Studies on Hypoglycaemia in Small-for-dates Newborns

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In the past few years, new knowledge has accumulated on the subject of transient neonatal hypoglycaemia. This problem has been fully reviewed by Cornblath and Schwartz (1966a, b) who attempt to clarify the incidence, clinical features, treatment, outcome, and pathogenesis of this syndrome. Their data indicate that hypoglycaemia occurs predominantly in infants whose birthweights are low for gestational age (Gruenwald, 1965a) ('small-for-dates'). In a significant number of cases there is, in addition, a history of pre-eclampsia or toxæmia of pregnancy. The association of toxæmia gravidis and neonatal hypoglycaemia might suggest a direct link between the two conditions (Cornblath, Odell, and Levin, 1959), but intrauterine malnutrition, rather than toxæmia gravidis by itself, is now known to predispose to hypoglycaemia in the newborn (Shelley and Neligan, 1966).

The real physiopathological mechanisms, however, have not been elucidated. By comparison with what has been observed in babies of diabetic mothers, hyperinsulinism has been suggested as a cause of hypoglycaemia, but this hypothesis is no longer tenable (Cornblath and Schwartz, 1966a).

The low level of hepatic glycogen found at necropsy by Shelley (1964) and Dawkins (1964) has led some observers (Brown and Wallis, 1963; Chance and Bower, 1966; Cornblath and Schwartz, 1966b; Shelley and Neligan, 1966) to incriminate exhaustion as a possible mechanism for hypoglycaemia. The high ratio of brain weight to liver weight (Cornblath and Schwartz, 1966b; Dawkins, 1964; Gruenwald, 1965b; 1966b; Shelley and Neligan, 1966), and the state of hypermetabolism (Silverman and Sinclair, 1966) found in these babies support the hypothesis advocated by Cornblath and

Schwartz (1966b) that relatively diminished liver glycogen in the presence of enhanced metabolic requirements might be an important factor in the hypoglycaemia of such infants.

None of these hypotheses is wholly satisfactory. For that reason, a study comparing 'small-for-dates' babies with normal infants is presented here.

Material and Methods

Two groups of children were studied* (Fig. 1 and 2).

Group I. 34 infants (28 term and 6 pre-term infants) whose weights were both less than mean weight minus 2SD according to Hendricks's (1964) chart and below the 5th centile (Gruenwald, 1966a).

Group II. 31 term controls (> 37 weeks' gestation) whose birthweights were more than the mean weight minus 1SD on Hendricks's chart.

No congenital abnormalities were noted in either group nor was any death recorded during the neonatal period. Delivery and the course after delivery were normal in all control subjects.

Table I includes information about weight, length, head circumference, pregnancy, delivery, and perinatal events for the group of small-for-dates infants.

The aim was to collect three blood samples from each infant but in few cases were all these samples taken. The first sample was taken within 24 hours of birth before the child had been fed, the second and third samples 6 hours after feeding between the first and third day, and between the third and fifth day.

Blood glucose was measured before, and 10, 20, and 30 minutes after intravenous injection of glucagon (300 µg./kg.). Blood samples obtained by heel-prick were carried out on 0.1 ml. of blood, according to the glucose oxidase method (Biochemica test, Boehringer). Other blood samples were obtained by venous femoral puncture for determination of free fatty acids (FFA), lactic acid, and pyruvic acid. After immediate centri-

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FIG. 1.—Birthweight in relation to gestational age. Values are plotted on Hendricks's chart (mean and SD, solid lines) and on Gruenwald's curve (5th centile, dotted line).

fugation, FFA were determined according to Dole (1956). After immediate deproteinization, enzymatic procedures were used for the determination of lactic

FIG. 2.—Birth length in relation to gestational age. Values are plotted on Lubchenko's chart (centiles) (Lubchenko, Hansman, and Boyd, 1966).

and pyruvic acids (Lundholm, Mohme-Lundholm, and Svedmyr, 1963; Gloster and Harris, 1962).

Results

The results are summarized in Tables II and III. The fasting mean blood sugar of babies with low birthweight for gestational age lay between 39 and 47 mg./100 ml., the control levels varying from 50 to 60 mg./100 ml.

Fig. 3 shows that the individual values in both groups are very scattered, hence a large standard deviation with much overlapping of results. There are no significant differences between the values of the two groups.

