Patterns of metabolic adaptation for preterm and term infants in the first neonatal week

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Abstract

There have been few comprehensive accounts of the relationships between glucose and other metabolic fuels during the first postnatal week, especially in the context of modern feeding practises.

A cross sectional study was performed of 156 term infants and 62 preterm infants to establish the normal ranges and interrelationships of blood glucose and intermediary metabolites in the first postnatal week, and to compare these with those of 52 older children. Blood glucose concentrations varied more for preterm than for term infants (1·5–12·2 mmol/l *v* 1·5–6·2 mmol/l), and preterm infants had low ketone body concentrations, even at low blood glucose concentrations. Breast feeding of term infants and enteral feeding of preterm infants appeared to enhance ketogenic ability. Term infants had lower prefeed blood glucose concentrations than children but, like children, appeared to be capable of producing ketone bodies.

This study demonstrates that neonatal blood glucose concentrations should be considered in the context of availability of other metabolic fuels, and that the preterm infant has a limited ability to mobilise alternative fuels.

The newborn infant at birth must adapt from the environment in utero, characterised by the transplacental intravenous delivery of nutrients, to the postnatal situation of alternating periods of enteral milk feeding and fasting. Aspects of the process of adaptation at birth and its control have been described previously.[1 2] It may be expected that the process would be different in an infant born prematurely, because the endocrine and enzyme controls of intermediary metabolism are not fully developed in the preterm infant.[3] Disburbance of glucose homoeostasis may result when this adaptation fails or is incomplete.

Hypoglycaemia is the most common manifestation of failure of metabolic adaptation in the newborn period, and was first documented over 50 years ago.[4 5] Since then many authors have commented on the incidence, clinical manifestations, and sequelae of hypoglycaemia, although there is still substantial controversy in these areas.[6]

Preterm infants are also at risk for the development of hyperglycaemia. Most at risk are very premature infants, infants who are stressed,[7] and those receiving high rates of intravenous glucose infusion.[8] However, glucose homoeostasis cannot be divorced from the consideration of other metabolic substrates and the integrity of metabolic pathways which are necessary for the hepatic production of glucose in adequate amounts. Thus, the concentrations and interrelationships of other metabolic fuels, including the gluconeogenic substrates, lactate, pyruvate, alanine and glycerol, and the fat derived fuels, non-esterified fatty acids and ketone bodies, are important as indicators of the efficiency of counter regulatory metabolic responses during glycopenia. Furthermore, interpretation of the measurements of these substrates in sick or hypoglycaemic infants is impossible without a comprehensive knowledge of the normal ranges of concentrations and interrelationships in the neonatal period, particularly during the first seven postnatal days.

Considerable attention has been given to the adaptation to enteral feeding, and its role in the prevention of hypoglycaemia.[9–11] More recently, the value of early feeding has been recognised, particularly with respect to the adaptation of the gastrointestinal and endocrine systems to extrauterine life.[12 13]

This study examines the normal concentrations and interrelationships of metabolic fuels during the critical first few days after birth, the differences between preterm infants, term infants and older children, and the effects of feeding practices on the patterns of metabolic adaptation.

Subjects and methods

A cross sectional study was performed on 218 healthy singleton infants, less than 1 week old, born in the Newcastle upon Tyne maternity units. No mother received intravenous glucose during labour. Excluded from the study were infants with birth weights below the 10th centile, infants of diabetic mothers, and infants born by instrumental or breech delivery. Non-white infants were excluded because of racial differences in birthweight distribution.

One hundred and fifty six babies were of 37 weeks' gestation or more (term infants). Up to day 4, 65 born by normal vaginal delivery and 51 born by caesarean section were studied to investigate the effect of the type of delivery on metabolic adaptation. Because any differences between the two groups had disappeared by 24 hours of age (see below), and as the policy was to discharge mothers of healthy term infants born by vaginal delivery by the fourth postnatal day, 36 of the 40 infants studied at the ages of 5 and 6 days had been born by caesarean section. Term infants were demand fed by

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Accepted 1 October 1991

breast or bottle and none received intravenous glucose. All were nursed on postnatal maternity wards.

Sixty two babies were of 36 weeks' gestation or less (preterm infants). Only clinically stable preterm infants were studied, that is those who had not been hypoxic, acidotic, or requiring inotropic support in the 24 hours before sampling. Those requiring minimal ventilatory support were included provided they were clinically stable. Enteral feeding or intravenous fluids were started within the first four postnatal hours and the total daily fluid intake was at least 120 ml/kg for each baby. Some infants were fully enterally fed, while some received intravenous 10% glucose infusions instead of, or in addition to, enteral feeds; none received intravenous amino acid solution or lipid emulsion before or at the time of study.

For all infants, note was made of the method of feeding, the time since the last feed, and the daily intake of milk or intravenous glucose.

Blood samples were taken by heelprick, the warmed foot being sufficiently vasodilated to allow free flow without compression. Cord blood (venous) was collected at the time of the delivery for those infants who were subsequently sampled at less than 6 hours of age, before enteral feeding or intravenous fluids were started. For older infants, in order to standardise conditions during sampling, blood samples were taken immediately before a feed and no less than two hours after the previous feed. Any infant receiving more than 5 mg glucose/kg/min intravenously, had the drip rate reduced to deliver 5 mg glucose/kg/min for one hour before sampling.

Samples of 40 µl blood were collected into a microcapillary tube and then placed into a tube containing 200 µl 3% perchloric acid (PCA); and 250 µl blood were collected into a heparinised container. The samples were immediately separated and frozen, pending assay by microenzymatic methods using a Cobas fast centrifugal analyser.[14] Whole blood concentrations of glucose, gluconeogenic precursors (pyruvate, alanine, lactate, glycerol), and ketone bodies (β-hydroxybutyrate, acetoacetate), together with plasma concentrations of non-esterified fatty acid (NEFA) were thus obtained. The intra-assay coefficient of variation for each assay was as follows: alanine 4·1%, pyruvate 4·6%, glucose 3·3%, lactate 5·8%, β-hydroxybutyrate 4%, acetoacetate 8%, and NEFA 1·5%. The lower limits of detection for concentrations of glucose, β-hydroxybutyrate, and acetoacetate were 1·5, 0·01, and 0·01 mmol/l respectively.

The data obtained from the study of infants after the first postnatal day were compared with metabolic data taken from a study of 52 healthy children, aged 1 month to 10 years, who had undergone an overnight fast before elective surgery.[15]

For 11 babies, there was insufficient plasma for NEFA measurement, six of these babies were preterm and five were term, ages were as follows: <12 hours (n=1), 12–24 (n=2), 2 days (n=1), 3 days (n=4), 4 days (n=1), and 6 days (n=2).

