Reviews / Analyses

Hypoglycaemia of the newborn: a review*

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It is almost a century since hypoglycaemia (a reduction in the glucose concentration of circulating blood) was first described in children, and over 50 years since the condition was first recognized in infants. Nevertheless, controversy still surrounds the definition, significance, and management of neonatal hypoglycaemia. Technological developments such as bedside glucose monitoring have, paradoxically, exacerbated rather than eased the situation.

This article reviews the literature on hypoglycaemia of the newborn, and covers the following: historical aspects; glucose homeostasis and metabolic adaptation at birth; the effect of low blood glucose levels on the central nervous system; the definition of hypoglycaemia; screening; prevention; treatment; research needs; and concludes with recommendations for prevention and management.

1. Historical background

The term "hypoglycaemia" refers to a reduction in the glucose concentration of circulating blood. It is almost 100 years since hypoglycaemia was first described in children and over 50 years since it was recognized in newborn and older infants (*1*). In view of the numerous advances that have subsequently occurred in the care of newborn infants, it is surprising that so much controversy still surrounds the definition, significance, and management of neonatal hypoglycaemia. Paradoxically, technological developments (bedside glucose monitoring) have exacerbated rather than eased the problem by facilitating screening for an ill-characterized clinical entity.

1.1. Patterns of hypoglycaemia

The vulnerability to hypoglycaemia of premature infants and of infants born to diabetic mothers was recognized early in the history of neonatal medicine (*2–5*). The transient nature of hypoglycaemia and the apparent infrequency of clinical manifestations led many to assume that low blood glucose concentrations among newborn infants were innocuous and "physiological", in contrast to hypoglycaemia caused by metabolic and endocrine disease. However, in 1959, Cornblath et al. (*6*) described eight, 2-day-old infants born to mothers with pre-eclamptic toxaemia whose symptoms (apnoea, cyanosis, coma and convulsions) were associated with reduced blood glucose concentrations (1–24 $mg.dl^{-1}$).[a] Infusion of intravenous glucose produced a clinical response in the infants and the course of their hypoglycaemia was self-limited but quite refractory. The outcome for this small group of infants was poor; five were normal when followed-up at 2 weeks to 11 months of age but one died and two had persistent neurological abnormalities. Subsequently further neurological sequelae associated with *symptomatic hypoglycaemia* (i.e. that associated with clinical signs[b]

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The following definitions are used in the article.

Exclusive breastfeeding: an infant is given no food or drink, including water, other than breast milk (except any medicinal drops or syrups that may be indicated).

Preterm: born before 37 completed weeks of gestation.

Small for gestational age: birth weight below the 10th percentile for infants of the some gestational age in the some population.

Very low birth weight: birth weight <1500 g.

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[a] 18 $mg.dl^{-1}$ = 1 $mmol.l^{-1}$ glucose.

[b] It is incorrect to speak of "symptoms" in the context of an infant because the term describes changes reported by a patient. The term "signs" more accurately describes clinical observations. Reference to "asymptomatic" and "symptomatic" hypoglycaemia has, nevertheless, been preserved throughout this article, since these terms have become widely adopted in the literature.

which resolve at increased blood glucose concentration) in the newborn were described.

Concern arose that hypoglycaemia without associated clinical signs (*asymptomatic hypoglycaemia*) might also lead to neurodevelopmental sequelae. This resulted in an attempt to define hypoglycaemia statistically as a blood glucose concentration greater than 2 SD below the mean for populations of well full-term and low-birth-weight infants. This, and the introduction in the early 1970s of reagent strip glucose assays (e.g. Dextrostix™) for cotside screening of newborns at risk, led to clinical classifications of neonatal hypoglycaemia (*7*, *8*). Gutberlet & Cornblath estimated the prevalence of hypoglycaemia (defined as serum glucose concentration <30 mg per 100 ml[a]) as 4.4 per 1000 total inborn live births (15.5 per 1000 low-birth-weight infants) (*8*). Lubchenco & Bard reported much higher levels: 11.4% of all nursery admissions and 20.3% of premature or low-birth-weight infants had blood sugar concentrations <30 mg per 100 ml if screened before feeding at 6 hours of age (*9*).

Estimating the exact frequency of asymptomatic hypoglycaemia clearly needs, as a prerequisite, a quantitative definition of the condition. This is dealt with in Section 4 but it is worth noting that transitional hypoglycaemia is a common problem in both industrialized and less developed countries, although few formal studies have been carried out in the latter. However, Anderson et al. observed that 38% of uncomplicated term infants born in Kathmandu, Nepal, had a blood glucose concentration of <2.6 mmol.l^{-1} during the first 50 hours of life (*10*). An approach aimed first at the prevention of hypoglycaemia, second at its reliable detection in neonates at risk, and third at appropriate treatment that will not be deleterious to breastfeeding is thus of global importance.

1.2. Symptomatic and asymptomatic hypoglycaemia

Despite clinical characterization of neonatal hypoglycaemia on the basis of blood glucose concentration, there was controversy as to whether hypoglycaemia, particularly in the absence of clinical signs, caused or was merely associated with neurodevelopmental sequelae. Some workers reported long-term neurological sequelae in up to 35% of neonates with symptomatic hypoglycaemia and in 20% of those with asymptomatic hypoglycaemia (*11*, *12*); other workers found no such relationship (*13*).

