Association of Hypoglycaemia with Symptoms in the Newborn

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The symptoms produced by hypoglycaemia in the newborn include apnoeic attacks, alterations of muscle tone, 'juddery' movements of the limbs, convulsions, and reluctance to feed. These symptoms are not specific for hypoglycaemia, for they can be caused by a variety of conditions, such as perinatal anoxia, intracranial haemorrhage, meningitis, or hypocalcaemia.

When infants with both hypoglycaemia and symptoms have died, an acceptable cause for death other than the hypoglycaemia is often found at necropsy (Tynan and Haas, 1963; Chance and Bower, 1966). It is therefore possible that the presence of both hypoglycaemia and symptoms may in many cases also be merely coincidental.

The relation between hypoglycaemia, symptoms, and death has been investigated in 1000 consecutive admissions to the special care unit of a maternity hospital.

Materials and Methods

During the 3½ years from January 1964 to May 1967 1000 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. 138 of these infants were born at home or in other hospitals, the remainder being among the 8736 live births which occurred in the Cardiff Maternity Hospital during this period.

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

The infant was 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 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 suggestive symptoms developed later. The heel was rubbed, but not otherwise 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.

Several conditions predispose to hypoglycaemia, and these underlying conditions rather than the hypoglycaemia itself may be responsible for symptoms. A further analysis was, therefore, undertaken of those infants with conditions known to predispose to hypoglycaemia, and the incidence of symptoms in hypoglycaemic and non-hypoglycaemic babies was compared within each group. The five groups were as follows: infants of diabetic mothers; infants with respiratory distress syndrome (RDS); anoxic infants (Apgar score 0-3); premature infants (less than 37 weeks' gestation); and infants of low birthweight for gestational age (more than 36 weeks but less than 2.5 kg., 33-36 weeks but less than 1.5 kg., 28-32 weeks but less than 1 kg.). The relation of this classification to the intrauterine growth curves of Lubchenco *et al.* (1963) is shown in the Fig.

FIG.—Classification of low birthweight infants in relation to the intrauterine growth curves of Lubchenco *et al.* (1963).

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TABLE I

Comparison of Incidence of Symptoms in Hypoglycaemic and Non-hypoglycaemic Infants, Subdivided According to Factors which Predispose to Hypoglycaemia

Predisposing Factor	Hypoglycaemic Infants (148)			Non-hypoglycaemic Infants (852)			χ^2	p
	Total	No. With Symptoms	Incidence of Symptoms (%)	Total	No. With Symptoms	Incidence of Symptoms (%)		
Anoxia	52	40	77	264	168	64	3.409	>0.05
Diabetic mother ..	9	6	67	12	9	75	0.176	>0.05
Prematurity ..	74	46	62	344	226	66	0.335	>0.05
RDS	35	24	69	157	112	71	0.106	>0.05
Low birthweight for gestation age	44	24	55	155	80	52	0.118	>0.05

For significance at $p = 0.05$, $\chi^2 = 3.841$.

Some of the 1000 infants fell into none of these groups while others fell into, and are therefore included in, more than one group.

Results

Of the 1000 infants, 148 had one or more blood glucose levels of less than 20 mg./100 ml., and of these, 128 were born in the Cardiff Maternity Hospital. The incidence of hypoglycaemia was therefore 14.8% among admissions to the special care unit or 1.7% of total live births in the hospital. The age of onset of hypoglycaemia was accurately recorded in 114 of 148 infants, and was within the first 24 hours of life in 97 (85%).

Among infants with proven hypoglycaemia 60.1% were recorded as showing symptoms, compared with 52.9% in infants without hypoglycaemia. The difference in incidence is not significant ($\chi^2 = 2.632$; $p = > 0.05$).

Table I compares the incidence of symptoms in infants with and without hypoglycaemia when they are subdivided according to certain factors known to predispose to hypoglycaemia. In no instance was there a significant difference in the incidence of symptoms at the $p = 0.05$ level, though this was almost attained in anoxic infants ($\chi^2 = 3.409$; $p = < 0.10 : > 0.05$).

There were 22 deaths among the 148 infants with hypoglycaemia (14.9%), and 124 deaths among the 852 infants without hypoglycaemia (14.6%). The death rates were thus the same in the two groups.

Necropsy records were available for 20 of the 22 infants with low blood glucose levels who died, and are summarized in Table II. Only in one infant (Case 4, Table II) could hypoglycaemia be regarded as the possible initiating factor in a chain of events ending in death. This infant had frequent cyanotic attacks which necessitated artificial ventilation, and though bronchopneumonia and a slight

subarachnoid haemorrhage were found at necropsy, these could well have been secondary to artificial ventilation.