Data were analysed using the SPSS-X package. Glucose concentrations of <1·5 mmol/l were included in parametric analysis as being equal to 1·5 mmol/l. As these values represented only 1% of the total number of glucose concentration values obtained, the results obtained were the same as if non-parametric analysis of glucose concentrations had been performed.

Pearson's correlation coefficients were used to define interrelationships between substrates, and χ^2 and t tests were used to compare groups of infants. Ketone body and NEFA concentrations were found to have a log normal distribution, and therefore $\log_{10}$ values for these concentrations (µmol/l) were used for statistical analysis, and the values presented in tables are geometric means. A multiple regression model was constructed to investigate the effects of feed volume, between feed interval, intravenous glucose administration rate, total energy intake, gestational age, and postnatal age on blood metabolite concentrations.

Ethical approval for the study was granted by

Table 1 Mean (SEM) concentrations of intermediary metabolites in mmol/l for healthy term infants in the first postnatal week

	No	*Glucose*	*Lactate*	*Pyruvate*	*Alanine*	*Glycerol*	*NEFA*	*Ketone bodies*
Cord								
Vaginal delivery	9	4·3	3·45	0·12	0·36	0·08	0·21	0·25
		(0·1)	(0·41)	(0·01)	(0·01)	(0·01)	(0·05)	(0·01)
Caesarean section	24	3·4*	1·60**	0·60**	0·29**	0·06	0·10*	0·24
		(0·1)	(0·17)	(0·01)	(0·01)	(0·01)	(0·01)	(0·01)
1–12 hours								
Vaginal delivery	11	3·1	2·03	0·08	0·39	0·19	0·40	0·04
		(0·3)	(0·46)	(0·02)	(0·03)	(0·02)	(0·01)	(0·01)
Caesarean section	11	3·3	1·79	0·07	0·29*	0·21	0·37	0·05
		(0·2)	(0·20)	(0·01)	(0·02)	(0·02)	(0·01)	(0·01)
12–24 hours								
Vaginal delivery	9	3·7	1·95	0·11	0·32	0·20	0·35	0·21
		(0·2)	(0·19)	(0·01)	(0·02)	(0·02)	(0·01)	(0·02)
Caesarean section	10	3·3	1·85	0·09	0·25*	0·19	0·33	0·26
		(0·2)	(0·16)	(0·01)	(0·02)	(0·03)	(0·01)	(0·02)
Day 2	27	3·5	1·84	0·09	0·23	0·17	0·50	0·41
		(0·2)	(0·14)	(0·01)	(0·01)	(0·01)	(0·01)	(0·01)
Day 3	27	3·4	1·46	0·07	0·21	0·16	0·47	0·43
		(0·1)	(0·09)	(0·01)	(0·01)	(0·01)	(0·01)	(0·01)
Day 4	21	4·1	1·45	0·06	0·28	0·12	0·20	0·10
		(0·1)	(0·16)	(0·01)	(0·02)	(0·01)	(0·01)	(0·01)
Day 5	20	4·0	1·32	0·06	0·29	0·18	0·19	0·08
		(0·1)	(0·10)	(0·01)	(0·01)	(0·01)	(0·01)	(0·01)
Day 6	20	4·2	1·68	0·07	0·32	0·11	0·12	0·12
		(0·2)	(0·16)	(0·01)	(0·02)	(0·01)	(0·01)	(0·01)

t test, vaginal delivery *v* caesarean section *p<0·05; **p<0·01.

the ethics committee of Newcastle Health Authority. Informed consent was obtained from parents for the inclusion of each baby in the study.

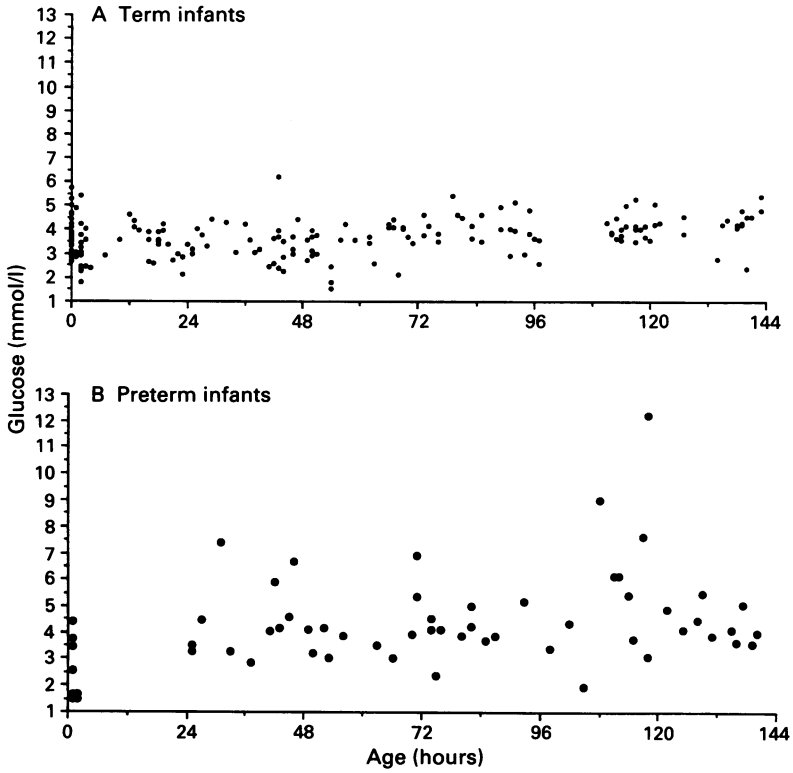

Figure 1 Relationship between blood glucose concentration and postnatal age: (A) term infants and (B) preterm infants.

