Alternative Cerebral Fuels in the First Five Days in Healthy Term Infants: The Glucose in Well Babies (GLOW) Study

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Objectives To determine plasma lactate and beta-hydroxybutyrate (BHB) concentrations of healthy infants in the first 5 days and their relationships with glucose concentrations.

Study design Prospective masked observational study in Hamilton, New Zealand. Term, appropriately grown singletons had heel-prick blood samples, 4 in the first 24 hours then twice daily.

Results In 67 infants, plasma lactate concentrations were higher in the first 12 hours (median, 20; range, 10-55 mg/dL [median, 2.2 mmol/L; range, 1.1-6.2 mmol/L]), decreasing to 12 mg/dL (range, 7-29 mg/dL [median, 1.4 mmol/L; range, 0.8-3.3 mmol/L]) after 48 hours. Plasma BHB concentrations were low in the first 12 hours (median, 0.9 mg/dL; range, 0.5-5.2 mg/dL [median, 0.1 mmol/L; range, 0.05-0.5 mmol/L]), peaked at 48-72 hours (median, 7.3 mg/dL; range, 1.0-25.0 mg/dL [median, 0.7 mmol/L; range, 0.05-2.4 mmol/L]), and decreased by 96 hours (median, 0.9 mg/dL; range, 0.5-16.7 mg/dL [median, 0.1 mmol/L; range, 0.05-1.6 mmol/L]). Compared with infants with plasma glucose concentrations above the median (median, 67 mg/dL [median, 3.7 mmol/L]), those with lower glucose had lower lactate concentrations in the first 12 hours and higher BHB concentrations between 24 and 96 hours. Lower interstitial glucose concentrations were also associated with higher plasma BHB concentrations, but only if the lower glucose lasted greater than 12 hours. Glucose contributed 72%-84% of the estimated potential adenosine triphosphate throughout the 5 days, with lactate contributing 25% on day 1 and BHB 7% on days 2-3.

Conclusions Lactate on day 1 and BHB on days 2-4 may contribute to cerebral fuels in healthy infants, but are unlikely to provide neuroprotection during early or acute hypoglycemia. *(J Pediatr 2021;231:81-6)*.

Trial registration The Australian and New Zealand Clinical Trials Registry: ACTRN12615000986572.

Blood glucose concentrations change rapidly in the hours after birth, and hypoglycemia is common.[1] The availability of alternative fuels to sustain cerebral cellular metabolism has long been proposed as an important mechanism to prevent injury when glucose availability is decreased, but the relationship between availability of glucose, lactate, and ketones in healthy infants remains unclear.[2-4] Glucose oxidation is estimated to supply up to 70% of cerebral fuel soon after birth, with the remaining cerebral fuel requirement provided largely from ketones and lactate.[5] The newborn brain is able to extract and use ketones at a rate that is between 4- and 5-fold greater than that of an adult.[6] The cerebral availability and use of both ketones and lactate is related to the plasma concentrations.[6,7] Factors including gestation, postnatal age, the type milk received, along with feeding intervals, all impact on the plasma concentrations of both fuels.[3,4,8] Ketogenesis also depends on the suppression of insulin secretion, allowing mobilization of fatty acids for ketogenesis.

Guidelines published to assist with the identification and treatment of infants at risk of hypoglycemia suggest that infants are able to compensate for low plasma glucose concentrations by using alternative cerebral fuels.[9,10] It has been suggested that breastfeeding is associated with enhanced ketogenesis, and breastfed infants may be protected from the adverse effects of hypoglycemia.[11,12] However, at-risk newborn infants are reported to have very low plasma ketone concentrations during hypoglycemic episodes, in part owing to a lack of suppression of insulin secretion in many of these infants.[11,13-15] Further, although lactate may provide an alternative energy source, concentrations are variable and in most well infants are low and decrease quickly after the first day.[11,16]

Previous reports from healthy infants have been cross-sectional, with a single sample taken from each infant. Hawdon et al reported values for glucose, lactate, pyruvate, alanine, glycerol, nonesterified fatty acids, and ketone bodies from 156 term infants in the first week.[3] A study from Nepal reported similar metabolites from 578 infants in the first 48 hours. However, the authors of this study reported the infants commonly had low birth weights and that maternal nutritional status was poor.[2]

We undertook this prospective observational cohort study of potential cerebral fuel concentrations in healthy, term, appropriately grown infants fed

ATP	Adenosine triphosphate
BHB	Beta-hydroxybutyrate
GLOW	Glucose in Well Babies Study

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according to parental choice, using repeated intermittent blood sampling for glucose, lactate, and beta-hydroxybutyrate (BHB) concentrations and continuous interstitial glucose monitoring over the first 5 postnatal days.

