogenic <i>Esch. coli</i> 055 cultured from stools; face bruised and subconjunctival haemorrhages	56	65	78	Valve inserted for hydrocephalus; fits at 18 mth; hyperactive and incoordinate	
	Juddery and hypotonic	Low thrombotest; chest infection; systolic murmur first heard at 18 mth	58	74	90	Retarded general development; hyperactive and distractable	
0% dextrose from 6 hr to 48 hr used to give 1 HCO ₃ for v pH)	Juddery	Circumvallate placenta of 750 g with large infarct; acidosis, pH 7.118 after birth	51	113	70	Slow motor development, squint, some spasticity of thigh muscles	

sarian section; ARM, artificial rupture of membranes.

tween the two groups, evidence of cerebral 'damage' being detected in 6 of the hypoglycaemic infants and 5 of the controls. If the infants with minimal involvement are excluded (Cases 50, 51, 76, and

50c) the ratio becomes 3 to 4, so there appears to be no significant difference in the incidence of cerebral damage between the two groups. The two grossly damaged children, however, with

severe subnormality (Cases 30 and 48) are both in the hypoglycaemic group, but even in this respect the difference between the groups is not significant ($P = 0.247$ Fisher's exact probability test).

One of the control infants with evidence of cerebral damage (Case 32c, Table III) had the initial glucose estimation at 84 hours, and this was borderline at 20 mg/100 ml. If this infant is considered to be hypoglycaemic, there would be 7 damaged children among 42 hypoglycaemic infants and 4 damaged children among the remaining 40 controls. Even this difference fails to achieve statistical significance ($P = 0.289$ Fisher's exact probability test).

(5) **Intelligence.** Of the 41 pairs, 8 were excluded from analysis for the reasons given below. When these criteria applied to only one member of a pair, both were excluded from analysis. 3 children were too severely handicapped for the IQ to be valid (these include the child with retrolental fibroplasia and the two children with gross cerebral palsy, all of whom were in the hypoglycaemic group), 3 were too young for the Terman Merrill test to be used (a matched pair and one other hypoglycaemic child), and 3 others were excluded as inability of members of the family to speak English made the test unreliable (one was hypoglycaemic, and the others controls).

The mean IQ of the 33 hypoglycaemic infants was 99.8 ± 10.2 and that of the control group 100.4 ± 11.9 . These are identical ($t = 0.002$ $P = > 0.9$). The distribution of IQ within each group is shown in Table IV. In order that valid

Three infants had an IQ less than 80, all of them in the control group (Table IV), though the difference between the groups in this respect is not significant ($P = 0.119$, Fisher's exact probability test). It is interesting to speculate that these three cases have their counterpart in the two hypoglycaemic infants excluded from the analysis because they were too severely handicapped to be tested (Cases 30 and 48).

It, therefore, appears that hypoglycaemia has no deleterious effect on the IQ of the majority of infants. However, one form of cerebral anoxia is known to reinforce the effects of another already present (Himwich and Fazekas, 1937; Yannet, 1939; White, Gilliland, and Ewalt, 1950; Courville, 1955), and insulin-induced hypoglycaemia acting as a form of histotoxic anoxia (Courville, 1957) has been shown to accentuate other anoxic states (Glickman and Gellhorn, 1938). A further analysis was therefore undertaken to determine whether the 12 infants who had been both hypoglycaemic and anoxic (Apgar score 3 or less) were at a disadvantage compared to those 14 infants who had only been anoxic. The mean IQs of the two groups, respectively, were 99.6 and 103.9, but the difference is not significant ($t = 1.208$; $P = < 0.3$, > 0.2).

(6) **Locomotor development.** An accurate assessment of locomotor score could not be obtained in 4 of the hypoglycaemic children: 3 of them had a severe handicap (2 (Cases 30 and 48) having severe cerebral palsy, and one retrolental fibroplasia), while the fourth was excluded because the combination of a chaotic household and non-English speaking parents made the test unreliable. These 4 children and their respective controls were therefore excluded from analysis.

The mean locomotor quotient in the 37 remaining hypoglycaemic children was 102.6 ± 8.1 , while

TABLE IV

Distribution of Terman Merrill IQ in Group of 33 Hypoglycaemic Children with Matched Controls

IQ	Hypoglycaemic Group	Control Group	χ^2	P
60-69	0	2	2.742	<0.5
70-79	0	1		
80-89	7	0		
90-99	5	9		
100-109	15	15	>0.3	>0.3
110-119	6	6		

(In applying the χ^2 test the three subdivisions of IQ which were <90 were combined, for significance at $P = 0.05$; $\chi^2 = 7.815$ when $n = 3$.)

comparison could be made using the χ^2 test, the small number of infants whose IQ fell into the three subdivisions which were less than 90 were considered as a single group. No significant difference between the distributions was detected ($\chi^2 = 2.742$; $P = > 0.3$).