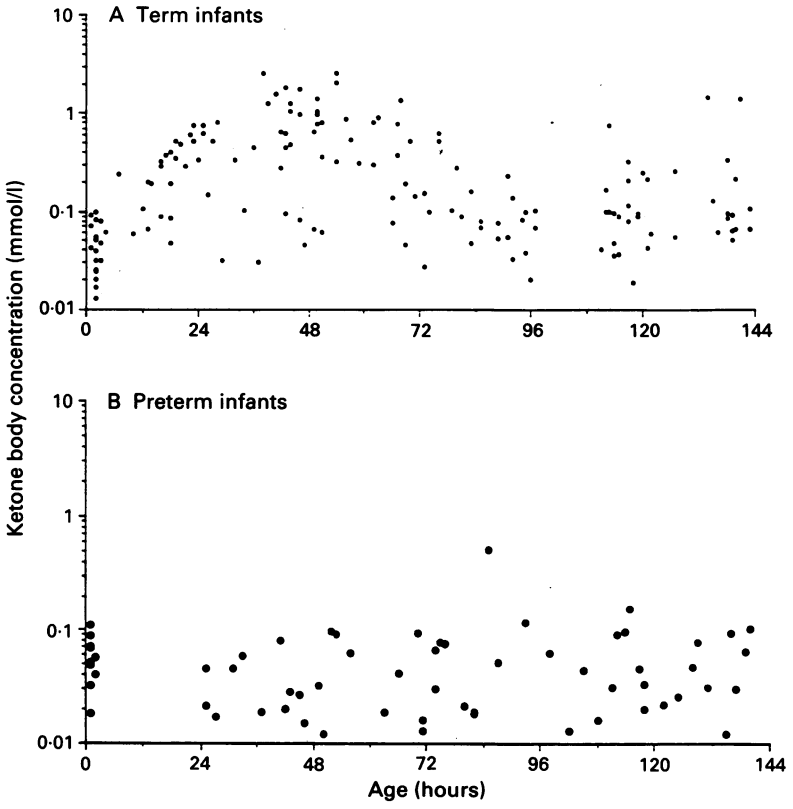

Figure 2 Relationship between ketone body concentration and postnatal age: (A) term infants and (B) preterm infants.

Results

TERM INFANTS

The median gestation of the group of term infants was 39 weeks (range 37–42 weeks), and the median birth weight was 3380 g (range 2575–4564 g). There were 83 boys and 73 girls.

The daily means (SEM) for the circulating concentrations of individual intermediary metabolites are shown in table 1. Significant differences in metabolite concentrations, between infants born by normal vaginal delivery and caesarean section, were confined to cord blood values (glucose, lactate, pyruvate, alanine, NEFA) or values on day 1 (alanine).

There were no significant differences in cord pH or between mean daily metabolite concentrations after the first postnatal day. As differences in metabolite concentrations according to mode of delivery were found only on day 1, data from infants more than 1 day old and born vaginally or by caesarean section have been analysed as one group, and babies sampled on days 5 and 6, mostly born by caesarean section, have been assumed to be representative of all babies on those days.

The range of blood glucose concentrations during the first six postnatal days was from <1·5 to 6·2 mmol/l, with the widest daily range on day 2. The lowest daily mean blood glucose concentration was found on day 1, a reflection of the low concentrations found for those infants sampled within the first six postnatal hours. Subsequently, there was a positive relationship for blood glucose concentration with postnatal age ($r=0{\cdot}41$, $p<0{\cdot}001$).

The distribution of individual blood glucose concentrations is show in fig 1A. Nineteen of 156 (12%) term infants had blood glucose concentrations below 2·6 mmol/l (the recently suggested functional definition of hypoglycaemia[16]) with all but two of these low values occurring in the first three days.

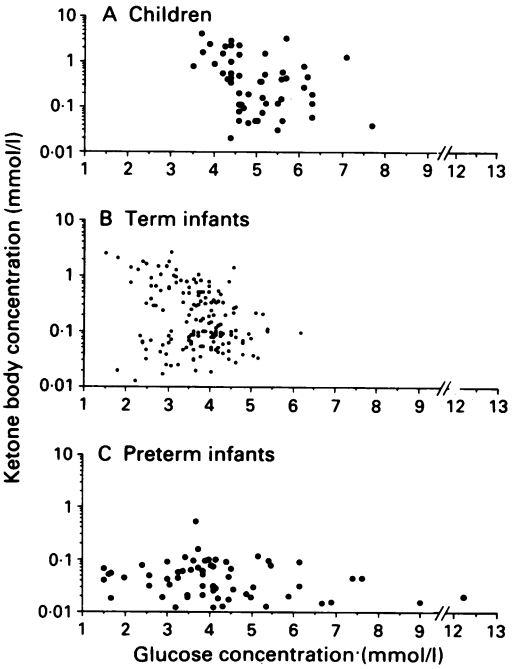

Figure 3 Relationship between blood glucose and ketone body concentrations: (A) children, (B) term infants, and (C) preterm infants.

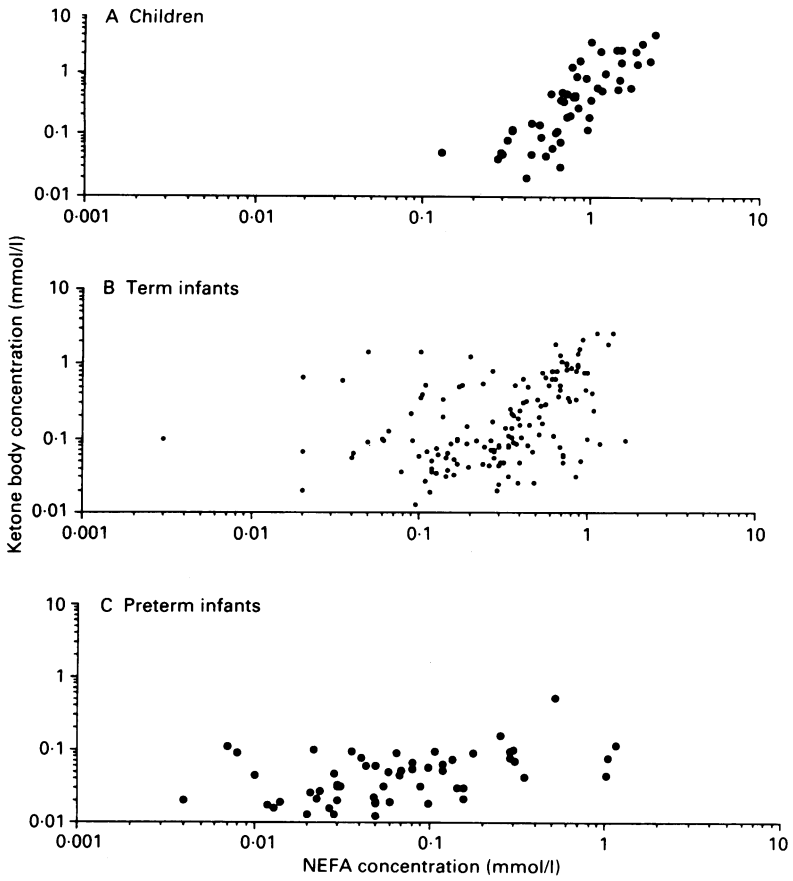

Figure 4 Relationship between ketone body and NEFA concentrations: (A) children, (B) term infants, and (C) preterm infants.