In a large retrospective case–control study, Koivisto et al. followed 151 cases of neonatal hypoglycaemia (defined as a blood glucose concentration <30 mg.dl^{-1}) for up to 4 years (*14*). The control series consisted of 56 concurrently treated asymptomatic neonates with no hypoglycaemia or neonatal disease. A total of 94% of 66 asymptomatic hypoglycaemia cases and 95% of the controls were classified as developmentally normal at follow-up. Among the 85 neonates who had suffered symptomatic hypoglycaemia, only 50% of those presenting with convulsions (8 infants) and 88% of those with nonconvulsive symptoms were developmentally normal. This study therefore identified no important neurodevelopmental abnormalities in infants with asymptomatic hypoglycaemia, and the tendency of symptomatic hypoglycaemia to present later in the clinical course than asymptomatic was stressed. Similar conclusions were drawn in an Indian follow-up study of 107 cases of asymptomatic or symptomatic neonatal hypoglycaemia (*15*).

Pildes et al. studied the effect of treatment on prognosis in a prospective study of 39 cases; as controls were selected 41 infants in the first week of life, matched as far as possible for sex, weight, gestation, ethnic group, mode of delivery, condition at birth, serum chemistry and birth date. At follow-up (5–7 years of age) "adequately treated" hypoglycaemia was the *sole* identifiable factor associated with neurological sequelae in only two cases. Unfortunately, despite strenuous efforts to match cases and controls prospectively, there was a striking difference in the number of small-for-gestational-age (SGA) infants (cases, 72.2%; controls, 28.8%). This emphasizes the weakness of the case–control methodology in studies of whether hypoglycaemia itself affects outcome or is merely a proxy for other risk factors. Sinclair has recently pointed out that all studies to date have been too flawed to demonstrate definitive correlation between hypoglycaemia and developmental outcome (*17*). A randomized intervention study seems likely to be the only means of studying this problem adequately.

1.3. Neonatal hypoglycaemia: current problems

Symptomatic hypoglycaemia is associated with a risk of long-term neurodevelopmental sequelae, but evidence for a causative link is weak. Controversy persists about the significance of asymptomatic hypoglycaemia for several reasons. First, glucose is only one of several brain fuels, and healthy term infants capable of mounting a counterregulatory response (Section 2) seem unlikely to develop sequelae if asymptomatic. A corollary is that preterm infants and SGA infants may be at greater risk of sequelae (*18*) because of metabolic immaturity (Section 2). Second, infants who develop symptomatic

hypoglycaemia are probably hypoglycaemic but asymptomatic at an earlier stage of their clinical course. Rigorous, dichotomous classification of symptomatic and asymptomatic hypoglycaemia is thus difficult.

2. Glucose homoeostasis and metabolic adaptation at birth

2.1. Fetal nutritional and metabolic environment

Glucose, amino acids, and lactate are the principal energy substrates during fetal life, with glucose alone providing about half the total energy requirement. Glucose crosses the placenta by facilitated diffusion along a concentration gradient between maternal and fetal plasma, fetal plasma glucose concentrations being 70–80% of those in maternal venous plasma. Net fetal glucose consumption is highly dependent upon both the maternal blood glucose concentration and the placental concentration gradient, but on average approximates 7 g.(kg fetal weight)$^{-1}$.d^{-1} (5 mg.kg^{-1}.min^{-1}), close to the rate of endogenous glucose production after birth. Enzyme systems involved in gluconeogenesis and glycogenolysis are present in the fetal liver, but remain inactive unless provoked by extreme maternal starvation. Weight for weight, fetal liver contains about three times more glycogen than adult liver and hepatic glycogen stores at birth comprise about 1% of the neonate's energy reserves at birth.

The rate of placental fatty acid transport varies between species in proportion to the adiposity of the newborn. Quantitatively fat oxidation is believed to be less important than amino acid/glucose oxidation, and rates of ketone body production are low during fetal life (*19*). The fetal endocrine milieu is dominated by insulin, which does not cross the placenta — fetal secretion being influenced by concentrations of both glucose and amino acids in fetal plasma. The fetal insulin axis is therefore independent of that of the mother. The β-cells of the fetal pancreas become responsive to glucose relatively late in gestation, and β-cell mass increases markedly in the last trimester of pregnancy. It has been proposed that this may be a critical developmental period at which substrate provision programmes pancreatic islet development, irreversibly influencing the metabolic response to glucose in later life and predisposing to certain patterns of adult disease (*20*). Insulin promotes anabolism in the fetus by stimulating uptake of glucose into muscle and adipose tissue (Table 1). Thus, the last trimester of pregnancy is a period of rapid fetal growth, particularly of deposition of fat in adipose tissue; in this way, energy stores are laid down in preparation for birth.

Table 1: **Metabolic effects of insulin**

	Effect[a]
Glucose uptake into muscle	+
Glucose uptake into adipose tissue	+
Release of amino acids from muscle	−
Release of fatty acids from adipose tissue	−
Gluconeogenesis	−
Ketogenesis	−

[a] + = stimulation; − = inhibition.

2.2. Regulation of blood glucose concentration after birth

Normally the concentration of blood glucose is regulated within a much narrower range than that of other metabolic fuels, varying only two- to threefold. In comparison, ketone body and nonesterified fatty acid concentrations may vary by ten- to one hundredfold according to the physiological conditions. This strict control of blood glucose concentration during both the postprandial and postabsorptive states is accomplished by balancing the utilization of glucose in tissues with its endogenous production. The liver is the principal site of endogenous glucose production, though after prolonged fasting up to 10% of circulating glucose may originate in the kidney. Glucose is produced by glycogenolysis or is synthesized from glycerol, lactate, pyruvate and glucogenic amino acid precursors, of which alanine is quantitatively the most important. The general term used to describe the processes by which the body makes glucose available in the fasted state is *counterregulation*.

