Blood Glucose Concentration in the Perinatal Period

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Low blood sugar concentrations are common in infants, and concentrations which in the adult would be considered pathologically low may be physiological in the newborn in whom hypoglycaemia is not necessarily associated with symptoms (Ketteringham and Austin, 1938; McKittrick, 1940; Hanley and Horn, 1943; Norval, Kennedy, and Berkson, 1949; Wachter, 1949; Pedersen, 1952; Desmond, 1953; Lowrey, Graham, and Tsao, 1954; Hartmann, 1955; Haworth and Ford, 1960; Kaye, Davidson, Williams, Kumagai, and Picou, 1961; Melichar, Novák, Hahn, and Koldovský, 1964; Neligan, 1964a; Stur, 1964; Hjelm and Sjölin, 1965).

Symptomatic hypoglycaemia has been described in infants with lesions which might be expected to lower the blood sugar concentration (Mason and Andersen, 1941; Sherman, 1947), and Hartmann and Jaudon (1937) attributed to hypoglycaemia certain symptoms in infants of diabetic mothers, though Pedersen (1952), Lowrey *et al.* (1954), and Farquhar (1956) found equally low blood sugar concentrations in patients with no symptoms. As early as 1934, Holman and Mathieu suggested that the blood sugar might fall to dangerously low concentration in infants of toxæmic mothers, but it is only since Cornblath, Odell, and Levin (1959) revived interest in such cases that symptomatic hypoglycaemia in the neonatal period has been accepted as a definite and not uncommon entity.

The association between foetal malnutrition and neonatal hypoglycaemia has been described by Brown and Wallis (1963) and by Neligan, Robson, and Watson (1963). Cornblath now feels that poor foetal growth was the most important aetiological factor in the cases of hypoglycaemia which he and his colleagues originally attributed to maternal toxæmia (Cornblath *et al.*, 1959; Neligan, 1964b). Even in asymptomatic babies with the foetal mal-

nutrition syndrome, low blood glucose concentrations have been found (Melichar *et al.*, 1964), and Smallpeice and Davies (1964) found that the mean of the lowest blood sugar concentrations in 13 infants who were below expected birth weight was significantly lower than in other premature infants.

The administration of glucose by intravenous injection is well established in the management of neonatal hypoglycaemia (Neligan, 1965), and oral therapy using laevulose has also been successful (Tynan and Haas, 1963). The use of glucocorticoids and corticotrophin is subject to controversy. Cornblath *et al.* (1959) administered corticotrophin and cortisone to one patient and, in a further paper, such treatment was strongly recommended (Cornblath, Wybregt, Baens, and Klein, 1964). Neligan *et al.* (1963) stated that 'the response to glucocorticoids is . . . good and merits further investigation'. On the other hand, Brown and Wallis (1963) suspected that hypoglycaemia might be associated with depleted glycogen stores, a suspicion borne out by Shelley's (1964) finding of 'unexpectedly low' tissue carbohydrate concentrations in infants who were small for duration of gestation, and they, therefore, avoided the use of glucocorticoids and corticotrophin on the grounds that these drugs might aggravate such depletion. Cortisone acetate had no effect on the hypoglycaemia of 4 infants studied by Stur (1964), but Creery (1963) stated that oral glucose combined with 25 mg. hydrocortisone by intramuscular injection was a safe and reliable means of treating neonatal hypoglycaemia, though oral glucose alone was ineffective.

Smallpeice and Davies (1964) believed that early feeding of premature infants prevented neonatal hypoglycaemia, but Haworth and Ford (1963) found that early feeding of premature infants had no significant effect on blood sugar concentration during the first 5 days of life.

In the present paper, observations on the relation between maternal venous and umbilical venous blood glucose concentrations at birth are reported,

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with particular reference to the possibility that duration of gestation independently of birth weight might influence that relation. The influence of various regimens on the postnatal blood glucose concentrations of infants who were under expected birthweight for the period of gestation (hereafter referred to as 'underweight') is described, and the effect on capillary blood glucose concentration of warming the extremity from which the blood is taken is reported.