Table 2 Mean (SEM) in mmol/l for prefeed metabolite concentrations for preterm infants, term infants, and older children

	Preterm (n=52)	*Term (n=132)*	*Child (n=52)*	*t test notes**
Glucose	4·56 (0·24)	3·75 (0·07)	5·01 (0·12)	1
Lactate	1·58 (0·12)	1·60 (0·06)	1·21 (0·07)	2
Pyruvate	0·05 (0·01)	0·08 (0·01)	0·05 (0·01)	3
Alanine	0·18 (0·01)	0·26 (0·01)	0·21 (0·01)	4
Ketone bodies	0·04 (0·01)	0·20 (0·01)	0·32 (0·01)	5
NEFA	0·06 (0·01)	0·28 (0·01)	0·77 (0·01)	6
Total gluconeogenic substrate	1·90 (0·12)	2·09 (0·06)	1·66 (0·09)	7
Lactate:pyruvate ratio	32 (2)	24 (1)	26 (2)	8

**t* test notes: 1: term/preterm $p<0·05$; term/child $p<0·001$; 2: preterm/child $p<0·01$; term/child $p<0·001$; 3: term/child $p<0·001$; 4: term/preterm $p<0·01$; preterm/child $p<0·01$; term/child $p<0·001$; 5: term/preterm $p<0·001$; preterm/child $p<0·001$; 6: term/preterm $p<0·001$; preterm/child $p<0·001$; term/child $p<0·001$; 7: term/child $p<0·001$; 8: term/preterm $p<0·001$; preterm/child $p<0·05$.

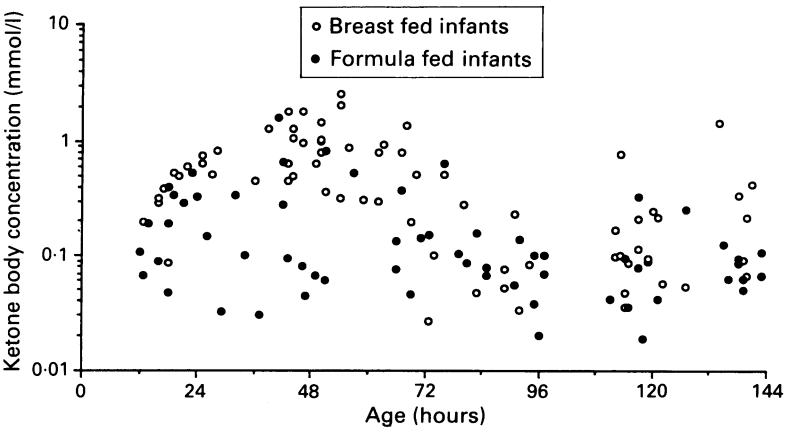

Figure 5 Relationship between blood ketone body concentration and postnatal age (term infants).

The relationship of blood ketone body concentration with postnatal age is shown in fig 2A. The highest blood ketone body concentrations were found on days 2 and 3, although the ranges of concentrations were wide on these days. On day 1 and from day 4 onwards most babies had low blood ketone body concentrations. As with older children, some term infants with low blood glucose had high ketone body concentrations (figs 3A, B). There was a significant negative relationship between log ketone body and glucose concentrations for infants aged 2–3 days ($r=-0·57$, $p<0·001$), but there was no such relationship for 1 day old infants or those older than 3 days.

The relationships between ketone body and non-esterified fatty acid concentrations for children and for term infants are shown in fig 4A, B. For term infants, Pearson's correlation coefficient for log ketone body and NEFA concentrations was 0·40 ($p<0·001$).

Some infants, particularly on the first postnatal day, had lactate concentrations that were above the reference ranges for older children and adults.[17] Total gluconeogenic precursor concentrations were widely scattered and were not related to blood glucose concentration. The concentrations of these substrates fell in parallel with each other in relation to increasing postnatal age (Pearson's correlation coefficient for total gluconeogenic substrate concentration with postnatal age, $r=-0·24$; $p<0·01$).

Differences between the prefeed metabolite concentrations of term infants and older children are shown in table 2. Term infants had lower mean blood glucose concentrations, but similar mean ketone body concentrations. Individual and total gluconeogenic precursor concentrations were significantly higher for term infants than for children.

Effects of feeding in term infants

Seventy one term infants were breast fed and 61 infants received formula feeds. There were no significant differences between these groups in terms of gestation, postnatal age, or distribution according to day of sampling. However, breast fed infants had significantly higher mean birth weights than formula fed infants (3507 *v* 3313 g, $p<0·05$) and had higher standard deviation scores for birth weight (0·67 *v* 0·28, $p<0·05$). Breast fed infants up to a week old had a significantly lower mean blood glucose concentration (range 1·5–5·3 mmol/l; mean 3·6 mmol/l) than formula fed infants of the same age (range 2·5–6·2 mmol/l; mean 4·0 mmol/l) ($p<0·05$). The distribution of blood ketone body concentrations with postnatal age, according to feed type is shown in fig 5. Breast fed infants had significantly higher blood ketone body concentrations than formula fed infants on days 2 and 3 (0·76 *v* 0·15 mmol/l, $p<0·001$), but after day 3 there was no significant difference in ketone body concentrations between the groups. Breast fed and formula fed infants demonstrated similar ketogenic responses to low blood glucose concentrations (fig 6).

Breast fed infants in the first postnatal week had higher total gluconeogenic substrate con-

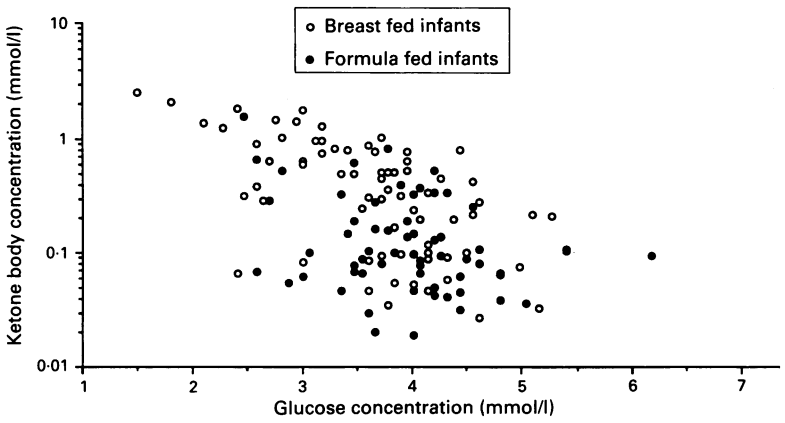

Figure 6 Relationship between blood ketone body and glucose concentrations (term infants).

centrations than formula fed infants (means, 2·2 *v* 1·9 mmol/l, $p<0·01$), but there was no difference in mean NEFA concentrations, and the method of feeding had no influence on the relationship between NEFA and ketone body concentrations.