2.2.1. Glycogen metabolism. Glycogen is synthesized either directly from glucose or indirectly from other precursors such as lactate, pyruvate and glycerol. The balance between glycogen synthesis and breakdown is determined by the relative activities of glycogen synthase and phosphorylase, respectively. A protein kinase, activated by increased cAMP concentrations in the hepatocyte, simultaneously activates hepatic phosphorylase and inactivates glycogen synthase. Thus, a rise in hepatocyte cAMP levels stimulates glycogen breakdown; a fall stimulates glycogen synthesis.

Changes in hepatocyte cAMP levels are effected by the hormones that regulate glucose metabolism. These fall into two groups: insulin and

the so-called counterregulatory hormones (glucagon, catecholamines, cortisol, and growth hormone).

Insulin is secreted in response to a rise in blood glucose concentrations. Hepatocyte cAMP levels fall in the presence of insulin, thereby stimulating glycogen synthesis. The principal counterregulatory hormones are glucagon and adrenaline. Both increase hepatocyte cAMP levels and favour glycogen breakdown. Adrenaline also promotes release of glucogenic substrates (lactate and alanine) from peripheral tissues through stimulation of peripheral β-receptors.

2.2.2. Gluconeogenesis. Glucose is synthesized from lactate or pyruvate (some of which is derived from alanine) essentially by the reversal of the glycolytic pathway. The following regulatory enzymes are subject to substrate and/or endocrine activation and inhibition: pyruvate dehydrogenase, pyruvate carboxylase, phospho*enol*pyruvate carboxykinase (PEPCK), pyruvate kinase and fructose-1,6-diphosphatase. The precise details of activation/inhibition at each of these steps are complicated (see *21*) but it should be noted that the overall effect of insulin is to *inhibit* gluconeogenesis, while glucagon directly *activates* it. Apart from the insulin/glucagon ratio, intracellular accumulation of precursors (e.g. pyruvate), the acetyl CoA concentration and the $NADH/NAD^+$ ratio are regulatory influences. Fat and fatty acids are not themselves converted into glucose. However, fat oxidation promotes gluconeogenesis by increasing the intracellular acetyl CoA concentration and the $NADH/NAD^+$ ratio. Adrenaline indirectly stimulates gluconeogenesis by promoting peripheral mobilization of nonesterified fatty acids from adipose tissue and their subsequent oxidation in the liver. Plasma adrenaline concentrations immediately after birth are higher than at any other time of life, indicating its key role in perinatal metabolic and cardiorespiratory adaptation.

2.2.3. Peripheral glucose utilization. Most tissues, including brain, take up glucose in proportion to the concentration gradient across the cell membrane, but in muscle, adipose tissue, and liver the process is insulin sensitive. Intracellular glucose is phosphorylated to glucose-6-phosphate through the action of hexokinase. When cells oxidize fat, cytoplasmic glucose-6-phosphate concentrations increase, inhibiting hexokinase and reducing the cell's ability to "trap" glucose by phosphorylation. Thus, provision of fat both reduces glucose uptake into cells and favours gluconeogenesis in the liver.

2.2.4. Turnover of glucose: the balance between production and utilization. In recent years it has been possible to measure rates of glucose production in newborn infants using stable (nonradioactive) isotopes of glucose labelled with deuterium (^2H) or carbon-13 (^{13}C) ([6,6-$^2H_2$]glucose, [1-^{13}C]glucose and [U-^{13}C]glucose). Experiments with ^2H-tracers yield estimates of glucose production about 15% higher than those obtained with ^{13}C-tracers, since some ^{13}C is recycled through the Cori cycle. Using [6,6-$^2H_2$]glucose, Bier et al. estimated that the rate of glucose production in infants over 1-day-old was 4.3–8.5 $mg.kg^{-1}.min^{-1}$ (*22*). In contrast, Kalhan et al. reported a level of 3.8–4.9 $mg.kg^{-1}.min^{-1}$ using [1-^{13}C]glucose in 2-hour-old infants (*23*). Gluconeogenesis is certainly demonstrable on the second day of life in healthy term newborns. Denne & Kalhan used ^2H-[U-^{13}C]glucose to measure rates of glucose production on the second day of life in infants starved for 9 hours (*24*). The estimated proportion of glucose manufactured from recycled glucose (measured from ^{13}C-1 enrichment) was approximately 36%, i.e., $1.87 \pm 0.74\ mg.kg^{-1}.min^{-1}$ of the total glucose production rate of $5.02 \pm 0.41\ mg.kg^{-1}.min^{-1}$.

Subsequent studies using [6,6-$^2H_2$]glucose have found comparable mean glucose production rates in appropriate-weight-for-gestational-age (AGA) preterm and term infants ($3.5 \pm 0.4\ mg.kg^{-1}.min^{-1}$ and $3.5 \pm 0.3\ mg.kg^{-1}.min^{-1}$, resp.). In the same experiment SGA infants showed higher rates of glucose production ($4.3 \pm 1.0\ mg.kg^{-1}.min^{-1}$). It has been suggested that this reflects the higher brain:body mass ratio of SGA babies (*25*) and that glucose requirements correlate more closely with brain than body weight (*22*).