Methods

Details of the Glucose in Well Babies (GLOW) study have been previously reported.[1,17] In brief, eligible infants were healthy singleton term infants, born in Hamilton, New Zealand, between November 2015 and August 2017. Each infant underwent capillary heel-prick sampling over 5 days (4 on the first day and 2 on each subsequent day), as well as continuous interstitial glucose monitoring from as soon after birth as possible. Infants were cared for in the hospital, a birthing center, and the home as determined by the parent and the midwife. All participants completed the study in their own homes. Infants were fed according to maternal choice. The researchers and families were blinded to all metabolite concentrations and remained so until the data collection phase was complete and statistical analysis plans were finalized. The minimum sample size of 50 infants was based on an estimation of a mean glucose concentration with a 95% CI of ±3 mg/dL (0.19 mmol/L).

Glucose and lactate concentrations were measured on either an epoch blood analyzer (Siemens Healthineers), or blood gas analyzer if the infant was still in the hospital (Radiometer ABL800 FLEX). Both systems use glucose oxidase and lactate oxidase methods. BHB concentrations were measured on a Stat-Strip point-of-care analyzer (Statstrip Meter, Nova Biomedical) using a BHB-dehydrogenase method.[18] Interstitial glucose data were obtained using Ipro2 subcutaneous sensors (Medtronic Minimed) and were recalibrated according to a previously published algorithm.[19] BHB concentrations that were below the level of detection of less than 1 mg/dL (<0.1 mmol/L]) were assigned a value of 0.5 mg/dL (0.05 mmol/L) for analyses.

We hypothesized that potential alternative cerebral fuel concentrations would be elevated when the plasma glucose concentration was low, and therefore we prespecified 5 different glucose thresholds (12, 36, 46, 59, and 72 mg/dL [1.5, 2.0, 2.6, 3.3, and 4.0 mmol/L]) and planned to examine the mean concentrations of lactate and BHB in infants with glucose concentrations above and below each threshold. We used the interstitial glucose recordings to identify the duration of glucose concentrations below and above the median glucose, grouped as 1 to less than 6, 6 to less than 12, 12-18, and more than 18 hours. We then compared the alternative fuel concentrations between groups, adjusting for the simultaneous plasma glucose concentration, age epoch (discussed elsewhere in this article), and weight loss.

We also compared cerebral fuel concentrations in prespecified subgroups of maternal body mass index, weight gain during pregnancy, weight loss from birth to 5 days of age (all above vs below the median), mode of delivery (vaginal vs cesarean), sex, and gestational age (<40 weeks vs ≥40 weeks). We estimated total potential cerebral fuel availability by attributing an adenosine triphosphate (ATP) equivalent to each fuel (glucose 31, lactate 15, BHB 21.5).[20]

Data were analyzed in age epochs: 0 to less than 12 hours, 12 to less than 24 hours, and then each subsequent 24 hours. The simple relationship between glucose and BHB concentrations was analyzed using linear regression within each epoch. All other analyses for BHB concentrations were log-transformed and the CIs were obtained by bootstrap with 1000 repeats. Mixed model analyses were used to account for repeated measures within the same infant, with covariance and residual structures chosen to minimize the Akaike information criterion. Percentile curves were calculated using the skewness median coefficient of variation method, and fitted using LMSchartmaker Light Version 2.54 (Institute of Child Health, 2011).[21] Bonferroni adjustment was used for repeated separate regressions where appropriate. Analyzes were undertaken using Stata V16, 2018 (StataCorp). Categorical variables are presented as frequencies and percentages, with comparisons presented as risk ratios and 95% CIs. Continuous variables are presented as mean (SD) or median (minimum-maximum). Mixed model results are presented as mean (95% CI).

The GLOW study was approved by the Northern A Health and Disability Ethics Committee Ref: 15NTA and is registered with the Australian and New Zealand Clinical Trials Registry Ref: ACTRN12615000986572. The study protocol is available online: http://hdl.handle.net/2292/32066. Written informed consent was obtained from all participating families.

Results

Sixty-seven infants completed the GLOW study with a mean birth weight of 3584 ± 349 g and gestation of 40.1 ± 1.2 weeks. Parents identified most infants as New Zealand European (**Table I**; available at www.jpeds.com). The first plasma samples were obtained at 2.1 ± 0.5 hours and the last samples at 123.9 ± 4.0 hours. The median number of samples per infant were glucose 13 (range, 11-14), lactate 13 (range, 11-14), and BHB 13 (range, 10-15).