TABLE V

Distribution of Locomotor Quotient in Group of 37 Hypoglycaemic Children with Matched Controls

Locomotor Quotient	Hypoglycaemic Group	Control Group	χ^2	P
70-79	0	1	1.508	<0.7
80-89	3	2		
90-99	5	9		
100-109	22	17		
110-119	7	7	>0.5	>0.5
120+	0	1		

(In applying the χ^2 test the three lowest subdivisions of locomotor score and also the two highest, were combined. For significance at $P = 0.05$ $\chi^2 = 5.991$ when $n = 2$.)

that of the respective controls was 102.3 ± 9.3 . These are identical ($t = 0.145$ $P = >0.9$).

The distribution within each group is also similar and is shown in Table V ($\chi^2 = 1.508$; $P = <0.7$, >0.5).

(7) **Behaviour.** There were 12 children whose behaviour was regarded as being a problem by their parents and who had high scores on the Stott guide. 5 of these were in the hypoglycaemic group and 7 were controls (Table VI).

TABLE VI
Children with Behaviour Problems

	Index No.	Stott Score	Main Behaviour Problems
Hypoglycaemic Children	12	10	Aggression and temper tantrums
	17	4	Timid, shy and fearful
	27	5	Timid, shy and fearful
	34	6	Problems with feeding and sleeping etc.
	76	5	Hyperactive and restless
Control Children	1 c	5	Problems with toilet, etc.
	30 c	6	Aggression and temper tantrums
	34 c	6	Aggression and temper tantrums
	50 c	8	Hyperactive and restless
	51 c	10	Hyperactive and restless
	61 c	5	Hyperactive and restless
	73 c	10	Aggression and temper tantrums

(8) **Deafness.** No evidence of deafness was detected in any of the children examined.

Discussion

In assessing the outcome of hypoglycaemia in the neonatal period, the results will to some extent depend on whether only symptomatic infants, or both asymptomatic and symptomatic infants are included in the study.

If the infant is symptomless at the time of the hypoglycaemic episode, the prognosis is thought to be good (Neligan—unpublished work quoted by Shelley and Neligan, 1966). Both Haworth and McRae (1965) who studied 14 cases, and Chance and Bower (1966) who studied 7 cases, found evidence of possible cerebral damage in 12% of such infants on follow up.

Symptoms may be associated with hypoglycaemia in a number of ways. The hypoglycaemia may itself produce the symptoms; such 'true' symptomatic hypoglycaemia usually presents after the first 24 hours of life, and is diagnosed by the disappearance or amelioration of symptoms after a therapeutic test dose of intravenous glucose. It is often difficult to maintain subsequent normal blood glucose

levels even with intravenous therapy in this variety of hypoglycaemia which is however rare with an incidence of 1.3 per 1000 term births (Zetterström, 1963), or between 2 and 2.9 per 1000 total births (Neligan *et al.*, 1963; Cornblath *et al.*, 1967). The reported incidence of cerebral damage following this condition varies between 20 and 50%. Cornblath and Schwartz (1966) found that 20% had obvious mental and neurological defects on follow-up, while a further 10% had died. Cornblath, Odell, and Levin (1959) studied 8 cases, 7 survived and 2 of these showed evidence of cerebral damage (29%). Haworth *et al.* (1963) found evidence of damage in 2 out of 6 infants (33%), while Brown and Wallis (1963) found such evidence in 4 out of 8 survivors (50%).

Both hypoglycaemia and symptoms may be attributed to a primary cause such as cerebral birth injury (Cornblath *et al.*, 1964; Haworth and McRae, 1965; Knobloch *et al.*, 1967). Creery (1966) found that all of 5 such infants studied had evidence of neurological damage at follow-up (100%), while Knobloch *et al.* (1967) found that 23 out of 26 infants of non-diabetic mothers with symptomatic neonatal hypoglycaemia had either died or survived with evidence of CNS dysfunction (89%). Without controls it is difficult to decide whether the hypoglycaemia so produced exacerbated the cerebral damage, though it is known that insulin-induced hypoglycaemia can accentuate other anoxic states (Glickman and Gellhorn, 1938) and that intravenous infusions of glucose and alkali prolong survival in newborn lambs and monkeys rendered anoxic (Dawes, 1963).

The association of symptoms with hypoglycaemia may also be coincidental. Griffiths (1968) found that hypoglycaemia was common when looked for routinely with an incidence of approximately 15% among admissions to a special care unit, or 1.7% among total live births, and the incidence of symptoms in infants with and without hypoglycaemia did not differ significantly. It is therefore likely that the majority of infants have no symptoms directly due to their hypoglycaemia.

The preliminary results of a follow-up of 16 hypoglycaemic infants and 18 controls matched for age and birthweight were reported by Cornblath *et al.* in 1966. They found that the hypoglycaemic infants had a lower mean IQ (81 compared with 91), a higher incidence of neurological abnormality (56% compared to 28%), and a higher proportion of abnormal EEG tracings (47% compared to 22%). The authors do not state if asymptomatic cases were included, and though they point out that 15% of the hypoglycaemic infants appear to have had

primary central nervous damage at the time they were hypoglycaemic, it is not clear whether this was a result of the hypoglycaemia or due to cerebral birth injury.