All controls had a fasting glucose level above 30 mg./100 ml. On the other hand, 13 samples obtained from 10 of the 28 children in group I were under 30 mg./100 ml., of which 6 samples obtained from 5 infants were below 20 mg./100 ml.

Intravenous glucagon in doses of 300 µg./kg. resulted, in both groups, in a prompt and similar increase in the level of glycaemia (Fig. 3). No correlation was found between the glucagon-induced hyperglycaemia, and the fasting blood glucose level ($r = 0.16$ for the controls; $r = 0.14$ for the small-for-dates).

In both groups, lactate/pyruvate ratio varied between 17 and 20, and the mean blood FFA level varied between 1200 and 1700 µEq/l. These values did not differ significantly (Fig. 3).

Discussion

A growth curve has not yet been devised for the heterogeneous population of Belgian and Mediterranean infants from which our material for study was derived. Since it was impossible to evaluate the importance of racial and socio-economic factors (Gruenwald, 1966a, b), we had to choose between Hendricks's curves and those of Gruenwald. The simultaneous use of both graphs led us to select the children whose birthweights were both less than the mean minus 2 SD according to Hendricks's charts, and below the 5th centile according to Gruenwald's.

Our group was not homogeneous, in the sense that growth retardation sometimes involves weight alone, and sometimes weight and length. We can, however, accept Gruenwald's hypothesis that long and emaciated infants have suffered subacute intrauterine malnutrition, whereas in thin and short subjects the role of a genetic factor or of an abnormal condition like chronic intrauterine deprivation must be taken into consideration (Gruenwald, 1965b). In any case, it is now established that both of these are high risk groups (Battaglia and

TABLE I
Small-for-dates Infants: Clinical Data

Patient No.	Sex	Gestational Age (wk.)	Birthweight (g.)	Birth Length (cm.)	Head Circumference (cm.)	Obstetric and Perinatal Events
1	F	37	1230	38	28.5	No increase of uterine height; pre-eclampsia
2	F	37	1660	44.5	29.5	Previous placental insufficiency, previous albuminuria, hypertension—no increase of uterine height; caesarean section for fall in oestriol
3	M	37	1680	41	29.5	—
4	F	37	2110	42	30	No increase of uterine height; muscular twitchings
5	F	38	1850	43	32	—
6	F	38	2220	44	32	Oedema of inferior limbs
7	F	39	1950	43	32	Excessive maternal weight gain
8	M	39	2200	45	32.5	No increase of uterine height; pre-eclampsia cyanosis, hypotonia
9	F	39	2350	45	31.5	Oedema of inferior limbs
10	F	39	2400	44	31	Pre-eclampsia
11	F	40	2130	46	32	Normal pregnancy and neonatal period
12	F	40	2180	42	32	Excessive weight gain, fetal distress; persistent muscular twitchings, cyanosis
13	F	40	2200	45.5	32	Normal
14	M	40	2210	45	34	Excessive weight gain, acute fetal distress
15	F	40	2240	45	32	Excessive weight gain, no increase of uterine height
16	F	40	2350	49	33	Acute fetal distress; cyanosis
17	F	40	2400	47.5	33	No increase of uterine height; pre-eclampsia
18	F	40	2420	47	32.5	Previous placental insufficiency; no increase of uterine height
19	M	40	2440	47	33	No increase of uterine height
20	F	40	2450	46	32	Excessive maternal weight gain
21	M	40	2470	47	31	Excessive maternal weight gain
22	F	41	2500	46.5	34	Normal
23	M	41	2560	47	31	Normal
24	F	42	2250	45	34	Normal
25	M	42	2430	46	—	Normal
26	F	42	2500	47.5	31	Previous placental insufficiency; excessive weight gain; cyanosis
27	M	43	2500	45	31.5	—
28	M	44	2350	43	31	Maternal hypertension

FIG. 3.—Mean values and confidence limits of the mean for fasting glycaemia, glycaemic increase after glucagon, lactate/pyruvate ratio, and FFA level. The mean is represented by the central horizontal line and the confidence limit of the mean ($SE \times t$ of student) by the vertical line ($p = 0.01$). Solid line: controls; dotted line: term infants (small-for-dates). The three pairs of lines in each category refer to days 1, 3, and 5 of life.