Lactate concentrations were higher in the first 12 hours (median, 20 mg/dL [median, 2.2 mmol/L]) and decreased to a steady state by 48 hours of age (median, 12 mg/dL [median, 1.4 mmol/L]), **Table II** and **Figure 1**). Lactate concentrations of greater than 22 mg/dL (>2.5 mmol/L) after 48 hours were above the 97th percentile. Conversely, BHB concentrations were low in the first 12 hours (median, 0.9 mg/dL [median, 0.1 mmol/L]), increased to a peak at 48 to 72 hours (median, 7.3 mg/dL [median, 0.7 mmol/L]), and decreased again by 96 hours of age (**Table II**).

As previously reported the mean glucose concentration in the first 12 hours was 57 ± 11 mg/dL (3.2 ± 0.6 mmol/L), increasing to 88 ± 13 mg/dL (4.6 ± 0.7) mmol/L after 72 hours, and remaining stable thereafter.[1] Because of this substantial change in glucose concentrations over time, the prespecified glucose thresholds resulted in too few infants above or below the threshold in some epochs to explore

Table II. Plasma concentrations of lactate and BHB at differing postnatal ages

	Lactate (mg/dL [mmol/L]) (n = 798 samples)		BHB (mg/dL [mmol/L]) (n = 798 samples)	
Postnatal ages (h)	No. of samples	Median (range)	No. of samples	Median (range)
0-12	158	20 (10-55) [2.2 (1.1-6.2)]	164	0.9 (0.5-5.2) [0.1 (0.05-0.5)]
12-24	105	17 (9-41) [1.9 (1.0-4.7)]	103	2.0 (0.5-13.5) [0.2 (0.05-1.3)]
24-48	138	14 (7-35) [1.6 (0.8-3.9)]	137	6.2 (0.5-21.8) [0.6 (0.05-2.1)]
48-72	133	12 (7-29) [1.4 (0.8-3.3)]	131	7.3 (1.0-25.0) [0.7 (0.05-2.4)]
72-96	134	13 (8-27) [1.4 (0.9-3.0)]	133	2.0 (0.5-31.2) [0.2 (0.05-3.0)]
96-120	130	13 (8-30) [1.4 (0.9-3.4)]	130	0.9 (0.5-16.7) [0.1 (0.05-1.6)]

relationships with lactate and BHB concentrations. We, therefore, compared lactate and BHB concentrations in infants with glucose concentrations above and below the overall median value for the 5 days of 67 mg/dL (3.7 mmol/L) (**Table III**). In the first 12 hours, lactate concentrations were higher in infants with higher glucose concentrations, but there were no differences thereafter. In contrast, BHB concentrations were higher in infants with lower glucose concentrations, after 24 and until 96 hours (**Table III** and **Figure 2** [available at www.jpeds.com]).

When interstitial rather than plasma glucose concentrations were considered, the BHB was higher when the interstitial glucose concentration was below compared with above the median for longer than 18 hours (4.3 mg/dL vs 1.6 mg/dL; adjusted mean difference, 2.7 (95% CI, 1.5-4.0 mg/dL [0.41 vs 0.15 mmol/L; adjusted mean difference, 0.26 (95% CI, 0.14-0.38) mmol/L; $P < .001$])), but not if the low glucose lasted less than 12 hours. This relationship between the duration of low interstitial glucose concentrations and higher BHB concentrations was seen on days 2, 3, and 4, which is consistent with the findings for blood glucose (**Figure 2**). There was no relationship between lactate concentrations and duration of low interstitial glucose concentrations (**Table IV**).

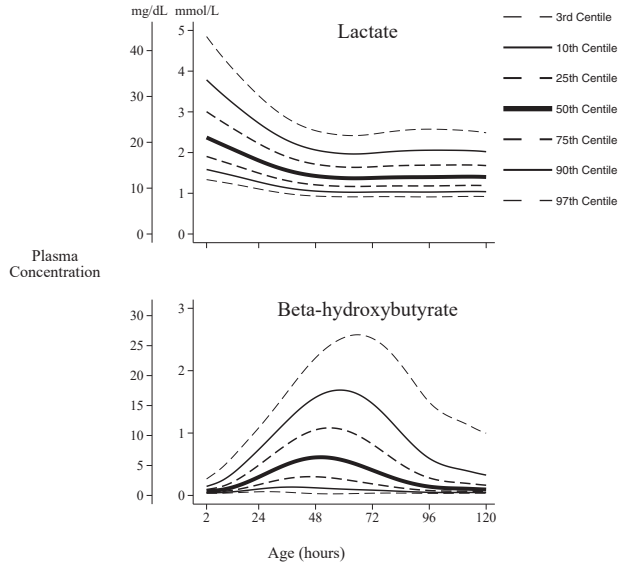

Figure 1. Lactate and beta-hydroxybutyrate centiles.