Methods

Estimation of blood glucose concentration.

Glucose concentration was estimated by the zinc hydroxide-glucose oxidase method of Hjelm and de Verdier (1963), using 0.1 ml. plasma or whole blood for each determination, and reading the absorbancy at 450 m μ in a Unicam SP 400 spectrophotometer. The estimations on umbilical cord and maternal blood at delivery were carried out on plasma from heparinized blood, and the estimations on postnatal specimens were on whole blood.

The accuracy of the method was assessed by estimations on 28 pairs of separately pipetted and analysed whole blood specimens with glucose concentrations ranging from 6 to 106 mg./100 ml. The results were evaluated by the method suggested by Cornblath, Levin, and Gordon (1956). For each pair, the difference of the two determinations from their mean was calculated, and from these values the standard deviation (SD) of the individual differences was found to be 2.49 mg./100 ml. The standard error (SE) of the difference between any two determinations is $\sqrt{2} \times$ SD of the individual differences, or 3.5 mg./100 ml. Hence, a difference between paired results (e.g. blood from warmed and unwarmed feet) of 2 SE of the difference (i.e. 7.0 mg./100 ml.) is significant in 95% of cases. In analysing the results, a difference of 7.5 mg./100 ml. has been accepted as significant. The corresponding value used by Cornblath *et al.* (1956) was 4.0 mg./100 ml.

Case Selection

Unselected cases at birth. Glucose concentration was estimated in plasma obtained from the umbilical vein and from a maternal antecubital vein at the moment of birth in 63 unselected deliveries. Of these mothers, 45 had regular menstrual cycles (28 ± 4 days) and were able to state with certainty the date of the last menstrual period. One mother was a diabetic. There was no case of severe maternal toxæmia but 3 mothers had mild pre-eclampsia and one had essential hypertension.

Postnatal study of 'underweight' infants. The 30 infants in this trial were selected on the criteria that their mothers had regular menstrual cycles and could state with certainty the dates of their last menstrual periods, and that the birthweights of the infants fell below the third percentile for the period of gestation. The percentile calculations were based on data obtained from 14,156 single legitimate births in the City of Aberdeen from 1956 to 1960 inclusive (Table I).

Excluded from the trial were multiple births, deformed infants, infants weighing over 5 lb. 8 oz. (2500 g.) (for administrative reasons), and infants with gestational ages of less than 36 weeks, the data available being inadequate for accurate percentile calculations below this period of gestation. One infant was removed from the trial because he began to vomit at the age of 18 hours.

The infants were allocated by predetermined random selection to 3 groups.

TABLE I

Third Percentile for Birthweight at Various Durations of Gestation
(based on data from 14,156 single legitimate births)

Duration of Gestation (wk.)	Third Percentile for Birthweight	
	(oz.)	(g.)
36	56.75	1606
37	67.25	1903
38	75.5	2137
39	83.0	2349
40	89.25	2526

Low calorie group. These infants received no feeds for the first 24 hours of life and were then fed every 3 hours during the next 24 hours with quarter-strength half-cream National Dried Milk reconstituted using 5% glucose in water. No other sugar was added. The volume given was 2 ml./lb. (4.4 ml./kg.) body weight per feed, giving an intake during the second 24 hours of 5.4 calories/lb. (11.9 calories/kg.) of which 74% were derived from carbohydrate. During the third 24 hours of life the feeds were half-strength half-cream National Dried Milk (reconstituted as above) 3 ml./lb. (6.6 ml./kg.) per feed, giving an intake of 11.5 calories/lb. (25.4 calories/kg.) during the third day, of which 63% were derived from carbohydrate. No other treatment was given to these infants.

High calorie group. These infants received no feeds for the first 24 hours of life. During the next 24 hours their feeds consisted of 10% glucose given at the rate of 4 ml./lb. (8.8 ml./kg.) body weight every three hours, a total calorie intake of 12.8/lb. (28.2 calories/kg.) during the second day, all derived from carbohydrate. During the third 24 hours of life the feeds consisted of half-cream National Dried Milk reconstituted with 10% glucose in a volume of 4 ml./lb. every 3 hours. The total calorie intake during the third day was 21.8/lb. (48.1 calories/kg.) of which 73% were derived from carbohydrate.