Infusion of glucose into adults suppresses endogenous glucose production both through a direct effect of glucose concentration and through enhancement of insulin secretion (see Section 2.2.2). The same phenomenon has been observed in normal newborn infants, though the degree of suppression is very variable and less marked in sick, stressed infants, particularly those who are very preterm (*26*, *27*). This probably demonstrates variable expression of the counterregulatory response in hypoglycaemic and stressed neonates.

In summary, moment-to-moment endocrine control of blood glucose concentration is achieved through the opposing actions of insulin and glucagon. Adrenaline "boosts" the counterregulatory response during stress. Other hormones act permissively; cortisol has little, short-term, direct effect on blood glucose concentrations but the effect of glucagon is reduced in cortisol deficiency. Substrate concentrations directly affect the rate at which gluconeogenesis proceeds. Administration of glucose

suppresses gluconeogenesis, whereas it is activated by lactate, pyruvate and glucogenic amino acids. Increased oxidation of nonesterified fatty acids facilitates gluconeogenesis indirectly in the liver by increasing acetyl CoA and NADH concentrations. It also reduces peripheral glucose requirements.

2.3. Metabolic events at birth: the role of insulin and substrates other than glucose

Insulin. At birth the newborn must switch abruptly from a state of net glucose uptake and glycogen synthesis to one of independent glucose production. The maintenance of normoglycaemia depends upon adequacy of glycogen stores, maturation of glycogenolytic and gluconeogenic pathways, and an integrated endocrine response. The following are believed to trigger the release of glucose and the mobilization of fat from peripheral stores: an increase in adrenalin secretion; and a rapid fall in the insulin:glucagon ratio during the first few hours of life, attributed to both a fall in the plasma insulin concentration and a surge in glucagon concentration (*28*). Whether the insulin concentration does fall is still under debate. Hawdon et al. were unable to confirm this in a cross-sectional study of healthy term and preterm neonates of appropriate weight for gestation (*29*). A methodological problem is the cross-reaction between insulin, proinsulin, and other propeptides in radioimmunoassays. Using highly specific assays, Hawdon et al. found that insulin:glucose ratios remain high in healthy preterm infants, while proinsulin and 32–33 split proinsulin account for 34–70% of the total insulin/insulin propeptide concentration (*30*). Healthy term infants have not been studied to date. Much remains to be learnt about the maturation of insulin and insulin propeptide secretion in the neonatal period and its relevance to metabolic regulation.

Metabolic substrates. Data on metabolic substrate concentrations during early postnatal adaptation in the human newborn are relatively few and many date from the era when early starvation was practised, and feeding (usually with formula) was postponed for hours or days after birth (*31–35*). The principal findings of these studies were that blood glucose concentration falls with the duration of starvation and that the concentrations of other metabolic substrates (free fatty acids, ketone bodies and glycerol) rise as blood glucose concentration falls.

For example, Beard et al. alternately allocated term and preterm infants to an "early feeding" group (fed with formula from 6 hours of age) and a group fasted for 72 hours (*31*). The mean blood glucose concentration at 72 hours was 40 $mg.dl^{-1}$ (2.2 $mmol.l^{-1}$) in the fasted term infants, compared with 68 $mg.dl^{-1}$ (3.8 $mmol.l^{-1}$) in the "early fed" group. A total of 58% of the fasted premature infants had a blood glucose concentration of <25 $mg.dl^{-1}$ (1.4 $mmol.l^{-1}$) by 72 hours of age, compared with only 4% (1 infant) among the early fed group; although no complications were noted. The fasted group also exhibited a reduced increment in blood glucose concentration on injection of glucagon and adrenalin, suggesting a relative reduction in their glycogen stores. Nevertheless, free fatty acid concentrations rose in the fasted infants, and over 50% of the fasted healthy premature infants exhibited ketonuria by 48–72 hours of age. Similarly, Persson & Gentz noted increases in free fatty acid, glycerol and ketone body levels among fasted term infants — the highest values being in babies with the lowest blood glucose concentrations (*33*). Increases in the concentration of glucogenic precursors (alanine and lactate) and ketone body concentrations with starvation at this time of life are nevertheless smaller than those in older children with similarly low glucose levels (*34*, *35*). Moreover it is important to emphasize that the so-called premature babies of 30 years ago were probably more mature as a group than today's preterm infants, whose adaptive capacity may be even less well developed.

More recently Hawdon et al. conducted a cross-sectional study of whole blood glucose concentration among 156 healthy term babies (*36*). This work is of importance for many reasons; first, infants were demand-fed; second, breastfed babies were studied (46% of the sample); third, metabolic substrates other than glucose (glycerol, lactate, pyruvate, alanine, nonesterified fatty acids, and ketone bodies) were measured; and finally, infants were studied throughout the first week and not only in the first 8 hours (*34*) to 3 days of life (*31*, *35*). Although healthy term breastfed babies had significantly lower blood glucose concentrations than those who were bottlefed (breastfed: mean, 3.6 $mmol.l^{-1}$ (range, 1.5–5.3 $mmol.l^{-1}$); bottle-fed: mean 4.0 $mmol.l^{-1}$ (range, 2.5–6.2 $mmol.l^{-1}$)), their ketone body concentrations were elevated in response. There was a statistically significant negative correlation between log (ketone body) and blood glucose concentration at 2–3 days of age, but not within the first 24 hours or after 3 days. Lucas et al. also found that breastfed babies had significantly higher ketone body concentrations than formula-fed babies studied on the 6th day of life (*37*).