When all 3 fuels (glucose, lactate, and BHB) were combined using their ATP equivalence, glucose contributed 72%-84% of potential ATP in all epochs (**Table V**; available at www.jpeds.com). Lactate contributed 25% of potential ATP on the first day and remained the largest potential source of ATP other than glucose throughout the 5 days. BHB was most available on days 2-3, but still only contributed 7% of potential ATP. Total potential ATP available from these fuels was 17% lower on days 1-2 than on days 4-5.

Weight loss over the first 5 days was common, with median change of −3.8% (range, −11.5% to 7.2%) of birthweight. Lactate concentrations were similar in infants whose weight loss was less than or greater than the median (**Table VI**; available at www.jpeds.com). However, the mean BHB concentrations were higher in infants who had weight loss greater than the median (3.1 mg/dL vs 1.7 mg/dL; difference, 1.4; 95% CI, 0.7-2.0; 0.30 mmol/L vs 0.16 mmol/L; difference, 0.13; 95% CI, 0.07-0.19; $P < .001$), even after adjustment for glucose concentration. Infants born at 40 or more weeks had higher lactate concentrations than those born earlier (mean difference, 1.7 mg/dL; 95% CI, 0.0-2.6; 0.2 mmol/L; 95% CI. 0.0-0.3; $P = .02$). Infants of mothers with lower body mass index (<23.1 kg/m^2) had higher BHB concentrations than those of mothers with a higher body mass index (mean difference, 0.6 mg/dL; 95% CI, 0.1-1.0; 0.05 mmol/L; 95% CI, 0.01-0.10; $P = .02$). Maternal weight gain, mode of delivery, and infant sex were not related to fuel concentrations.

Discussion

We describe the plasma concentrations of BHB and lactate over the first 5 postnatal days in term, healthy, appropriately grown infants, most of whom were breastfed. Although most infants were born in a hospital, all completed the study in their family homes and were cared for by their parents. BHB concentrations increased after day 1, peaking on day 3, and then decreasing by 96 hours, whereas lactate concentrations were higher on the first day and then fell to concentrations similar to those found in children and adults. Glucose contributed 72%-84% of the estimated potentially available ATP throughout the 5 days.

When glycogen stores within the liver are low, BHB is produced from fatty acids via acetyl coenzyme A. BHB is then available to be used within the Krebs cycle, and within the mitochondria it is converted to ATP. The availability

Table III. Plasma concentrations of alternative fuels when simultaneous blood glucose concentrations were either below or above the overall median (67 mg/dL [3.7 mmol/L)

	Glucose below median		Glucose above median		Difference		
Ages (h)	No.	Mean	No.	Mean	Estimate	95% CI	*P* value
Lactate							
0-12	138	21 [2.4]	20	27 [3.0]	−6 [−0.6]	(−8 to −2) [−0.9 to −0.2]	<.001
12-24	88	19 [2.1]	17	19 [2.2]	0 [−0.1]	(−4 to 3) [−0.5 to 0.3]	1
24-48	103	15 [1.7]	35	14 [1.6]	1 [0.1]	(−2 to 4) [−0.2 to 0.4]	1
48-72	63	14 [1.6]	70	12 [1.3]	2 [0.2]	(0 to 4) [0.0 to 0.5]	.08
72-96	13	13 [1.5]	121	13 [1.5]	0 [0.0]	(−4 to 4) [−0.4 to 0.5]	1
96-120	8	15 [1.7]	122	13 [1.5]	2 [0.2]	(−3 to 7) [−0.3 to 0.8]	1
0-120	413	16 [1.8]	385	17 [1.9]	−1 [0.0]	(−1 to 1) [−0.1 to 0.1]	.87
BHB							
0-12	137	0.9 [0.09]	27	0.7 [0.07]	0.2 [0.01]	(0.0 to 0.3) [0.00 to 0.03]	1
12-24	86	2.1 [0.20]	17	2.1 [0.20]	0.1 [0.01]	(−0.7 to 0.8) [−0.07 to 0.08]	1
24-48	103	5.7 [0.55]	34	3.7 [0.36]	2.0 [0.19]	(0.5 to 3.5) [0.05 to 0.34]	.03
48-72	62	7.9 [0.76]	69	3.7 [0.36]	4.2 [0.40]	(2.5 to 5.9) [0.24 to 0.57]	<.001
72-96	13	5.5 [0.53]	120	2.2 [0.21]	3.3 [0.32]	(0.6 to 6.0) [0.06 to 0.58]	.001
96-120	8	2.1 [0.20]	122	1.4 [0.13]	0.8 [0.08]	(−0.7 to 2.3) [−0.07 to 0.22]	.84
0-120	409	3.0 [0.29]	389	1.9 [0.18]	1.1 [0.11]	(0.3 to 2.0) [0.03 to 0.19]	<.001