TABLE II
Normal Newborns: Biological Data

Case No.	Glycaemia (mg./100 ml.)			Δ Glycaemia* (mg./100 ml.)			Lactate/Pyruvate Ratio			Free Fatty Acids (μ Eq/l.)		
	0-24 hr.	24-72 hr.	72-120 hr.	0-24 hr.	24-72 hr.	72-120 hr.	0-24 hr.	24-72 hr.	72-120 hr.	0-24 hr.	24-72 hr.	72-120 hr.
1	—	—	70.0	—	—	36.6	—	—	—	—	—	1230
2	53.1	—	—	81.0	—	—	—	—	—	1880	—	—
3	—	—	45.5	—	—	60.0	—	—	16.87	—	—	1280
4	—	—	—	—	—	—	13.89	—	—	—	—	—
5	34.5	—	—	65.0	—	—	—	—	—	1300	—	—
6	38.7	—	—	68.0	—	—	15.16	—	—	1630	—	—
7	—	—	37.9	—	—	60.0	—	—	—	—	—	1770
8	—	—	36.3	—	—	54.0	—	—	—	—	—	1540
9	60.0	—	—	25.0	—	—	14.45	—	—	1020	—	—
10	—	38.6	—	—	77.0	—	—	12.14	—	—	1320	—
11	—	40.1	—	—	46.3	—	—	16.93	11.21	1150	1280	—
12	63.3	—	—	46.2	—	—	14.38	—	—	—	—	—
13	—	37.4	—	—	50.0	—	—	—	—	—	1500	—
14	—	—	—	—	—	—	25.54	—	—	1800	—	—
15	—	—	93.3	—	—	21.5	—	—	10.49	—	—	2200
16	42.0	—	—	58.0	—	—	10.69	—	—	750	—	—
17	—	61.7	—	—	46.0	—	—	17.88	—	—	1530	—
18	—	—	61.0	—	—	74.0	—	—	15.42	—	—	940
19	—	75.9	—	—	23.0	—	—	10.61	—	—	1250	—
20	—	55.5	—	—	56.0	—	—	11.20	—	—	1770	—
21	—	—	46.2	—	—	41.7	—	—	26.28	—	—	1530
22	62.7	—	—	76.0	—	—	22.89	—	—	1200	—	—
23	—	—	80.0	—	—	130.0	—	—	6.77	—	—	1130
24	—	—	45.1	—	—	74.0	—	—	24.76	—	—	1730
25	—	—	60.0	—	—	73.0	—	—	9.51	—	—	1980
26	—	41.6	—	—	64.0	—	—	11.62	—	—	1400	—
27	—	—	—	—	—	—	—	15.38	—	—	1800	—
28	—	—	57.0	—	—	44.0	—	—	10.15	—	—	2640
29	—	—	85.3	—	—	52.7	—	—	32.00	—	—	—
30	—	53.4	—	—	40.0	—	—	15.25	—	—	1440	—
31	41.8	—	—	63.0	—	—	44.60	—	—	760	—	—
Mean	49.5	50.5	59.8	60.2	50.2	60.0	20.20	13.87	16.04	1276	1476	1633
SE	4.4	5.2	5.7	6.7	6.1	8.2	4.18	1.06	3.00	147	70	158

* Increase in mg./100 ml. of glycaemia after glucagon.

Lubchenco, 1967; Yerushalmy, 1967), in particular as regards neonatal hypoglycaemia (Cornblath *et al.*, 1959; Neligan, Robson, and Watson, 1963). Whatever the criteria of selection used (low birth-weight, symptomatic hypoglycaemia, poor nutrition), most authors agree in establishing an intimate relation between hypoglycaemia and low birth-weight for maturity.

The mean blood glucose level was not statistically different in 'small-for-dates' babies from those of controls. Individual results nevertheless show a glycaemic level below 30 mg./100 ml. in 10 small-for-dates babies, 5 of whom had levels below 20 mg./100 ml. Of the 13 determinations performed on these 10 children, low levels were observed on 8 occasions within the first 24 hours of life, on 3 occasions between 24 and 72 hours, and on 2 between 72 and 120 hours. 2 subjects had typical clinical manifestations of hypoglycaemia (persistent tremor, jitteriness, cyanosis, limpness, and irritability). Of the 6 newborn infants less than 37 weeks' gestation, 3 had symptomatic hypoglycaemia

(blood glucose < 20 mg./100 ml.). All 31 controls had blood glucose levels above 30 mg./100 ml. and were asymptomatic. Our results thus confirm the observations of earlier workers that hypoglycaemia, symptomatic and non-symptomatic, occurs more frequently in 'small-for-dates' babies. Three further points remain to be discussed.