Multiple regression analysis with method of feed, between feed interval, volume of feed, and postnatal age as independent variables demonstrated that only between feed interval (minutes) was significantly correlated with blood glucose concentration ($B=-0·003$, $SE=0·001$, $\beta=-0·32$; $p<0·05$). None of these variables, nor blood glucose concentration, could be shown to relate to total gluconeogenic substrate concentration, nor to (log) ketone body concentration when multiple regression analysis was performed either for infants 2–3 days old or for those more than 3 days old.

PRETERM INFANTS

The median gestation of the infants studied was 31 weeks (range 25–36 weeks) and median birth weight was 1760 g (range 830–3203 g). There were 40 boys and 22 girls. In terms of antenatal influences, mothers of the preterm group had a greater incidence of obstetric problems in pregnancy (for example, antepartum haemorrhage, pregnancy induced hypertension) and in labour, than mothers of the term group ($p<0·001$ and $p<0·01$, respectively), and there was a higher incidence of fetal distress in the preterm group ($p<0·05$). Despite this, the groups of infants were metabolically similar at birth, with no significant differences in umbilical venous blood pH, glucose concentration, or concentration of any other metabolite measured.

However, the preterm group subsequently had a lower mean blood glucose concentration in the first few postnatal hours than the term group (2·5 *v* 3·2 mmol/l, $p<0·05$), and a higher mean total gluconeogenic substrate concentration (4·2 *v* 2·5 mmol/l, $p<0·05$). The daily means (SEM) for the concentrations of individual intermediary metabolites are shown in table 3.

There were no significant differences between infants born by normal vaginal delivery and those born by caesarean section in terms of cord blood pH, cord blood metabolite concentrations, or blood metabolite concentrations in the first week or on each postnatal day.

The mean blood glucose concentration during the first six postnatal days was 4·2 mmol/l (range <1·5 to 12·2 mmol/l). Only on day 1 was the mean blood glucose concentration significantly lower than on subsequent days ($t=3·7$, $p<0·01$). The distribution of individual blood glucose concentrations by age is shown in fig 1B. Nine of 62 infants had blood glucose concentrations below 2·6 mmol/l, but seven of these infants were sampled on the first postnatal day before starting enteral or intravenous feeding.

The relationship of blood ketone body concentration with postnatal age is shown in fig 2B. Compared with term infants, preterm infants had low ketone body concentrations which varied little during the first postnatal week. The one infant who had a high ketone body concentration (on day 4) had a blood glucose concentration of 3·7 mmol/l.

For preterm infants, there was no significant relationship between log ketone body and glucose concentrations (fig 3C), with no rise in ketone body concentrations at low blood glucose as seen in most term infants and older children (figs 3A, B).

The relationship between ketone body and non-esterified fatty acid concentrations is shown in fig 4C. Most of the preterm infants had low NEFA concentrations, but there was a direct relationship between log ketone body and log NEFA concentrations ($r=0·46$, $p<0·001$).

Table 3 Mean (SEM) concentrations of intermediary metabolites in mmol/l for healthy preterm infants in the first postnatal week

	No	*Glucose*	*Lactate*	*Pyruvate*	*Alanine*	*Glycerol*	*NEFA*	*Ketone bodies*
Cord	11	4·2 (0·3)	2·73 (0·44)	0·10 (0·01)	0·38 (0·05)	0·07 (0·01)	0·10 (0·01)	0·16 (0·01)
Day 1	10	2·5 (0·3)	3·54 (0·76)	0·12 (0·03)	0·39 (0·07)	0·17 (0·04)	0·07 (0·01)	0·05 (0·01)
Day 2	11	4·5 (0·4)	1·49 (0·18)	0·05 (0·01)	0·19 (0·02)	0·09 (0·01)	0·05 (0·01)	0·03 (0·01)
Day 3	10	4·1 (0·4)	1·57 (0·31)	0·06 (0·01)	0·16 (0·01)	0·10 (0·01)	0·05 (0·01)	0·04 (0·01)
Day 4	10	4·1 (0·2)	1·43 (0·20)	0·05 (0·01)	0·21 (0·03)	0·09 (0·01)	0·12 (0·01)	0·06 (0·01)
Day 5	11	5·7 (0·9)	1·93 (0·38)	0·06 (0·01)	0·14 (0·02)	0·10 (0·02)	0·04 (0·01)	0·04 (0·01)
Day 6	10	4·3 (0·2)	1·46 (0·15)	0·05 (0·01)	0·20 (0·03)	0·08 (0·01)	0·10 (0·01)	0·04 (0·01)
Overall	62	4·2 (0·2)	1·90 (0·18)	0·06 (0·01)	0·22 (0·02)	0·10 (0·01)	0·07 (0·01)	0·04 (0·01)

Effects of feeding in preterm infants

The distribution of methods of feeding is shown in table 4. There were no significant differences in concentrations of glucose or other metabolites, when comparisons of groups were made according to method of feeding, although the numbers in subgroups were small. Concentrations of glucose and other intermediary metabolites were not significantly different when infants receiving any breast milk were compared with those receiving formula milk only, or when those infants receiving Pregestemil (a protein hydrolysate formula containing medium chain triglycerides, Bristol-Myers) were compared with infants receiving other types of milk formula.

Multiple regression analysis was performed with blood ketone body concentration as the dependent variable and glucose intake, total volume of feed, intravenous glucose intake, total energy intake, postnatal age, and gestational age as independent variables. Volume of feed (mk/kg/day) was found to have a significant positive correlation with log ketone body concentration (B=0·004, SE=0·001, β=57; p<0·001), but no significant relationship was found for the other independent variables. The relationship between ketone body concentration and volume of enteral feed is shown in fig 7.

Table 4 Distribution of infants according to feeding method

	No of infants	
	Term	Preterm
Breast	71	4
Bottle	61	2
Nasogastric tube, bolus	0	14
Nasogastric tube, continuous	0	17
Combination bottle/breast/tube	0	2
Fully intravenous fed	0	8
Partial enteral/partial intravenous feed	0	15

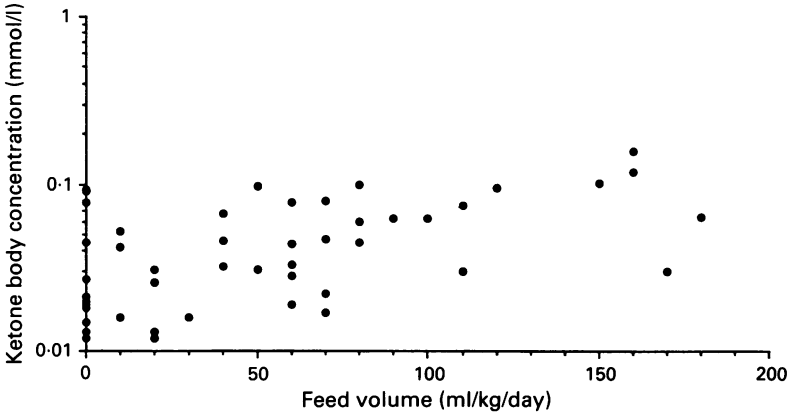

Figure 7 Relationship between blood ketone body concentration and volume of feed (preterm infants).