Values are mg/dL [mmol/L]. BHB analyzed after log conversion, results obtained by bootstrap (1000 repeats), *P* values obtained after Bonferroni correction.

of essential enzymes to allow the conversion of ketones to acetyl coenzyme A is tissue specific, but includes the nervous tissue.[22]

BHB concentrations increased between 24 and 96 hours, but were generally low before and after this age. Hawdon et al reported similar time-related changes in ketone body concentrations (BHB + acetoacetate).[3] In the study by de L Costello et al, BHB concentrations were reported to be increasing up to 48 hours of age, consistent with our findings, but their data did not go beyond this.[2] The post-term infants in that study were also reported to have a higher BHB:glucose concentration ratio, but we did not find a difference in BHB related to gestation. It is possible that the relatively low birthweight of that cohort may have contributed to these differences.

Our data show that BHB is not available as a potential alternative cerebral fuel initially, but many infants begin to produce it in low concentrations by 24 hours of age, and some have high concentrations (>20 mg/dL [2 mmol/L]) between 48 and 96 hours of age. Infants with lower glucose concentrations tended to have higher BHB concentrations, although this seemed to require more than 12 hours of low glucose concentrations. However, even the higher BHB plasma concentrations seen on days 2-4 in our data are much lower than those reported in starving children and adults.[23] It is possible that many infants experience a period of relative fasting in the first 3 days after birth before secondary lactogenesis, during which fatty acid mobilization provides the substrates required for ketogenesis. The association between higher BHB concentrations and greater weight loss is likely to reflect a similar process, with infants whose mothers produce sufficient breast milk soon after birth producing little BHB. The same may apply to infants who receive formula milk and for whom greater volumes of formula milk are reported to correlate with lower concentrations of ketone bodies.[4] However, there were too few formula-fed infants in our cohort to allow further exploration of this relationship.

Our data suggest that BHB is a potential contributor to cerebral fuels in infants with low glucose concentrations, but only after prolonged and non acute periods of low glucose

Table IV. Plasma concentrations of alternative fuels when interstitial glucose concentration has been below of above the overall median (67 mg/dL [3.7 mmol/L] for different periods of time

	Interstitial glucose below median		Interstitial glucose above median		Difference		
Durations of glucose concentration (h)	No.	Mean	No.	Mean	Estimate	95% CI	*P* value
Lactate							
1-6	77	14 [1.6]	110	15 [1.7]	−1 [−0.1]	(−3 to 1) [−0.3 to 0.1]	.33
6-12	55	15 [1.7]	44	14 [1.6]	1 [0.1]	(−1 to 4) [−0.1 to 0.4]	.34
12-18	30	17 [1.9]	29	16 [1.8]	1 [0.1]	(−2 to 4) [−0.2 to 0.5]	.38
≥18	100	15 [1.7]	83	16 [1.8]	−1 [−0.1]	(−3 to 2) [−0.3 to 0.2]	.67
All	262	15 [1.7]	266	15 [1.7]	0 [0]	(−2 to 2) [−0.2 to 0.2]	.88
BHB							
1-6	78	2 .4 [0.23]	107	2.5 [0.24]	0.1 [−0.01]	(−0.1 to 0.7) [−0.09 to 0.07]	.8
6-12	55	3.0 [0.29]	45	2.2 [0.21]	0.8 [0.08]	(−0.3 to 1.9) [−0.03 to 0.18]	.18
12-18	29	2.5 [0.24]	28	1.5 [0.14]	0.8 [0.10]	(0 to 2.1) [0.00 to 0.20]	.05
≥18	99	4.3 [0.41]	82	1.6 [0.15]	2.7 [0.26]	(1.5 to 4.0) [0.14 to 0.38]	<.001
All	261	3.1 [0.30]	262	2.0 [0.19]	1.1 [0.11]	(0.2 to 2.0) [0.02 to 0.19]	.01

Values are mg/dL [mmol/L]. BHB analyzed after log conversion, results obtained by bootstrap (1000 repeats). Analysis of difference is adjusted for repeated measures, epoch, simultaneous blood glucose, and weight loss.

concentrations. We are unable to provide data on the critical concentration of this alternative fuel that might prevent brain injury in a infants who is hypoglycemic, but our data suggest that the BHB response to hypoglycemia is too low and too slow to be useful in the acute situation.