Hydrocortisone group. These infants had exactly the same feeding regimen as the infants in the high calorie diet group, but in addition they were given hydrocortisone acetate by intramuscular injection in a dosage of 25 mg. at the age of 24 hours and 12.5 mg. at the age of 36 hours.

Capillary blood for glucose estimation was taken from a heel-stab from each infant at 12-hourly intervals from

the age of 12 hours to the age of 72 hours. The limb used for obtaining blood was not specially warmed, but the infants were all in incubators or warm nurseries and had no obvious peripheral circulatory stasis. It will be shown below that a highly significant positive correlation existed between the glucose concentrations of blood from warmed and unwarmed feet (though significant differences were present between individual paired concentrations).

Study of capillary glucose concentrations in blood from unwarmed and warmed feet. During the course of the above studies and in other infants in whom glucose concentration was being estimated for various reasons, the opportunity was taken to compare the glucose concentration in capillary blood from an unwarmed foot with that collected immediately afterwards from the other foot which had been warmed for 1 minute in water at 100° F. (37·8° C.). To obviate any bias that might have been produced by local circulatory abnormalities, alternate feet were used for 'cold' specimens. In these infants there was no apparent peripheral circulatory stasis, and all were nursed in incubators or warmed cots. In all, 57 pairs of blood specimens were obtained.

In 4 instances blood samples were taken in quick succession from (a) a catheter introduced through the umbilical artery (for other investigations), (b) an unwarmed foot, and (c) a warmed foot.

Results

Unselected cases at birth

63 unselected cases. In the 63 unselected cases the mean concentration of glucose in the maternal venous plasma was 123·1 mg./100 ml. (SD = 35·8 mg./100 ml.) and in the umbilical venous plasma was 83·2 mg./100 ml. (SD = 29·8 mg./100 ml.). The mean difference in glucose concentration was 39·8 mg./100 ml. (SD = 27·8 mg./100 ml.).

The correlation between the glucose concentrations in the maternal venous plasma (M) and in the umbilical venous plasma (U) was highly significant ($r_{MU} = 0.649$; $p < 0.001$). There was a positive correlation between the sum (S) of maternal venous and umbilical venous plasma glucose concentrations and their difference (D), but this was not statistically significant ($r_{SD} = +0.238$; $0.1 > p > 0.05$).

45 cases with gestation of known duration. In these cases the mean maternal umbilical venous plasma glucose concentration difference was 41·6 mg./100 ml. (SD = 27·8 mg./100 ml.).

There was a statistically significant positive correlation between duration of gestation (G) and glucose difference (D) ($r_{GD} = +0.337$; $0.05 > p > 0.02$) and a positive correlation which was not significant between birthweight (W) and glucose difference ($r_{WD} = +0.237$; $p > 0.1$).

Although the glucose concentration difference was more closely related to duration of gestation than to birth weight, the partial correlation coefficient for glucose concentration difference and duration of gestation, with birth weight constant, was not significant ($r_{DG.W} = 0.248$; $p = 0.1$).

Postnatal study of 'underweight' infants.

The blood glucose concentrations in the three groups of infants described above are shown in Table II.

In the low calorie group the blood glucose concentration fell slightly between 12 and 72 hours, giving a pooled regression coefficient for the 10 infants of -0.72 , the linear component of this regression being just significant ($p < 0.05$). In the high calorie group the blood glucose concentration showed a clear tendency to increase with time; the pooled regression coefficient for this group was $+1.56$, and the linear component of the regression was highly significant ($p < 0.001$). There was a significant difference ($p < 0.05$) between the pooled regression coefficients for these two groups.