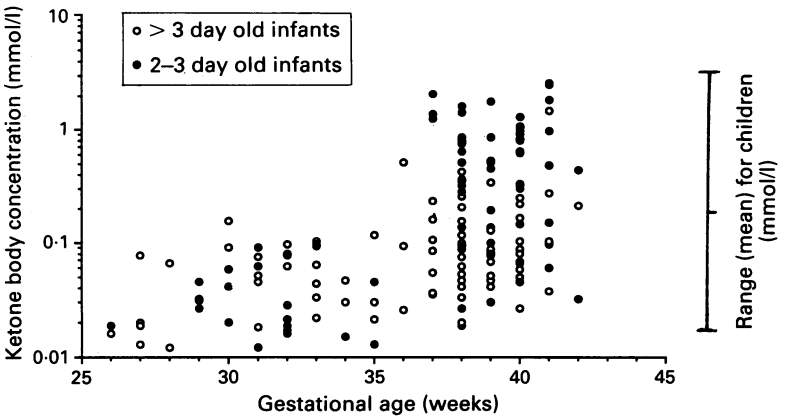

Figure 8 Relationship between ketone body concentration and gestational age.

EFFECT OF GESTATIONAL AGE

Significant differences between metabolite concentrations of preterm infants, term infants, and older children are summarised in table 2. Preterm infants had higher mean prefeed glucose concentrations than term infants, but had lower mean NEFA and ketone body concentrations than term infants and children. However, unlike term infants, gluconeogenic substrate concentrations were similar to those of older children.

On multiple regression analysis, gestational age was the most important determinant of cord blood ketone body concentration (B=0·03, SE=0·01, β=0·34, p<0·05), independently of size, and glucose and NEFA concentrations. Gestational age was not significantly related to cord glucose or NEFA concentrations. Once enteral or intravenous feeding was established, feed interval was the most important determinant of blood glucose concentration, there being a negative relationship between these two variables. Independently of blood glucose concentration, size or feed variables, gestational age correlated with ketone body concentration both for 2–3 day old babies (B=0·05, SE=0·02, β=2·6, p<0·05) and >3 day old babies (B=0·03, SE=0·01, β=3·4, p<0·01). Figure 8 demonstrates that an appreciable rise in ketone body concentrations occurred at 36 weeks' gestation.

Discussion

This study comprehensively describes the metabolic adaptation of a well defined group of infants, excluding any factors which may disrupt metabolic homoeostasis, with well standardised and accurate sampling and analytical techniques. Before the present study, there have been few reports of metabolic fuel profiles in the neontal period, and previous studies have been limited either by the heterogeneity of the groups studied, by studying infants over a short postnatal period, or by differences in maternal nutrition or glucose administration in labour. For example, Stanley *et al* studied only infants who were less than 8 hours old, and an earlier study of Perrson and Gentz was of subjects of mixed gestation.[18 19]

The principal findings of this study, not previously reported, are first, that vigorous ketone body production appears to be a normal part of the adaptation to extrauterine life of term babies during the first three postnatal days; second, even in mature babies, ketogenesis frequently has a different relationship to circulating concentrations of glucose and non-esterified fatty acids when compared with older children; third, that ketogenesis is severely

Table 5 Definition and incidence of hypoglycaemia

	Term				*All ages*	*Preterm*
	5 Hours		*<48 Hours*	*≥48 Hours*		
Definition (mg/dl)	<35	<30	<30	<40		<20
(mmol/l)	<1·9	<1·6	<1·6	<2·2		<1·1
Incidence (%)						
Cornblath and Reisner (1965)[20]			5	0	5	
Lubchenco and Bard (1971)[35]					7·5	
Sexson (1984)[36]		8·1				
Srinivasan *et al* (1986)[37]						
Vaginal delivery	1–2					
Caesarean section	25					
Heck and Erenberg (1987)[38]			7·9			
Chance and Bower (1966)[39]						4·3
Fluge (1974)[40]						15
Present study		0	0	3·4	3·4	3·2

limited in preterm babies. For these reasons, data from older children cannot be applied directly to the diagnosis of inborn errors of fatty acid β-oxidation. Similarly, the normal lactate: pyruvate ratio derived from older children's data may not be a reliable indicator of neonatal metabolic disorders. The profiles of metabolic fuels described in this study provide useful reference data against which disordered metabolic adaptation or inborn errors of metabolism can be considered.

HYPOGLYCAEMIA

The definition and incidence of hypoglycaemia in the newborn period have been the subjects of much controversy. Comparison of blood glucose concentrations between the present and earlier studies is hampered by the heterogeneity of infants studied previously, blood sampling and assay methods, feeding practises and intravenous administration of glucose to mothers in labour. A comparison of the incidence of hypoglycaemia between studies is shown in table 5, using early definitions of hypoglycaemia, which vary according to gestation and postnatal age of the baby.[20 21]

More recently, statistical definitions of hypoglycaemia have been challenged. It has long been suspected that neonatal hypoglycaemia has acute and long term effects on the central nervous system even at term[5 22–24] and a functional definition of hypoglycaemia has been proposed, based on neurophysiological studies and retrospective outcome analysis.[16 25] These workers suggested that the level for neonatal blood glucose concentration above which neurological dysfunction is unlikely to occur is 2·6 mmol/l.

In the present study, all umbilical venous blood glucose concentrations were above 2·6 mmol/l, suggesting adequate placental transfer of glucose before delivery. Using the functional definition, rather than Cornblath's definition, we found the incidence of hypoglycaemia for fed term infants in the first six postnatal days (10%) to be substantial, but the incidence was lower (4%) for preterm infants receiving enteral or intravenous feeds, suggesting that glucose requirements of preterm babies were being met adequately. Even when receiving enteral feeds, term and preterm infants had lower blood glucose concentrations after relatively short fasts, than had children after an overnight fast (table 2). Practical recommendations resulting from these data must take into account the ability of these babies to provide alternative fuels to glucose by metabolic counter regulation.