In summary, blood glucose concentration falls in babies who are not fed, but healthy term (AGA) babies mobilize alternative metabolic substrates (free fatty acids and ketone bodies) in response. Breastfed babies as a group have lower blood glucose concen-

trations (referred to below as "suckling hypoglycaemia") and higher ketone body levels than those who are bottle-fed. It is not clear whether this reflects specific promotion of ketogenesis (e.g. by breast milk fat or another milk component) or whether it is simply the result of differences in blood glucose concentrations and postprandial increments in plasma insulin concentration.

2.4. Abnormal glucose homeostasis

2.4.1. Preterm babies. Blood glucose concentrations in preterm infants tend to be lower than those in term infants. This was considered "physiological", although there is no evidence that preterm infants are more resistant to the effects of hypoglycaemia than term infants. There are various reasons for the preterm infant's propensity to hypoglycaemia.

- First, energy reserves at birth, both as liver glycogen and fat, are greatly reduced. Differences in fat content are particularly important; fat accounts for only 2% of body weight at 28 weeks of gestation but about 16% at term. Although fat is not itself convertible to glucose, mobilization and oxidation of fat reduces glucose uptake and oxidation (see Section 2.2.3).

- Second, recent evidence indicates that preterm infants have plasma insulin concentrations greater than those of term infants, when related to plasma glucose concentration. It appears that the elevated insulin:glucose ratio and relative immaturity of ketogenesis persist for some months after birth (*38*). This phenomenon is as yet not understood, though it is possible that the greater protein intake of preterm infants, necessary to match their faster growth potential, is an insulinogenic stimulus. Insulin secretion in term infants (as reflected by C-peptide excretion) is modified by dietary protein intake and related to the plasma valine:glycine ratio (*39*).

- Third, it is likely that gluconeogenic pathways are less mature than in term infants. For example, expression of microsomal glucose-6-phosphatase is reduced in liver necropsy samples obtained from preterm infants up to 1 year of age and ranging from 24–36 weeks of gestation at birth. This enzyme catalyses the final step of both glycogenolysis and gluconeogenesis (*40*).

In view of the increased risk of hypoglycaemia associated with preterm birth, some recent research has focused on the adequacy of the counterregulatory response. Hawdon et al. studied 62 clinically stable preterm babies (median gestation, 31 weeks (range, 25–36 weeks); median birth weight, 1760 g (range 830–3203 g)) (*36*). The non-esterified fatty acid and ketone body concentrations of preterm infants were significantly lower than those of term infants. Moreover, preterm infants with low blood glucose levels did not show increased ketone body concentrations, as did infants born at term. The range of gestational age in this study is remarkable: at a gestational age of 36 weeks a dramatic increase in ketogenic potential appeared, but the study did not make clear whether this was a developmental event, or whether it simply reflected differences in the clinical management of babies of <36 weeks' gestational age. In Section 2.3 it was mentioned that Beard et al. observed ketonuria in over 50% of premature infants after prolonged fasting (48–72 hours) (*31*); however, the blood ketone concentrations were not measured.

In summary. Preterm infants show an increased incidence of hypoglycaemia and a reduced capacity to mobilize alternative metabolic fuels. From the point of view of managing breastfeeding in mildly preterm infants (32–36 weeks' gestation), more data on maturation of the counterregulatory response are required if excessive intervention is to be avoided.

2.4.2. Small-for-gestational-age infants. SGA infants have long been recognized to be at increased risk of neonatal hypoglycaemia (*6*). More recently, hypoglycaemia has been detected at the fetal stage among infants who are small for gestational age at birth. The following factors may account for this: a high brain:body mass ratio (with corresponding increase in glucose consumption); reduced fat stores; failure of counterregulation (including delayed maturation of gluconeogenesis); and hyperinsulinism.

Kalhan et al. noted that SGA infants in the basal (fasting) state on the first day of life had significantly higher rates of endogenous glucose production ($4.25 \pm 0.98\ mg.kg^{-1}.min^{-1}$) than AGA infants ($3.53 \pm 0.32\ mg.kg^{-1}.min^{-1}$; $P < 0.03$) (*25*). It was suggested that this reflected the greater brain weight of SGA infants relative to AGA infants. Several studies have shown that, relative to AGA infants, SGA infants have increased plasma concentrations of glucogenic substrates particularly alanine and lactate (*41–44*). When alanine is infused into SGA infants its concentration falls more slowly than in normal, AGA full-term neonates (*44*) and has less effect on blood glucose concentrations (*45*). These changes are most marked in the early hours of life, and it has been suggested that they reflect a delay in the maturation of glucogenic pathways, in particular the induction of PEPCK (*43*). Hawdon & Ward Platt, in a longitudi-

nal study of 33 SGA infants throughout the first postnatal week, found that increased blood levels of lactate and other total gluconeogenic substrates persisted until the 4th postnatal day in preterm SGA infants but fell within the first 24 hours in term SGA infants, thereafter being lower than those of AGA infants (*46*). This is consistent with the hypothesis that elevated concentrations of gluconeogenic substrates reflect delayed maturation of gluconeogenic pathways in SGA infants, particularly those born preterm.