In all the remaining 19 infants there were gross pathological changes which appeared to be the cause of death.

Discussion

If hypoglycaemia is an important cause of symptoms in the newborn, as suggested by Brimblecombe (*Brit. med. J.*, 1967), an increased incidence of symptoms would be expected in infants who are hypoglycaemic compared to those who are not. The present paper has shown that this expected increase does not occur, despite the fact that the method of selection of the infants studied favours such an association, for while all symptomatic infants would be admitted to the special care unit, asymptomatic infants with hypoglycaemia might be left undiagnosed in the main nurseries.

When infants of diabetic mothers, anoxic infants, prematures, infants with RDS, and infants of low birthweight for gestational age were studied separately, no statistical preponderance of symptoms occurred in those with hypoglycaemia as compared to those without hypoglycaemia, though this was almost achieved in the anoxic group.

Thus, in the majority of infants, symptoms are seemingly unrelated to the presence of hypoglycaemia, and it follows that many infants do not develop symptoms despite glucose levels of less than 20 mg./100 ml.

This apparent resistance of the newborn to low glucose levels has been commented on by several workers (Hartmann and Jaudon, 1937; McKittrick, 1940; Norval, Kennedy, and Berkson, 1949; Haworth and Ford, 1960; Baird and Farquhar, 1962; Yu *et al.*, 1965), and various explanations have been proposed. Stur (1964) suggested that the glucose values of blood obtained

TABLE II
Clinical and Necropsy Findings in Hypoglycaemic Infants who Died

Infant No.	Maturity (wk.)	Birth-weight (kg.)	Maternal Age (yr.)	Gravida	Pregnancy	Neonatal Course				Main Findings at Necropsy
						Glucose Levels (mg./100 ml.)	Relevant Therapy	Other Details	Age at Death	
1	37	1.2	35	II	Severe PET; meconium-stained liquor	26 hr.-9 3rd dy.-76	Oral 10% fructose + milk only	Apgar 3; raised respiratory rate at 38 dy.-'cot' death	40 dy.	Acute pulm. infection; cerebral oedema with uncal herniation
2	34	1.6	29	III	Severe APH; Rh incompatibility	5 hr.-355 38 hr.-10 51 hr.-79 75 hr.-16	I.V. dextrose 10% 4 ml./hr. from 3 hr. for RDS, discontinued at 80 hr.	Apgar 1-2; intubated; RDS; cyanotic attacks; no exchange transfusions	4 dy.	Massive pulm. intraventricular, and subdural haemorrhage, resolving hyaline membrane disease; haemolytic disease
3	32	NW	20	I	Membranes ruptured 3 dy. prematurely	2½ hr.-18 16 hr.-4	I.V. dextrose 10% 2 ml./hr. from 18 hr. until death	RDS; cyanotic attacks, oedema	1 dy.	Hyaline membrane disease
4	33	2.025	18	I	Hypertension	½ hr.-12 4 dy.-288 5 dy.-97	Chloral hydrate, oral fructose + milk; I.V. dextrose 10% 5 ml./hr. from 3rd dy. until death	Rapid birth; Apgar 9; frequent cyanotic attacks; IPPV	7 dy.	Broncho-pneumonia patent ductus, cerebral oedema, slight subarachnoid haemorrhage
5	37	1.9	30	VII	Uneventful	2 hr.-5	I.V. dextrose 5% from 5 hr. infant transferred for surgery; at 48 hr. I.V. therapy discontinued	Imperforate anus, low thrombotest; colostomy within 24 hr.; cardiac arrest after definitive repair at 10 wk.	10 wk.	Surgery for imperforate anus and recto-vesical fistula; single umbilical artery; absent (R) kidney
6	35	NW	32	III	APH at 35 wk.	1st dy.-6	[Records missing; other details from post-mortem report]	Melaena; cold and hypotonic; abdominal distension	3 dy.	Haemorrhagic disease, cerebral oedema, and haemorrhage; congenital amputation of (R) leg
7	30	1.9	42	V	Fetal distress; meconium-stained liquor	4 hr.-16 29 hr.-43 58 hr.-30 90 hr.-35	None	Dysmature, low thrombotest, cerebral signs, septicaemia	20 dy.	Cerebral oedema and anoxic changes in Ammon's horn; monilia septicaemia, pneumonia, agonal intussusception