The pooled regression coefficient of $+0.65$ for the hydrocortisone group was not significant ($p \geq 0.05$), and it was not possible to compare this group with the low and high calorie groups. In the hydrocortisone group an apparent peak in glucose concentration at 36 hours was not significant when the 36-hour concentrations were compared with those at 24 hours and 48 hours by a 't' test for difference in pairs (for rise, $t = 1.153$, $0.3 > p > 0.2$; for fall, $t = 2.242$, $0.1 > p > 0.05$).

One infant (low calorie, Case 5A) developed clinical evidence of hypoglycaemia: at the age of 72 hours he was found to be limp and apathetic. His blood glucose concentration at that point was 4 mg./100 ml., and he responded to intravenous glucose therapy.

Capillary blood glucose concentration from warmed and unwarmed feet. The mean glucose concentration in blood from the warmed feet was 44·0 mg./100 ml., and that in blood from the unwarmed feet was 2·8 mg./100 ml. lower. Over-all there was a highly significant correlation between the values in the two groups ($r = +0.871$, $p < 0.001$), while the paired results differed significantly ($t = 2.01$, $0.05 > p > 0.02$).

In 35 cases the glucose concentration was higher in blood from the warmed foot (average difference = 7·06 mg./100 ml.; SD = 4·39 mg./100 ml.); in 19 it was higher in blood from the unwarmed foot (average difference = 3·91 mg./100 ml.; SD = 1·98 mg./100 ml.), and in 3 the concentrations were equal.

Accepting as significant a difference of 7·5 mg./

TABLE II
Blood Glucose Concentrations from 12 to 72 Hours of Life in Three Groups of Underweight Infants

Case No.	Glucose Concentration (mg./100 ml.)						Regression Coefficient
	Age (hr.)						
	12	24	36	48	60	72	
<i>A. Low Calorie Group*</i>							
1A	41	48	50	54	—	54	+ 2.473
2A	52	51	57	57	45	59	+ 1.743
3A	34	36	43	29	20	18	- 4.057
4A	52	52	45	36	47	43	- 1.971
5A	40	40	31	18	9	4	- 7.486
6A	59	66	52	68	49	46	- 2.857
7A	41	32	35	20	36	50	+ 1.200
8A	54	36	45	36	34	25	- 4.571
9A	38	63	58	54	61	52	+ 1.714
10A	41	36	37	36	28	50	+ 0.571
Mean	45.2	45.2	45.3	40.8	36.6	40.1	
<i>B. High Calorie Group†</i>							
1B	51	62	53	—	71	73	+ 4.244
2B	40	45	65	37	52	62	+ 2.943
3B	52	43	37	55	55	52	+ 1.543
4B	30	36	27	61	62	—	+ 8.900
5B	69	45	59	60	50	55	- 1.542
6B	43	43	35	51	54	60	+ 4.094
7B	20	21	33	35	35	39	+ 3.971
8B	39	41	40	40	54	48	+ 2.400
9B	26	24	19	45	40	55	+ 6.257
10B	58	74	69	100	51	63	- 0.371
Mean	42.8	43.3	43.7	53.8	52.4	56.3	
<i>C. Hydrocortisone Group‡</i>							
1C	63	69	58	55	73	67	+ 0.829
2C	58	65	89	44	56	47	- 3.630
3C	43	56	62	68	45	43	- 0.771
4C	57	25	28	34	39	61	+ 1.943
5C	66	83	62	58	75	72	+ 0.057
6C	24	87	65	34	62	76	+ 4.800
7C	29	30	70	43	54	60	+ 5.714
8C	55	55	62	66	52	59	+ 0.429
9C	23	16	53	40	—	44	+ 5.054
10C	65	51	68	51	—	60	- 0.608
Mean	48.3	53.7	61.7	49.3	57	58.9	

* Pooled regression coefficient = - 0.72. † Pooled regression coefficient = + 1.56. ‡ Pooled regression coefficient = + 0.65.

100 ml. (as calculated above), it was found that significant differences existed between 15 of the 57 pairs, the glucose concentration being higher in the warmed foot in 13 pairs, and in the unwarmed foot in 2 pairs.