Lactate concentrations are higher in the first 48 hours, falling from a birth range of 13-44 mg/dL (1.5-5.0 mmol/L) to between 9 and 22 mg/dL (1.0 and 2.5 mmol/L) after 48 hours. These data are consistent with other reports from more restricted cohorts. Hawdon et al showed a nearly identical pattern in single samples taken from 71 breastfed infants.[3] Nielsen et al reported a mean lactate concentration of 11 mg/dL (95% CI, 2.6-19.5 [1.2 mmol/L; 95% CI, 0.3-2.2]) on day 4 in 141 infants.[24] However, a cross-sectional study of 558 infants over 48 hours did not show a decline in lactate, contrary to our findings.[2]

The production of lactate from glucose can produce ATP in anaerobic conditions, and hence a high lactate concentration is frequently interpreted as an adverse health indicator. However, both muscle and brain can produce lactate in the presence of adequate amounts of oxygen, and lactate can also be used as a fuel source, being metabolized via pyruvate through the tricarboxylic pathway and releasing amounts of energy that are comparable with glucose.[16,25] In adults, infusions of lactate improved cerebral function in the presence of hypoglycemia, supporting the potential role of lactate as a cerebral fuel.[26,27]

It is possible that the higher lactate concentrations on the first day after birth may reflect anaerobic metabolism during the stresses of labor or aerobic glycolysis to assist with energy provision, or some combination of the two. Our data show no relationship between low glucose and high lactate concentrations at any age, and notably in the first epoch (<12 hours) higher glucose concentrations were seen with higher lactate concentrations. It is possible that this finding reflects stressed infants developing both anaerobic lactate production and catecholamine-induced glucose production in the first few hours after birth.

The total energy available from the 3 fuels we studied suggests a small potential role for lactate on day 1, and BHB on days 2 and 3 as alternative cerebral fuels if glucose supply is limited. However, these estimates of available ATP are made based on plasma concentrations, and although cerebral uptake of lactate and BHB has been shown to be proportionate to plasma concentrations, the intracellular availability of these fuels for ATP production may not be well-reflected in our estimates.[5,7] Nonetheless, our data suggest that glucose remains the major circulating cerebral fuel in well infants over the first 5 days.

The strengths of this study include analyses of repeated blood samples from a cohort of healthy term infants from birth until 120 hours of age, while they were being cared for according to current practice recommendations. Continuous glucose monitoring also made it possible to examine the relationship between alternative fuels and duration of changes in glucose concentration. Possible limitations include that although our data were obtained by repeated sampling of individual infants, our analyses of percentile curves are nonetheless cross-sectional. We were not able to measure BHB concentrations of less than 1.0 mg/dL (<0.1 mmol/L), but this factor is unlikely to have influenced our findings because the concentrations of interest were well above that lower limit of detection.

We present percentile curves for plasma concentrations of BHB and lactate in healthy term newborn infants over the first 5 days. Our data show that circulating plasma BHB on days 2-4 and lactate on day 1 may provide a small contribution to the overall available cerebral fuels. However, when plasma glucose concentrations are low, the lactate concentration does not increase, and an increase in BHB plasma concentration is slow and only seen after the first postnatal day. Therefore, we conclude that these potential cerebral fuels are unlikely to provide neuroprotection in the face of early or acute neonatal hypoglycemia. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Epidemiology and Determining Etiologies of Respiratory Tract Infections: Both Have Changed!

Maletzky AJ, Cooney MK, Luce R, Kenny GE, Grayston T. Epidemiology of viral and mycoplasmal agents associated with childhood lower respiratory illness in a civilian population. J Pediatr 1971;78:407-14.

This study, performed in the offices of 12 pediatricians in the greater Seattle area, attempted to identify infectious etiologies of mild, nonhospitalized cases of lower respiratory tract illnesses in children <6 years of age. Over a 12-month period, 574 eligible illnesses were recorded among almost 11 000 children under the care of these pediatricians (annual incidence of 52.5 per 1000 children <6 years of age).

There are several noteworthy aspects of this study and its findings. This was a yeoman effort at capturing etiologies of illnesses, including collection and transport of throat swabs to the laboratory where they were inoculated into ≥3 cell lines, and virus growth was detected using multiple steps/methods. Culture for *Mycoplasma pneumoniae* was performed. Acute and convalescent blood samples were drawn when possible for different serologic assays for a panoply of pathogens. Almost 50% of illnesses had 1 of 4 viruses (respiratory syncytial virus, influenza, parainfluenza, and adenovirus) or *Mycoplasma* identified. *Mycoplasma* was associated with approximately 7% of illnesses. In all cases, rales were found on examination, and one-half of cases occurred in the >5-year-old (oldest) age group. Serology added little to *Mycoplasma* diagnosis (by culture) but substantially added to viral diagnoses. All pathogens except adenovirus were clustered in the fall and winter. Recognition of respiratory syncytial virus as a cause of mild illness, especially in those >1 year of age was new. Adenovirus detection rates and timing were similar in study patients to a group of well children being investigated by the authors, suggesting that adenoviruses when isolated may not be pathogenic.