At birth, the ketone body concentrations of SGA and AGA infants do not appear to differ, although by 24 hours of age (*43*), and throughout the first postnatal week (*46*), the ketone body levels of both term and preterm SGA infants remain low relative to those in AGA infants at equivalent blood glucose concentrations. Whether this reflects an inability of the SGA infant to mount a ketogenic response, or simply a more scrupulous attention to nutritional management and prevention of hypoglycaemia among the infants studied, is open to debate. Hawdon & Ward Platt reported that fewer SGA than AGA infants had a blood glucose concentration $<3\,mmol.l^{-1}$ (*46*).

There is some evidence that SGA infants with abnormal metabolic adaptation exhibit abnormal end diastolic flow velocities (EDV) in the umbilical artery in Doppler studies. Hawdon et al. found that a group of 11 fetuses with absent EDV showed lower blood glucose and free fatty acid concentrations in the first 6 hours of life than a group of 14 control SGA infants with normal EDV. In this small study, the group with absent EDV had lower mean birth weight (1525 g (range, 688–2020 g) versus 1903 g (range, 859–2296 g)); the difference was, however, not statistically significant ($P = 0.065$).

Endocrine adaptation in SGA babies has also been studied by several workers. Most have found no differences between AGA and SGA infants in terms of insulin and glucagon concentrations, although the range seen in both populations is wide. Nevertheless, some SGA babies appear to have both high plasma insulin concentrations and high glucose requirements, consistent with hyperinsulinism (*48–50*). A prospective study of SGA infants admitted to a single neonatal unit over 1 year found that 10 of 27 became hypoglycaemic and that half of them had inappropriately high plasma insulin concentration at the time of hypoglycaemia (*50*). Although the assay used did not discriminate insulin from its propeptides, and hence may have overestimated the true insulin concentration (*30*), low plasma free fatty acid concentrations and high glucose requirements ($>10\,mg.kg^{-1}.min^{-1}$ in 2 infants) provided functional evidence of hyperinsulinism.

Some of the babies also showed low plasma glucagon concentrations, raising the possibility that failure of the glucagon surge after birth plays as great a part in the etiology of hypoglycaemia in SGA infants as does hyperinsulinism (*51*). Mestyan et al. studied this by infusing glucagon into normoglycaemic and hypoglycaemic SGA infants; only the former group responded by showing a reduction in concentration of glucogenic amino acids (*52*). It was suggested that SGA infants may show glucagon resistance (see Section 7.3.1).

2.4.3. Stress hypoglycaemia. Hypoglycaemia may be present in a number of neonatal conditions associated with severe stress, most commonly sepsis and perinatal asphyxia, but also in congenital heart disease (heart failure and severe cyanotic heart disease) and neonatal cold injury with fat necrosis.

Although the catecholamine response to stress is a central feature of counterregulation, peripheral circulatory failure in sepsis and asphyxia may lead to both reduced mobilization of substrate from the periphery and accumulation of lactate in the presence of anaerobic glycolysis. This leads to exhaustion of liver glycogen and reduced capacity for gluconeogenesis, which may be compounded by anoxic liver injury. Hyperinsulinism and increased insulin sensitivity may also be present in these circumstances.

2.4.4. Transient hyperinsulinism. Hypoglycaemia associated with transient hyperinsulinism is seen most commonly among infants born to diabetic mothers, but also occurs in infants affected by erythroblastosis fetalis. Iatrogenic factors, including the use of glucose infusions in labour and maternal administration of β-sympathomimetics, may give rise to maternal hyperglycaemia and associated fetal hyperinsulinism. Less commonly, hyperinsulinism is associated with the rare Beckwith–Wiedemann syndrome or can be idiopathic.

The macrosomic infant born to a diabetic mother (IDM) has a characteristic habitus. Whereas infants who are simply large for dates have proportionate increases in both brain size and abdominal circumference, macrosomic IDMs have increased muscle, fat and liver mass, as might be predicted from the known effects of insulin (Table 1). Thus, in fetal life IDMs have increased abdominal circumference:head circumference ratios (*53*). For many years fetal hyperinsulinism was ascribed to maternal, and consequent fetal, hyperglycaemia (*54*); more recently it has been suggested that other factors, including amino acid concentrations, must operate, since mid-trimester human pancreatic tissue shows little insulin response *in vitro* to glucose (*55*).

The risk of hypoglycaemia during the neonatal period (*56*) may be reduced by careful control of maternal blood glucose concentration during pregnancy, but is still greater in IDMs of appropriate weight for gestational age than in the normal neonatal population. Hyperinsulinism leads to reduced concentrations of free fatty acids and ketone bodies in association with hypoglycaemia, which reflects both an increased rate of glucose uptake and a reduced rate of glucose production (*57*); a reduced postnatal glucagon surge appears to accompany the hyperinsulinism (*58*).