First to be considered is the frequency of hypoglycaemia in our series as compared with that found by other workers. In our investigation of 28 term infants, 5 had glucose levels below 20 mg./100 ml., the incidence of hypoglycaemia thus appearing relatively low. However, if we add 4 'small-for-dates' seen during the period of investigation who, while satisfying our criteria, could not be investigated because of severe hypoglycaemia requiring urgent treatment, the frequency reaches about one-third of cases studied, which is similar to the frequency reported by Neligan *et al.* (1963) in infants belonging to the 'poor nutrition group'.

The second point concerns the frequent occur-

TABLE III
Small-for-dates Newborns: Biological Data

Case No.	Glycaemia (mg./100 ml.)			Δ Glycaemia* (mg./100 ml.)			Lactate/Pyruvate Ratio			Free Fatty Acids (μ Eq/l.)		
	0-24 hr.	24-72 hr.	72-120 hr.	0-24 hr.	24-72 hr.	72-120 hr.	0-24 hr.	24-72 hr.	72-120 hr.	0-24 hr.	24-72 hr.	72-120 hr.
1	16.6	—	31.1	72.0	—	111.0	—	—	—	1510	—	1500
2	16.0	—	—	49.0	—	—	15.04	—	8.93	840	1060	1390
3	—	53.0	65.7	—	53.0	72.3	—	—	9.62	2003	1640	1000
4	43.0	53.0	56.9	55.0	24.0	37.0	—	11.48	25.75	2100	1250	1700
5	62.0	35.8	—	29.8	26.2	—	10.33	—	17.48	2400	—	1690
6	26.6	—	—	54.0	—	—	—	10.22	—	2000	—	—
7	28.9	52.0	51.0	85.0	41.0	63.0	13.95	16.61	8.41	1730	1520	1710
8	16.0	—	—	30.0	—	—	21.29	—	—	1440	—	—
9	57.0	19.0	29.0	17.0	60.0	—	12.88	8.51	13.98	2200	1400	1300
10	78.0	61.0	43.0	34.0	—	52.0	—	—	14.06	1100	700	1100
11	51.0	—	—	69.0	—	—	10.62	20.86	—	1200	2400	—
12	29.0	0.0	0.0	32.0	37.0	36.1	—	14.53	11.42	1940	1920	1800
13	29.0	—	—	35.5	—	—	—	—	—	—	—	—
14	41.8	51.0	66.0	54.0	49.0	48.0	16.00	17.95	—	1500	1103	1020
15	41.0	—	—	51.0	—	—	14.44	—	—	—	700	—
16	—	32.0	46.0	—	37.0	38.0	20.55	10.32	—	1500	2000	1200
17	—	26.2	34.8	—	84.0	75.0	—	16.94	33.63	—	2120	1750
18	71.0	54.0	66.0	45.0	70.0	33.0	25.30	23.25	—	1400	1360	1200
19	26.0	34.0	41.0	47.0	47.0	62.0	52.71	31.61	27.92	1200	1030	700
20	69.6	35.8	46.4	47.0	73.0	71.0	12.02	11.76	—	2400	1670	990
21	47.2	—	—	44.0	—	—	18.62	—	—	1250	—	—
22	—	—	—	—	—	—	20.71	—	—	1100	—	—
23	38.0	45.0	44.0	38.0	39.0	41.0	16.88	19.50	11.75	—	1663	1100
24	33.0	—	—	78.0	—	—	—	—	—	2000	—	—
25	37.0	—	—	34.0	—	—	19.26	—	—	—	—	—
26	—	—	56.0	—	—	59.0	—	—	22.21	980	—	1000
27	53.0	32.8	52.0	43.0	26.4	53.0	—	—	14.86	1640	660	1470
28	40.0	—	62.0	35.0	—	54.0	—	—	—	1440	—	900
Mean	41.3	39.0	46.5	46.9	47.6	56.5	18.81	16.42	16.92	1603	1422	1290
SE	6.1	4.3	4.2	3.3	5.1	5.1	2.57	1.84	2.31	96	128	78

* Increase in mg./100 ml. of glycaemia after glucagon.

ence of asymptomatic states in our observations. Apparent differences of opinion might partly be attributed to the method of selection used. Most authors study only newborns with symptoms attributable to hypoglycaemia (Cornblath *et al.*, 1964; Tynan and Haas, 1963); others systematically determine blood glucose in low birthweight infants, including true premature and 'small-for-dates' (Baens, Lundeen, and Cornblath, 1963; Pildes *et al.*, 1967). Chance and Bower (1966) approach the problem in the same way as we did; when suspicion arises about 'placental insufficiency', a blood sample for glycaemia is collected. In this way, they were able to detect 20 cases of hypoglycaemia, two-thirds of which were symptomatic, and this proportion is higher than ours.