Cox and Dunn (1967) followed up 14 low birth-weight hypoglycaemic infants together with 14 controls matched for age, plurality, and birthweight. They found evidence of neurological abnormality in 11 of the hypoglycaemic group but only four of the controls—a significant difference. They included only symptomatic infants, however, and there was also a higher proportion of dysmature infants in the hypoglycaemic group. Furthermore two of the damaged infants in the hypoglycaemic group developed their hypoglycaemia after the age of 6 months.

The majority of hypoglycaemic infants in the present study were diagnosed as a result of routine blood glucose testing. The sample of 41 cases contains symptomatic and asymptomatic hypoglycaemic infants in a similar ratio (7:3) to that found during a survey of hypoglycaemia among 1000 admissions to a special care unit (6:4) (Griffiths, 1968). The outcome is therefore likely to be a true reflection of that of neonatal hypoglycaemia generally. 12 infants had no symptoms in the neonatal period, and none of these infants showed evidence of cerebral damage at follow-up. 12 infants had definite 'cerebral' symptoms consisting of convulsions, apnoeic attacks, awkward movements, etc., while 17 had other symptoms such as judderiness, hypotonia, or signs of respiratory distress syndrome. 3 cases in each group had evidence of cerebral damage on follow-up, giving an incidence of 25% and 18%, respectively. The overall incidence of cerebral damage among the hypoglycaemic infants is therefore 6 among 41 cases, or 14.6%. This does not differ significantly from the 12.2% incidence found among the control group ($\chi^2 = 0.104$ $P = <0.8$, >0.7). In addition the mean IQs and locomotor scores, and the incidence of convulsions, squints, and behaviour disorders, did not differ between the two groups. It, therefore, appears that the majority of infants not only have no symptoms directly attributable to hypoglycaemia, but also that their prognosis for normal neurological development is no worse than that of a control group without hypoglycaemia, but including similar numbers of infants with low birthweight, perinatal anoxia, and dysmaturity, etc. The deleterious effects of 'true' symptomatic hypoglycaemia would be unlikely to affect the overall statistical outcome, because of the rarity of this condition compared to the relative frequency of 'coincidental' hypoglycaemia.

As some of the hypoglycaemic infants in the present study had been treated with intravenous dextrose, it could be argued that the effects of hypoglycaemia were thereby mitigated. This is unlikely to be the case, however, as no damaged children were found among the 12 who had experienced symptomless hypoglycaemia and only 5 of these had received intravenous dextrose. Furthermore the incidence of cerebral damage among those children who had had symptomatic hypoglycaemia was 23.5% in the treated group (4 out of 17 cases), and only 16.7% in the untreated group (2 out of 12 cases).

Although there is no difference in the incidence of cerebral damage between the hypoglycaemic and control groups, the two most severely damaged infants with severe cerebral palsy and epilepsy were both in the hypoglycaemic group.

One of these infants (Case 30, Table III) was well until the third day of life when apnoeic attacks and convulsions occurred. Meningitis was excluded by lumbar puncture and both serum calcium and thrombotest values were normal. The blood glucose was only 18 mg/100 ml. The onset of symptomatic hypoglycaemia after the first day of life and the partial response to intravenous dextrose make it likely that this infant had 'true' symptomatic hypoglycaemia.

Similar arguments apply to the other damaged child (Case 48, Table III) as a glucose level of 12 mg/100 ml was recorded as late as 40 hours after birth despite the fact that a glucose infusion was in progress. In addition, however, this infant had experienced severe perinatal asphyxia and also a probable cerebral haemorrhage. Both were treated with intravenous dextrose.

There is, therefore, a possibility that while hypoglycaemia may be harmless to an otherwise healthy infant, it might exacerbate the effect of previous or concurrent anoxia on the nervous system as suggested previously. The mean IQ of 14 control infants who had been anoxic (Apgar score 3 or less) in the present study was 103.9 compared to a mean of 99.6 on 12 infants who had been both anoxic and hypoglycaemic. These values do not differ significantly ($t = 1.208$; $P = <0.3$, >0.2). One of the 14 anoxic infants had evidence of cerebral damage (7.2%) compared to 2 of the 12 infants with both anoxia and hypoglycaemia (16.7%). This difference is not significant ($P = 0.440$, Fisher's exact test). Because the numbers involved are small, the results must be interpreted with caution, but it appears that any effect the hypoglycaemia may have in exacerbating the effects of anoxia in the newborn period is minimal.

The results of this investigation confirm the opinion (Griffiths, 1968) that hypoglycaemia does not invariably have the serious import attributed to it, and while it is important to identify and treat cases of 'true' symptomatic hypoglycaemia the large majority of infants appear to tolerate low blood glucose levels with sequelae. The prognosis for infants with asymptomatic hypoglycaemia is particularly good.

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