Some aspects of obstetric management can result in transient hyperinsulinism and hypoglycaemia among otherwise normal infants. Lucas et al. found that intravenous infusion of >10 g of glucose. h^{-1} during labour was associated with significantly increased cord blood insulin concentrations (*59*). Subsequent randomized studies of the effect on blood glucose concentrations and incidence of hypoglycaemia in the newborn have been reviewed by DiGiacomo & Hay (*60*). Mothers who were infused with >25 g of glucose. h^{-1} in the 2 hours prior to delivery experienced a 17% mean increase (95% confidence interval (CI), 5–30%) in the incidence of hypoglycaemia (blood glucose <2.2 mmol.l^{-1}). On average, the blood glucose concentration in such babies was 0.8 mmol.l^{-1} (95% CI, 0.5–1.1) lower at 2 hours of age than in babies born to mothers who had received no glucose; the difference at 1 hour of age was not statistically significant. Smaller differences in 2-hour blood glucose concentrations were also apparent in the babies even when <25 g glucose. h^{-1} had been infused (mean 0.4 mmol.l^{-1}; 95% CI, 0–0.8), although the incidence of hypoglycaemia was not significantly different (mean odds ratio, 2.6; 95% CI, 0.61–11.34).

Use of both prolonged oral (*61*), and short-term intravenous, administration of β-agonists (*62*) to suppress preterm labour has been associated with increased cord plasma insulin concentrations. This may be the result of both transplacental passage of the drug and the presence of hyperglycaemia in the mother (*63*). Epstein et al. noted transient hypoglycaemia in babies (*61*), but Jouppila et al. noted an increase in babies' blood glucose concentration when fenoterol was administered briefly to suppress uterine contractions before Caesarean section (*64*).

2.4.5. Persistent hyperinsulinism, endocrine disorders and inborn errors of metabolism. Neonatal hypoglycaemia that persists or recurs after the first few days of life raises the diagnostic possibility of an endocrine disorder or inborn error of metabolism (Table 2).

Table 2: **Causes of recurrent and persistent neonatal hypoglycaemia** (*71*)

Endocrine deficiency
Hypopituitarism
Growth hormone deficiency
Glucagon deficiency
Cortisol deficiency/ACTH unresponsiveness
Hyperinsulinism
Beckwith-Wiedemann syndrome
Islet cell dysregulation syndrome
Disorders of carbohydrate metabolism
Glycogen storage disease type I
Fructose intolerance
Galactosaemia
Glycogen synthase deficiency
Fructose-1,6-diphosphatase deficiency
Disorders of amino acid metabolism
Maple syrup urine disease
Propionic acidaemia
Methylmalonic acidaemia
Tyrosinaemia
3-Hydroxy-3-methylglutaryl CoA lyase deficiency
Disorders of fatty acid metabolism
Medium chain acyl CoA dehydrogenase deficiency
Long chain acyl CoA dehydrogenase deficiency

Among the commoner endocrine disorders are adrenocortical insufficiency, hypopituitarism, and the "islet cell dysregulation syndrome" (nesidioblastosis). The first two may be associated with abnormalities of the external genitalia; septo-optic dysplasia may also be associated with hypopituitarism. Infants with organic hyperinsulinism have a habitus resembling IDMs in the absence of gestational diabetes mellitus in the mother. Infants with congenital or acquired glucagon deficiency also show severe and protracted hypoglycaemia (*65–67*), illustrating the importance of this hormone in perinatal adaptation.

Inborn errors of metabolism that may present as hypoglycaemia in the neonatal period include glycogen storage diseases, defects in β-oxidation (dicarboxylic aciduria), defects in gluconeogenesis (e.g. fructose-1,6-bisphosphatase deficiency), and some defects in amino acid metabolism (for recent reviews, see *68–71*).

3. Hypoglycaemia and the central nervous system

Despite the lack of clinical evidence in human infants that hypoglycaemia is causal in inducing sequelae of symptomatic hypoglycaemia, evidence from animal studies and postmortem studies of human infants indicate that severe and prolonged hypoglycaemia can be correlated with particular

neuroanatomical patterns of brain damage. In recent years much has also been learnt about the excitotoxic mechanisms that lead to injury in hypoglycaemia.

3.1. Pathology of brain damage associated with hypoglycaemia

The cerebral cortex, hippocampus, and caudate nucleus are the regions principally affected by experimentally induced hypoglycaemia sufficient to create an isoelectric electroencephalogram (EEG). This differs from the distribution of hypoxic/ischaemic damage; the dentate gyrus is particularly rarely affected by ischaemia but characteristically damaged in hypoglycaemia. Brain stem and posterior fossa structures are least affected by hypoglycaemia (for reviews, see *72*, *73*).

Neuronal death attributable to hypoglycaemia is not simply the result of metabolic attrition but an active excitotoxic process. Electron microscopy reveals the axon-sparing, dendritic lesion characteristic of this process. Understanding the nature of the cellular injury has potential importance in the prevention of hypoglycaemic brain damage, since pre-treatment with *N*-methyl-D-aspartate (*N*-MDA) antagonist drugs (notably dizocilpinum) affords protection in both cell culture and animal models (reviewed in *73*, *74*).

3.2. Cerebral defences in hypoglycaemia

Alternative substrates. Hypoglycaemia reduces cerebral glucose consumption in newborn animals without a commensurate reduction in cerebral oxygen consumption. This suggests that alternative metabolic fuels are used, with the primary candidates being lactate and ketone bodies. Lactate reverses stupor associated with insulin-induced hypoglycaemia in suckling–weaning mice (*75*) and serves as a cerebral fuel in other species of newborn animals (*76*). Insulin-induced hypoglycaemia (blood glucose $<0.5\,mmol.l^{-1}$) in newborn dogs was accompanied by a more than 50% reduction in cerebral metabolic rate for glucose and a more than 15-fold rise in cerebral metabolic rate for lactate, which became the predominant metabolic fuel (*77*). Recent studies of hypoglycaemic, diabetic, human adults have also demonstrated that the brain consumes lactate (*78*). Lactic acidosis is believed to be protective during the profound and protracted episodes of hypoglycaemia observed in infants with glycogen storage disease type-I (glucose-6-phosphatase deficiency) (*79*).