The third point concerns the time of initiation of the hypoglycaemia, and is still controversial. Tynan and Haas (1963) and Chance and Bower (1966) found, as we did, that more than half of their cases showed symptomatic hypoglycaemia in the first 24 hours. On the other hand, Cornblath and Schwartz (1966b) conclude from their own

studies and a review of the literature (Brown and Wallis, 1963; Haworth *et al.*, 1963) that hypoglycaemia becomes evident in the majority of cases after 24 hours of life, only one-quarter of the cases manifesting themselves before that time. In Neligan's work, the samples were obtained after 24 hours in most of the cases (30 out of 33), so that it is not possible to ascertain whether the level was already low during the initial 24 hours (Neligan *et al.*, 1963).

The blood FFA level was found to be very high in both our groups and not significantly different. This observation agrees with the experience of Laron *et al.* (1967), the high level expressing the intense activity of lipid katabolism in the newborn (Melichar *et al.*, 1965, 1966; Novák *et al.*, 1961, 1965; Persson and Gentz, 1966; Van Duyne and Havel, 1959; Werner, 1967). Like the mean glycaemic levels, the blood FFA fluctuated over a wide range. A close relation between free fatty acids and glucose was therefore impossible to establish.

Irregular variations of lactate/pyruvate ratio

led us to a similar conclusion. Our average level for lactate/pyruvate ratio was the same in the two groups, and was higher than that reported by Znamenáček and Příbylová (1964).

Glucagon raised the blood glucose level to a similar extent in all our cases. The absence of correlation between fasting glycaemia level and increase of glycaemia after glucagon is illustrated by the fact that in Case 12, even with no glucose in the fasting sample, glycaemia reached a level of 36 mg./100 ml. after glucagon.

There are few reports of glucagon tests in 'small-for-dates' infants. A negative response was obtained in 3 cases described, respectively, by Cornblath *et al.* (1959), by Neligan (1964), and by Brown and Wallis (1963); a weak response was observed in 4 cases reported, respectively, by Cornblath *et al.* (1964), by Reisner, Forbes, and Cornblath (1965), by Brown and Wallis (1963), and by Haworth *et al.* (1963). Reisner *et al.* (1965) found, however, 4 other cases which responded satisfactorily, as did 1 case reported by Haworth *et al.* (1963).

The absence of a normal response to glucagon suggested to Cornblath and Schwartz (1966b) an exhaustion of hepatic glycogen stores. It was tempting to combine these findings with observations in hypoglycaemic 'small-for-dates' infants who died in the neonatal period with a reduction of hepatic cells (Naeye, 1967) and of hepatic total carbohydrate (Shelley, 1964). In these cases, however, the exhaustion of liver glycogen may have been related to the mechanism of death. Where infantile hypoglycaemia is unquestionably due to exhausted liver stores of glycogen, glucagon never increases glycaemia (H. Loeb, 1968, unpublished data). It is still surprising to find in our cases that glycogenolysis is available but not called into action, even in the presence of very low levels of circulating glucose.

Summary

Fasting blood sugar, lactate/pyruvate ratio, blood FFA level, and response to intravenous glucagon (300 µg./kg.) were determined on the first, third, and fifth day of life in 34 children of low birthweight for gestational age (<expected weight minus 2 SD), and in 31 normal infants.

There was considerable overlap of the average results of both groups for all these values, and no statistical differences were noted.

Hypoglycaemia was found in 10 of 28 term children of low birthweights and occurred most often during the first 24 hours of life.

Intravenous glucagon induced a satisfactory

rise in blood glucose at all fasting blood glucose levels.

It is concluded that depletion of hepatic glycogen stores plays no significant role in the genesis of hypoglycaemia in 'small-for-dates' infants.

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