The main findings of this study have been replicated, and the conclusions validated. Rapid molecular detection of many more pathogens is now available. However, we still struggle with assigning detected agents with causality for symptomatology. A few "side dishes" in the report are noteworthy 50 years later. All 12 participating pediatricians were included using the pronoun "he." Only 10% of 5-year old children were attending Kindergarten and only 9% attended earlier preschool. Without thinking much about it prospectively, the epidemiology of viral respiratory tract illnesses was soon to change profoundly when women routinely entered the workforce and very young children entered out-of-home collective environments.

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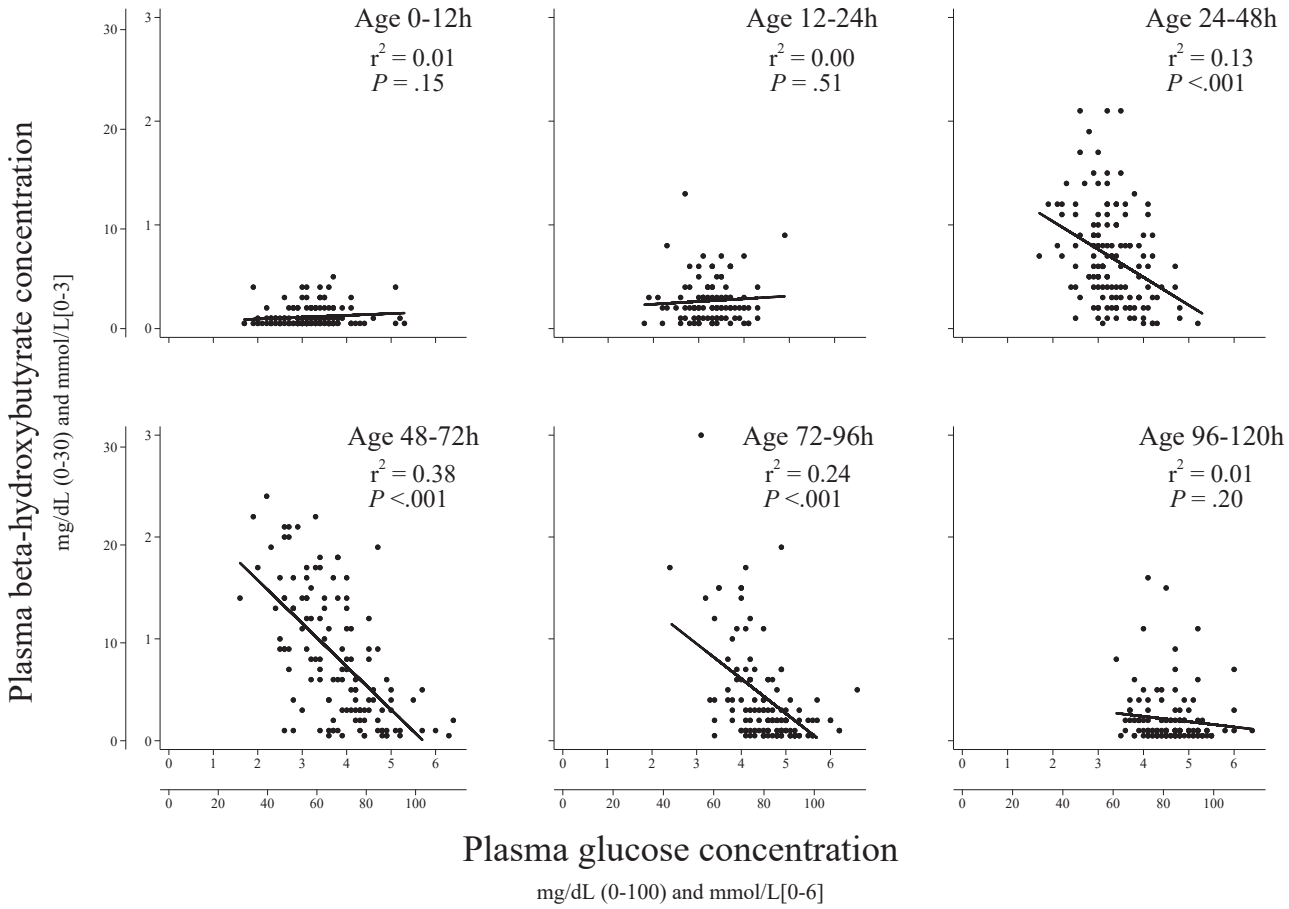

Figure 2. The relationship between plasma BHB and glucose concentrations at differing postnatal ages. The r^2 and *P* values are for simple linear regression analyses.