The results of the 4 cases where arterial blood samples were obtained are shown in Table III. The results for glucose concentration of blood from warmed and unwarmed feet in these 4 cases were not included in the statistical analysis above. Using the above criterion, significant differences were present between the triple results in several instances, but the glucose concentration was not always highest in the arterial sample nor lowest in the capillary sample from the unwarmed foot.

Discussion

Maternal and umbilical venous blood glucose concentrations. It is currently believed that maternal-foetal glucose transfer depends on an active transport mechanism rather than on simple

diffusion (Chinard, Danesino, Hartmann, Huggett, Paul, and Reynolds, 1956; MacRae and Palavradji, 1964). Numerous investigators, including Morriss (1917), Slemmons (1919), Naeslund (1928), Pedersen (1952), Spellacy, Goetz, Greenberg, and Ells (1964), have shown that the sugar concentration in maternal

TABLE III

Simultaneous Blood Glucose Estimations in Postnatal Period from (i) umbilical artery, (ii) heel-stab from warmed limb, (iii) heel-stab from unwarmed limb

Patient	Blood Glucose Concentration (mg./100 ml.)		
	Arterial	Capillary	
		Limb Warmed	Limb Not Warmed
1(a)*	147	137	128
(b)	187	196	182
2(a)	65	—	46
(b)	58	60	65

* In infant No. 1 was on intravenous therapy.

blood is higher than in umbilical venous blood at birth, though almost identical levels were reported by Bergsma (1912) and Holman and Mathieu (1934). In the present series the maternal plasma glucose concentration was higher than that in the umbilical vein by an average of 39.8 mg./100 ml.

Ketteringham and Austin (1938) used Jegher-Myer's modification of Folin-Malmroos's micro-method, and Furuhjelm (1956) and Spellacy *et al.* (1964) used the Nelson and Somogyi method to show that the umbilical venous blood sugar concentration correlated well with the maternal blood sugar concentration at birth. In the present cases, where the glucose oxidase method was used, a similar close correlation was found.

A highly significant correlation between the sugar concentration in maternal venous blood and the concentration difference between maternal venous and umbilical venous blood was demonstrated by Furuhjelm (1956). In the present study the statistically preferable procedure of correlating the sums of the maternal and umbilical glucose concentrations with their differences was adopted, and no significant correlation was found.

Whether the transplacental transfer of glucose is by passive diffusion or by an active mechanism, the process will depend on normal placental function. In infants who are underweight at birth as a consequence of placental insufficiency, glucose transfer might be impaired, and under these circumstances the maternal-foetal blood glucose concentration gradient might be influenced. One would expect, if this were so, that for a given birthweight duration of gestation would have a significant effect on the glucose concentration gradient across the placenta. This was not so in the present series (partial correlation coefficient for glucose concentration gradient and duration of gestation with birthweight constant, $r_{\text{D.G.W.}} = 0.248$; $p = 0.1$), but it must be pointed out that few of the babies were unduly small for dates, only 3 falling within the 10th birthweight percentile for duration of gestation (using the Aberdeen figures discussed above). It would be of interest to compare, in normal and underweight infants, the concentration gradients across the placenta for a wide range of nutriment.

Effect of feeding regimen and hydrocortisone therapy on postnatal blood glucose concentration in 'underweight' infants. Early feeding of low birthweight infants such as was advocated by Smallpeice and Davies (1964) has more recently been shown by Wharton and Bower (1965) to be associated with an increased mortality rate. The former authors suggested that early feeding was

advantageous to the 'small for dates' infant, while Wharton and Bower (1965) found more examples of symptomatic hypoglycaemia in their late feeding than in their early feeding group, and further noted among the 18 dysmature infants in their series that low blood sugar concentrations on the second day of life occurred more often with delayed feeding.