COUNTER REGULATION

It is likely that healthy infants may be able to tolerate low blood glucose concentrations, with compensatory mechanisms such as changes in cerebral blood flow to increase glucose delivery during hypoglycaemia,[26 27] or the use of alternative metabolic fuels such as ketone bodies, lactate or fatty acids.[28–31]

Evidence for the latter mechanism is provided by the present study, in that high ketone body concentrations were seen in term infants on days 2 and 3, with levels at this age similar to those seen after overnight fasting in older children (figs 3, 4). Turnover studies have demonstrated that there is a direct relationship between ketone body turnover rate and ketone body concentrations,[32] suggesting that the high ketone body concentrations in these babies were secondary to high rates of ketogenesis. Variation between babies may be related to the establishment of milk feeds, which may stimulate the ketogenic process, or may represent maturational differences in individual infants. Figure 3 demonstrates that, in the neonatal period, the blood glucose concentration threshold for ketogenesis is lower than for older children, and some term infants and all preterm infants with low blood glucose concentrations did not appear to mount a ketogenic response at all. The relationships between NEFA and ketone body concentrations for each group (fig 4) suggests that lipolysis and ketogenesis are less closely linked in the neonatal period especially for preterm infants, and that low ketone body concentrations in preterm babies may be related to a combined failure of lipolysis and ketogenesis. Studies of ketone body turnover would confirm these speculations.

It is interesting to note that, at birth, there appear to be few metabolic differences between term and preterm infants. This may reflect the selection of infants who all had uncomplicated deliveries and were of an appropriate birth weight for gestational age. However, in the first few hours after birth, there was a significantly greater fall in blood glucose concentration for preterm infants, suggesting that they were less able than term infants to adapt to cessation of intrauterine nutrition. The high gluconeogenic substrate concentrations for preterm infants at this age suggests that gluconeogenic ability was impaired; glucose turnover studies are required to confirm this. No mother received intravenous glucose during labour, so neonatal hyperinsulinism was unlikely to be responsible for early postnatal hypoglycaemia.

Effect of feeding

It appears that feeding affects metabolic profiles. The low glucose concentrations of breast fed term infants may reflect the low energy content of breast milk in the first few postnatal days, so that counter regulatory ketogenesis is activated.

Alternatively, the raised ketone body concentrations may be secondary to a direct ketogenic effect of breast milk, by virtue of its lipase content allowing the delivery of fatty acids to the liver via the portal venous system. Lucas *et al* studied 6 day old breast and formula fed term infants.[33] They found no differences between fasting concentration or post feed increment of glucose between the groups, although, as with the present study, ketone body concentrations were higher in breast fed infants.

For all term infants in the present study, the major determinant of blood glucose concentration was the interval between feeds, with lower blood concentrations when feed intervals were prolonged. This is in keeping with the data of Lucas *et al* who found that there were surges in blood glucose concentrations after milk feeds.[33] However, the present study demonstrates that prolonged intervals between feeds, of up to eight hours, were not associated with excessively low blood glucose concentrations. Breast fed infants, who had the lowest blood glucose concentrations, demonstrated effective counter regulation. This is reassuring in the light of current policies which encourage demand feeding of infants, and exclusivity of breast feeding when this is the mother's preference.

This study was unable to examine any differences effected by method of feeding (for example, continuous nasogastric, bolus nasogastric, bottle, breast) or type of milk on the metabolic profile of preterm infants as the groups were too small. However, after examining, by multiple regression analysis, all the factors that may affect metabolic adaptation in preterm infants, we found that there was a positive relationship between blood ketone body concentrations and the volume of enteral feed. This is the reverse of the situation found for term infants. The relationship may reflect the constituents of preterm formula feeds, but the exclusion from multiple regression analysis of infants receiving feeds containing medium chain triglycerides did not affect the findings. Alternatively, it may be that enteral feeding induces the enzymes of ketogenesis, so that metabolic adaptation, as found for term infants, can occur. This process may occur via gut hormones released in response to the presence of milk in the gastrointestinal tract, as a result of delivery of substrates other than glucose to the liver, or as a result of the carnitine content of milk enabling hepatic uptake and metabolism of fatty acids.

Much attention has been paid to the 'correct' definition of hypoglycaemia. This study demonstrates that factors other than absolute blood glucose concentration are important in the neonatal period, and while guidelines are important for clinical management, rigid definitions are inadequate and should be avoided. The influences of gestational age, feeding practises, and counter regulatory ability have also been demonstrated and these also must be considered in the interpretation of neonatal metabolic data.

We do not recommend that all asymptomatic term infants with blood glucose concentrations <2·6 mmol/l be treated with intravenous glucose, as there is evidence that, when the infants are healthy and of an appropriate weight for gestational age, ketone body production provides alternative fuels for brain metabolism. However, infants who are sick, small for gestational age, or have persistent or symptomatic hypoglycaemia, should be investigated and treated. Preterm infants appear less able to counter regulate than term infants, and hypoglycaemia should be avoided by providing adequate enteral and parenteral energy. There is evidence that enteral feeding of preterm infants is a stimulus for postnatal metabolic adaptation to occur, and this supports the view that early milk feeding to preterm infants, even at the 'minimal' level, when tolerated, should be encouraged.[12 13 34]

Future work should be directed, in all groups of infants, to blood concentration of glucose and other metabolic fuels and their relationship with neurological function, in order to identify those at most risk of neurological dysfunction at low blood glucose concentrations. Turnover studies, using stable isotopes, gas chromatography and mass spectrometry, and measurement of counter regulatory hormones will demonstrate the dynamics of endogenous glucose production and counter regulatory responses, and lead to a more scientific basis for nutritional management during the first postnatal days.

Dr Hawdon was supported by the Scientific and Research Committee of Newcastle Health Authority and by a Foundation for the Study of Infant Deaths training fellowship.

We thank the parents who gave consent for the inclusion of their babies in the study, and Angela McGann for assistance with biochemical analyses. This paper has been presented in parts at meetings of the British Paediatric Association, 1990, European Society for Paediatric Research, 1990, and British Association of Perinatal Medicine, 1990.