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TABLE II—continued

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						Glucose Levels (mg./100 ml.)	Relevant Therapy	Other Details	Age at Death	
8	36	NW	22	I	Uneventful	11 hr.—15 18 hr.—97 2nd dy.—92 3rd dy.—30 11th dy.—72	I.V. dextrose 10% 5 ml./hr. from 12 to 48 hr.	Breech delivery; perinatal anoxia, hydrocephalus after birth trauma, meningitis, and subdural effusion	5 mth.	No necropsy
9	29	NW	19	I	APH; membranes ruptured for 48 hr.	9 hr.—42 31 hr.—61 55 hr.—9 61 hr.—132 4 dy.—47 5 dy.—54	I.V. dextrose 5% 2·6 ml./hr. from 1 hr. for RDS; stopped spontaneously at 42 hr. restarted when hypoglycaemia diagnosed and continued until death	RDS; frequent cyanotic attacks required IPPV	5 dy.	Bronchopneumonia; (R) ventricular haemorrhage; cerebral oedema
10	28	NW	28	III	APH; twin pregnancy (I)	1½ hr.—6 7 hr.—24 20 hr.—96	I.V. dextrose 5% 2·5 ml./hr. from 4½ hr. until death; chloral hydrate	Apgar 3; RDS	1 dy.	Hyaline membrane disease, intraventricular, subdural, and subarachnoid haemorrhage; subcapsular haematoma of liver
11	28	1·025	28	III	APH; twin pregnancy (II)	1½ hr.—9 7 hr.—10 20 hr.—30 44 hr.—45	I.V. dextrose 5% 2·5 ml./hr. from 3½ hr. until death	Apgar 0—1; intubated	3 dy.	Intracranial haemorrhage, bronchopneumonia, intussusception, ruptured gut, and peritonitis
12	30	1·7	18	I	APH; membranes ruptured for 3 dy.	8 hr.—10 32 hr.—15 56 hr.—35 80 hr.—35	I.V. dextrose 5% 5 ml./hr. from 11 hr. to 25 hr; oral 10% fructose 4 ml. 3-hourly	Assisted breech delivery; rubella syndrome; exchange transfusion × 3 for haemolytic anaemia	39 dy.	Bronchopneumonia; cerebral oedema
13	36	1·825	25	III	APH; fetal distress	3 hr.—2 8 hr.—56 26 hr.—20 50 hr.—25	I.V. dextrose 5% 2 ml./hr. from 8½ hr. until death; hydrocortisone 20 mg. 6-hrly from 10 hr.; chloral hydrate	Apgar 2; intubated, dysmature with low thrombocytopenia, cerebral signs and ECG changes of bundle-branch block	3 dy.	Bronchopneumonia, bilateral haemorrhagic papillary necrosis

TABLE II—continued

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						Glucose Levels (mg./100 ml.)	Relevant Therapy	Other Details	Age at Death	
14	32	1.76	39	IV	APH due to placenta praevia	2½ hr.—65 24 hr.—11 48 hr.—15	I.V. dextrose 5% 1 ml./hr. from 5½ hr. (for RDS) until death	Caesarean section; Apgar 1-2; intubated and ventilated by IPPV; RDS; cerebral signs	3 dy.	Intraventricular haemorrhage; basal cisterns distended with blood; hyaline membrane disease
15	39	1.56	27	II	Uneventful	1½ hr.—5 10 hr.—10 21 hr.—25 45 hr.—29 69 hr.—5	Chloral at 1½ hr. oral fructose 10% from 5 hr. I.V. dextrose 5% 3 ml./hr. from 24 hr. reduced to 1 ml./hr. at 44 hr. and continued until death	Severe perinatal asphyxia, Apgar 2-3; intubated; dysmature; heart failure with large heart and ischaemic ECG changes	3 dy.	Haemorrhagic broncho-pneumonia; congenital heart disease (VSD, PDA); hydro-ureters
16	32	1.775	26	IV	Slight APH at 27 wk. after fall	1 hr.—6 19 hr.—25	I.V. dextrose 5% 5 ml./hr. from 1 hr. (to administer alkali for pH 6.9) and continued until death	Perinatal asphyxia, Apgar 1-2 intubated; low thrombotest; ventilated for broncho-pneumonia	2 dy.	Tentorial tear with intracranial haemorrhage; broncho-pneumonia
17	27	NW	31	I	Uneventful	5 hr.—19 53 hr.—10	Oral feeds of ½-strength milk only	Apgar 7-8; extreme prematurity; apnoeic attacks	2 dy.	Almost complete atelectasis
18	28	0.975	20	III	APH	4½ hr.—10 13 hr.—20 34 hr.—35	Intragastric drip of ½-strength milk and dextrose 5%	Perinatal asphyxia, Apgar 1; intubated; RDS; ventilated for cyanotic attacks from 5th day until death	7 dy.	No necropsy
19	27	1.2	24	III	No antenatal care	6 hr.—11 10½ hr.—10 12 hr.—12 30 hr.—30	Oral feeds of 10% fructose and milk from 12 hr.	Apgar 3-4; low thrombotest; apnoeic attacks; gastro-enteritis	7 dy.	Severe prematurity, small intracerebral and subarachnoid haemorrhage; <i>Klebsiella aerogenes</i> cultured from intestine
20	28	0.7	25	V	APH	15 hr.—4 21 hr.—3 25 hr.—141 39 hr.—23 44 hr.—22 63 hr.—6 87 hr.—13 111 hr.—17 135 hr.—3 141 hr.—10 7 dy.—60	I.V. dextrose 10% 1.5 ml./hr. from 23 hr.; changed to dextrose 5% at 39 hr.; increased to 3 ml./hr. at 144 hr. and continued until death; hydro-cortisone 5 mg. t.d.s. from 144 hr.	Severe perinatal asphyxia; cyanotic attacks	9 dy.	Severe prematurity, intraventricular and subarachnoid haemorrhage; early broncho-pneumonia; thrombosis of umbilical vein