In the present series the three groups of 'underweight' infants all started feeds at 24 hours, while the volume and calorie intake were varied. The 'low calorie' group were given a calorie intake on the second and third days of life, which was lower than that used by Wharton and Bower (1965) for their 'later' fed infants, while the 'high calorie' group were given an intake above Wharton and Bower's 'later' fed infants but considerably less than their 'immediate' feeding group. The results of the study suggest that the higher calorie intake was associated with significantly higher concentrations of blood glucose over the first three days of life, and the only infant who developed symptomatic hypoglycaemia was in the low calorie group. The number of cases involved, however, is small, and the failure of the hydrocortisone group to show a regression coefficient for blood glucose similar to that of the high calorie group which was on the same diet suggests that a larger series should be studied. In future observations on low birthweight infants, whether premature or not, it will be necessary to study a range of feeding regimens between those used here and the early feeding advocated by Smallpeice and Davies (1964). It is advisable that frequent estimations of blood glucose concentrations are carried out over the first few days of such studies, since precise correlation between symptomatic and asymptomatic neonatal hypoglycaemia and later evidence of brain damage is not clear, though Wharton and Bower (1965) found such evidence only in their symptomatic cases. Meantime the feeding regimen for 'underweight' infants should provide a calorie intake at least as high as that of the high calorie diet given above, and it may be advisable to commence feeds on the first day. The above high calorie regimen has been well tolerated by over 30 'underweight' infants, none of whom has developed symptomatic hypoglycaemia. Hydrocortisone in the dosage used produced no significant rise in blood glucose concentration above that already produced by diet alone, and further evaluation of this form of therapy is necessary as regards both dosage and duration of administration.

Capillary blood glucose concentration in warmed and unwarmed feet. It was first suggested by Hagedorn (1920) that capillary blood

was equivalent to arterial blood in sugar content, and Lundsgaard and Möller (1922) concluded from their observations on capillary and arterial blood oxygen concentrations that cutaneous blood should have the same sugar content as arterial blood. Since then it has been confirmed in the adult that capillary blood sugar concentration approximates to arterial blood sugar concentration (Foster, 1923; Langner and Fies, 1942; Somogyi, 1948), and studies on arteriovenous blood sugar concentration differences have been based on this assumption (Russell and Bruce, 1964). In the newborn infant, however, Cornblath *et al.* (1956) found a significant difference between the glucose concentration in arterial blood and that in the capillaries of a warmed foot in 7 of 16 cases studied. Both Foster (1923) and Somogyi (1948) recommended that the limb be warmed before capillary blood was obtained, but the object of this manoeuvre was rather to increase the blood flow than to arterialize the blood. It has recently been demonstrated in infants with impaired skin circulation that the glucose concentration of capillary blood drawn from a heel-stab may be significantly lower than the glucose concentration of blood in the inferior vena cava (Stur, 1964).

Our findings indicate that in newborn infants the capillary blood glucose concentration may be significantly lower in samples obtained from unwarmed limbs than in samples from warmed limbs, even in the absence of obvious peripheral circulatory stasis, and the suggestion by Haworth (1965) that misleadingly low glucose levels may be found in capillary blood from infants with impaired skin circulation should be extended to all infants. The relation between capillary blood and arterial blood is variable, though it can reasonably be assumed that the glucose concentration of capillary blood from a warmed limb more closely approximates to that of arterial blood than does that of capillary blood from an unwarmed limb.

Summary

Plasma glucose concentrations were determined in maternal and umbilical venous blood samples. The two glucose concentrations were closely correlated, and the maternal was consistently higher than the umbilical by a mean of 39.8 mg./100 ml. The maternal-umbilical glucose concentration gradient was significantly related to the duration of gestation, but not independently of birthweight.

The influence of diet on the blood glucose concentration of 30 infants whose birthweights were low for the period of gestation was studied. The blood glucose concentration was significantly raised

over the first 3 days of life by a high calorie diet compared with a low calorie diet. The addition of intramuscular hydrocortisone medication to the high calorie regimen produced no significant effect on blood glucose concentration.

Prior warming of the feet significantly raised the glucose concentration of blood obtained by heel-stab in infants even in the absence of obvious peripheral circulatory stasis. It is recommended that the foot must always be warmed before withdrawing capillary blood for glucose estimation.

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