Table I. Characteristics of mothers and infants

Characteristics	Value
Mothers (n = 67)	
Age (years)	32.3 (4.1)
Parity	0 (0-3)
Maternal body mass index (kg/m^2)	23.1 (19.3-29.3)
Maternal weight gain (kg)	14.0 (0-27)
Vaginal delivery (n)	57 (85)
Arrival home after birth (h)	60.9 (19.5)
Infants (n = 67)	
Males (n)	41 (61)
Birth weight (g)	3584 (349)
Gestation (weeks)	40.1 (1.2)
Apgar score at 5 minutes of age	10 (8-10)
Ethnicity	
New Zealand European	56 (84)
Maori	2 (3)
Other*	9 (13)
Exclusively breast fed (n)	57 (85)
Weight change (% of birth weight)	−3.8 (−11.5-7.1)

Data are mean (SD), number (%), or median (range).
*Asian (4), English (2), South African (1), Australian (1), Spanish (1).

Table V. ATP equivalents from 3 metabolic fuels in different periods after birth

Ages (hours)	No.		Percent of total ATP			ATP total (mmol/L)
	Samples	Babies	Glucose	Lactate	BHB	
0-24	256	67	72.2	25.2	1.9	138.5 (2.3)
24-48	134	67	72.5	17.4	7.4	142.1 (2.1)
48-72	129	67	75	13.9	6.9	157.0 (2.2)
72-96	130	67	81.9	13.1	2.8	172.3 (2.1)
96-120	126	67	84.2	13.2	1.6	169.2 (2.2)

Data are number or mean (SE).
Assumes ATP equivalents to be 31 mmol ATP per 180 g [1 mmol] of glucose, 15 mmol ATP per 89 g [1 mmol] of lactate, 21.5 mmol ATP per 104 g [1 mmol] of BHB.

Table VI. Plasma concentrations of alternative fuels in infants with different maternal and birth characteristics

Variables	Yes		No		Difference		
	No.	Mean	No.	Mean	Estimate	CI	*P* value
Lactate							
Maternal body mass index <23.1 kg/m^2	33	16 [1.8]	34	15 [1.7]	1 [0.1]	(–1 to 2) [–0.1 to 0.2]	.24
Maternal weight gain <14 kg	32	16 [1.8]	35	16 [1.8]	1 [0.1]	(–1 to 2) [–0.1 to 0.2]	.49
Vaginal delivery	57	16 [1.8]	10	16 [1.8]	0 [0.0]	(–2 to 3) [–0.2 to 0.3]	.76
Male	41	17 [1.9]	26	15 [1.7]	1 [0.1]	(–1 to 3) [–0.1 to 0.3]	.07
Gestation <40 weeks	32	15 [1.7]	34	17 [1.9]	−2 [–0.2]	(–3 to 0) [–0.3 to 0.0]	.02
Weight loss >3.8%	33	16 [1.8]	34	16 [1.8]	0 [0.0]	(–2 to 1) [–0.2 to 0.1]	.82
BHB							
Maternal body mass index < 23.1 kg/m^2	33	2.6 [0.25]	34	2.0 [0.19]	0.6 [0.05]	(0.1 to 1.0) [0.01 to 0.10]	.02
Maternal weight gain <14 kg	32	2.1 [0.20]	35	2.5 [0.24]	−0.4 [–0.04]	(–0.8 to 0.0) [–0.08 to 0.00]	.08
Vaginal delivery	57	2.2 [0.21]	10	3.0 [0.29]	−0.8 [–0.08]	(–1.7 to 0.5) [–0.16 to 0.05]	.05
Male	41	2.3 [0.22]	26	2.2 [0.21]	0.1 [0.01]	(–0.3 to 0.6) [–0.03 to 0.06]	.61
Gestation <40 weeks	32	2.3 [0.22]	34	2.3 [0.22]	0.0 [0.00]	(–0.5 to 0.4) [–0.05 to 0.04]	.91
Weight loss >3.8%	33	3.1 [0.30]	34	1.7 [0.16]	1.4 [0.13]	(0.7 to 2.0) [0.07 to 0.19]	<.001

Data are in mg/dL [mmol/L]. BHB estimates derived from bootstrap (1000 repeats). Maternal weight gain refers to weight gain during pregnancy.