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						Glucose Levels (mg./100 ml.)	Relevant Therapy	Other Details	Age at Death	
21	33	1.825	36	IV	Hypertension	15 hr.—10	I.V. dextrose 5% 2 ml./hr. from 3 hr. (for RDS) changed to dextrose 10% 3 ml./hr. when hypoglycaemia diagnosed and continued until death	RDS	3 dy.	Hyaline membrane disease; bronchopneumonia; dilatation of heart; hydrops of meninges
22	34	1.75	39	VIII	Intrauterine transfusion for haemolytic disease	24 hr.—5 28 hr.—25 30 hr.—30 48 hr.—15 72 hr.—20	I.V. dextrose 5% 2 ml./hr. from birth (for RDS); increased to dextrose 10% 3 ml./hr. when hypoglycaemia diagnosed; reduced to % 3 ml./hr. at 35 hr. and continued until death	RDS; exchange transfusion	4 dy.	RDS; haemolytic disease; intraventricular, intracerebral, and subarachnoid haemorrhage with cerebral softening; needle track through liver

APH, antepartum haemorrhage; IPPV, intermittent positive pressure ventilation; NW, not weighed; PDA, patent ductus arteriosus; PET, pre-eclamptic toxemia; RDS, respiratory distress syndrome; VSD, ventricular septal defect.

by heel stab were falsely low due to peripheral stasis, but Cornblath, Levin, and Gordon (1956) have shown that heel-prick blood has a 'true' sugar content similar to that of femoral artery blood. The findings of Edwards (1964) in calves and of Scopes (1964) in babies suggest a resistance of the brain of the neonate to hypoglycaemia, dependent upon its ability to metabolize lactate, symptoms being absent as long as the lactate level is adequate. It is, therefore, probable that the infant's resistance is in some way dependant on the biochemical and metabolic environment, which is rapidly changing during the neonatal period.

While the present statistical analysis shows that in the majority of infants symptoms are unrelated to hypoglycaemia, in one case (Case 4, Table II), it is possible that the hypoglycaemia was the underlying cause of death. Shelley and Neligan (1966) demonstrated that in a small proportion of cases hypoglycaemia was the cause of symptoms, and emphasized the importance of the diagnostic

therapeutic test with a large dose of glucose (1-3 g.) intravenously. The incidence of such 'true' symptomatic hypoglycaemia is low, 2 per 1000 total births (Neligan, Robson, and Watson, 1963), 2.9 per 1000 total births (Cornblath, 1967), and 1.3 per 1000 term births (Zetterström, 1963), compared to the over-all incidence of infants with both hypoglycaemia and symptoms of 10.1 per 1000 in the present series, and a total incidence of hypoglycaemia (with or without symptoms) of 17 per 1000 live births.

Anderson, Milner, and Strich (1966), on the basis of 2 cases, imply that the finding of hypoglycaemia in the neonate is of serious import and that urgent therapy is required. The results of the present investigation serve to place these findings in perspective. While a diagnostic therapeutic test is indicated, especially if anoxia has occurred, the treatment of every infant with a blood glucose of less than 20 mg./100 ml. seems unnecessary, and if the umbilical vein is used, therapy

may be harmful (Scott, 1965; Sanerkin, Edwards, and Jacobs, 1966).

Summary

Studies were made of 1000 newborn infants admitted to a special care nursery. Hypoglycaemia (blood glucose level below 20 mg./100 ml.) was frequently found when looked for routinely (17/1000 live births). When infants with and without hypoglycaemia were compared, the incidence of symptoms did not differ significantly between the groups, and the death rates were identical.

In those hypoglycaemic infants who died, an acceptable cause of death other than the hypoglycaemia was established, with but one possible exception.

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