1 Aynsley-Green A, Soltesz G. Disorder of blood glucose homeostasis in the neonate. In: Roberton NRC, ed. *Textbook of neonatology*. Edinburgh: Churchill Livingstone, 1986.
2 Hetenyi G, Cowan JS. Glucoregulation in the newborn. *Can J Physiol Pharmacol* 1980;**58**:879–88.
3 Pildes RS, Pyati SP. Hypoglycemia and hyperglycemia in tiny infants. *Clin Perinatol* 1986;**13**:351–75.
4 Van Creveld S. Carbohydrate metabolism of premature infants. *Am J Dis Child* 1929;**38**:912–23.
5 Hartman AF, Jaudon JC. Hypoglycemia. *J Pediatr* 1937;**11**: 1–36.
6 Koh THHG, Eyre JA, Aynsley-Green A. Neonatal hypoglycaemia—the controversy regarding defintion. *Arch Dis Child* 1988;**63**:1386–98.
7 Lowick C, Mitchell AA, Esptein MJ, Shapiro S. Risk factors for neonatal hyperglycemia associated with 10% dextrose infusion. *Am J Dis Child* 1985;**139**:783–6.
8 Dweck HS, Cassidy G. Glucose tolerance in infants of very low birthweight. I. Incidence of hyperglycemia in infants of birthweights 1100 g or less. *Pediatrics* 1974;**53**:189–95.
9 Smallpiece V, Davies PA. Immediate feeding of premature infants with undiluted breast milk. *Lancet* 1964;**ii**:1349–56.
10 Wharton BA, Bower BD. Immediate or later feeding for premature babies? A controlled trial. *Lancet* 1965;**ii**: 969–72.
11 Beard AG, Parcos TS, Marasian BV, Eminians J, Frazier-Kennedy H, Lamb J. Perinatal stress and the premature neonate. II. Effect of fluid and calorie deprivation on blood glucose. *J Pediatr* 1966;**68**:329–43.
12 Lucas A, Bloom SR, Aynsley-Green A. Gastrointestinal peptides and the adaptation to extrauterine nutrition. *Can J Pharmacol* 1985;**63**:527–37.
13 Aynsley-Green A. Metabolic and endocrine interrelationships in the human fetus and neonate. *Am J Clin Nutr* 1985;**41** (suppl 2):399–417.
14 Harrison J, Hodson AW, Skillen AW, Stappenbeck R, Agius L, Alberti KG. Blood glucose, lactate, pyruvate, glycerol, 3-hydroxybutyrate and acteoacetate measurements in man using a centrifugal analyser with fluorimetric attachment. *J Clin Chem Clin Biochem* 1988;**26**:140–6.
15 Ward Platt MP, Tarbit MJ, Aynsley-Green A. The effects of anesthesia and surgery on metabolic homeostasis in infancy and childhood. *J Pediatr Surg* 1990;**25**:472–8.

16 Koh THHS, Aynsley-Green A, Tarbit M, Eyre JA. Neuronal dysfunction during hypoglycaemia. *Arch Dis Child* 1988;**63**:1353–8.
17 Lamers KJB, Doesburg WH, Rabriels FJM, *et al.* Reference values of blood components related to fuel metabolism in children after an overnight fast. *Clin Chim Acta* 1985;**145**: 17–26.
18 Stanley CA, Anday EK, Baker L, Delivoria-Papadopolous M. Metabolic fuels and hormone responses to fasting in newborn infants. *Pediatrics* 1979;**64**:613–9.
19 Perrson B, Gentz J. The pattern of blood lipids, glycerol and ketone bodies during the neonatal period, infancy and childhood. *Acta Paediatr Scand* 1966;**55**:353–62.
20 Cornblath M, Reisner SH. Blood glucose in the neonate and its clinical significance. *N Engl J Med* 1965;**273**:378–80.
21 Cornblath M, Schwartz R. Hypoglycaemia in the neonate. *Disorders of carbohydrate metabolism in infancy*. Philadelphia: Saunders, 1966.
22 Anderson JM, Milner RDG, Strich SJ. Effects of neonatal hypoglycaemia on the nervous system: a pathological study. *J Neurol Neurosurg Psychiatry* 1967;**30**:295–310.
23 Cornblath M, Joassin G, Weisskpof B, Swiatck KR. Hypoglycaemia in the newborn. *Pediatr Clin North Am* 1966;**13**: 905.
24 Koivisto M, Blanco-Sequrios M, Krause U. Neonatal symptomatic and asymptomatic hypoglycaemia: a follow-up study of 151 children. *Dev Med Child Neurol* 1972;**14**: 603–14.
25 Lucas A, Morley R, Cole T. Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. *BMJ* 1988; **297**:1304–8.
26 Anwar M, Vannucci RC. Autoradiographic determination of regional cerebral blood flow during hypoglycaemia in newborn dogs. *Pediatr Res* 1988;**24**:41–5.
27 Pryds O, Christensen NJ, Friis-Hansen B. Increased cerebral blood flow and plasma epinephrine in hypoglycemia preterm neonates. *Pediatrics* 1990;**85**:172–6.
28 Patel MS, Johnson CA, Rajan R, Owen OE. The metabolism of ketone bodies in developing human brain: development of ketone-body-utilising enzymes and ketone bodies as precursors for lipid synthesis. *J Neurochem* 1975;**25**:905–8.
29 Edmond J, Auestad N, Robbins RA, Bergstrom JD. Ketone body metabolism in the neonate: development and the effect of diet. *Fed Proc* 1985;**44**:2359–64.
30 Levitsky LL, Paton JB, Fisher DE. Cerebral utilization of alternative substrates to glucose: an explanation for asymptomatic neonatal hypoglycemia. *Pediatr Res* 1973;**7**:418.
31 Vannucci RC, Nardis EE, Vanucci JS, Campbell PA. Cerebral carbohydrate and energy metabolism during hypoglycamia in newborn dogs. *Am J Physiol* 1981;**240**: R192–9.
32 Bougneres PF, Zemmel C, Ferre P, Bier DM. Ketone body transport in the human neonate and infant. *J Clin Invest* 1986;**77**:42–8.
33 Lucas A, Boyes S, Bloom SR, Aynsley-Green A. Metabolic and endocrine responses to a milk feed in 6 day old term infants: differences between breast and cow's milk formula feeding. *Acta Paediatr Scand* 1981;**70**:195–200.
34 Lucas A, Bloom SR, Aynsley-Green A. Metabolic and endocrine consequences of depriving preterm infants of enteral nutrition. *Acta Paediatr Scand* 1983;**72**:245–9.
35 Lubchenco LO, Bard H. Incidence of hypoglycaemia in newborn infants classified by birthweight and gestational age. *Pediatrics* 1971;**47**:831–8.
36 Sexson WR. Incidence of neonatal hypoglycemia; a matter of definition. *J Pediatr* 1984;**105**:149–50.
37 Srinivasan G, Pildes RS, Cattamanchi G, Viora S, Lillien LD. Plasma glucose values in normal neonates: a new look. *J Pediatr* 1986;**109**:114–7.
38 Heck LJ, Erenberg A. Serum glucose levels in term neonates during the first 48 hours of life. *J Pediatr* 1987;**110**:119–22.
39 Chance GW, Bower BD. Hypoglycaemia and temporary hyperglycaemia in infants of low birth weight for maturity. *Arch Dis Child* 1964;**41**:279–85.
40 Fluge G. Clinical aspects of neonatal hypoglycaemia. *Acta Paediatr Scand* 1974;**63**:826–32.