The neonate's capacity to promote ketogenesis in the face of suckling hypoglycaemia has been described in Section 2.3. Newborn term infants rapidly increase ketone body flux to the rates observed in adults, but only after several days of fasting, with the flux being correlated with plasma ketone body concentration (*80*). Furthermore, free fatty acid, glycerol (*33*) and ketone body concentrations (*36*) are inversely related to blood glucose concentration. Extensive evidence from animal species (*81*, *82*), including primates (*83*), demonstrates that ketone bodies are important cerebral energy substrates. Owen et al. first demonstrated that the human brain consumes ketones in a study in which they catheterized the cerebral vessels of three adults and found that ketone bodies became the predominant cerebral fuel upon prolonged (5–6 weeks) starvation (*84*). Similar catheterization studies in infants (mean age, 5 months) undergoing elective surgery demonstrated higher rates of ketone body uptake than those measured in adults (*85*). Enzyme systems necessary for the metabolism of ketones are present in human fetal brain (*86*), and uptake of ketone bodies has been demonstrated in perfused brain obtained from fetuses aborted at 12–21 weeks of gestation (*87*). Kraus et al. studied the cerebral arteriovenous difference (ΔAV) in ketone body concentration among 11 preterm and 2 term newborns fasted for 6 hours. ΔAV and ketone body concentration were positively correlated with cerebral uptake of ketone bodies, accounting for around 10% of overall brain energy balance (*88*). In these studies there was net cerebral production of lactate and pyruvate, suggesting that ketone bodies are more important than lactate as an alternative cerebral fuel to glucose.

Cerebral blood flow. In fully grown animals local cerebral blood flow is well matched to the local cerebral metabolic rate for glucose. In newborn dogs total cerebral blood flow was conserved even at blood glucose concentrations $<0.5\,mmol.l^{-1}$ (*77*). However, the developmental time course of the mechanisms responsible may vary from species to species (reviewed in *89*) and extrapolation to human neonates must be done cautiously. Pryds et al. identified increased plasma adrenalin concentrations and cerebral blood flow (measured using ^{133}Xe) in preterm infants whose blood glucose fell below $1.7\,mmol.l^{-1}$ (*90*, *91*). In further studies a fall in cerebral blood volume (measured using near infrared spectroscopy) accompanied restoration of normal blood glucose concentration in hypoglycaemic preterm infants (*92*). The authors hypothesized that the rate of change reflects the existence of a cerebral blood glucose "sensor", which maintains cerebral glucose supply by recruitment of underperfused capillaries.

3.3. Summary

Hypoglycaemic brain damage differs from ischaemic brain damage in both the distribution and the mechanism of cellular injury. The neonate shows adaptive responses to hypoglycaemia, which may be protective to cerebral metabolism. These responses include an increase in cerebral blood flow and the use of alternative metabolic substrates, particularly ketone bodies and lactate. Increasing understanding of the mechanism of hypoglycaemic brain injury indicates that *N*-MDA antagonists may have a clinical role in cerebral protection.

4. Definition of hypoglycaemia

Confusion about the definition of "neonatal hypoglycaemia" has seen documented by Koh et al. (*93*), who surveyed paediatric textbooks and the opinions of consultant paediatricians in the United Kingdom (Table 3). Subsequent review articles have restated the controversy (*17*, *69*, *71*, *94–96*).

As discussed below, various approaches to defining abnormally low blood glucose concentration have been used.

Table 3: **Some definitions of neonatal hypoglycaemia** (*93*)

	Modal range for blood glucose ($mmol.l^{-1}$)	
	Textbooks:	Paediatricians:
Term AGA	<1.7 (<1.0 to 2.5)	<2.0 (<1.0 to <4.0)
Preterm or SGA	<1.1 (<1.0 to 2.5)	<1.1 (<1.0 to <4.0)

4.1. Statistical definition

In general, a "low" value for any normally distributed biochemical variable is defined as <2 SD of the mean for a healthy population. Unfortunately this approach has many problems where blood glucose is concerned.

First, the result is dependent upon the source of the blood sample, the assay method, and whether blood or plasma glucose concentration is determined. These aspects are discussed further in Section 5. Second, early feeding schedules have a prominent effect on blood glucose concentrations but have changed a great deal since early studies (*7*, *9*, *97*, *98*). Even now they vary greatly from hospital to hospital and few breastfed infants have been studied (*10*, *36*). Third, there is a difficulty in defining what is meant by a "normal healthy term baby" in this context; in one study (*99*) 72% of inborn babies had one or more of the risk factors for hypoglycaemia set out by Cornblath & Schwartz (*100*). Fourth, there is an ethical dilemma over longitudinal blood sampling of healthy babies simply to define a normal biochemical range. Thus, the only available data for breastfed babies are cross-sectional (*36*).

Cornblath & Reisner first published data on blood glucose concentrations in normal newborns (*97*), finding that 95% of values among term infants were $>30\,mg.dl^{-1}$ and 98.4% of values in "premature" infants were $>20\,mg.dl^{-1}$. Hypoglycaemia in "full-size" term infants was defined as a blood glucose value $<30\,mg.dl^{-1}$ in the first 48 hours and <40–$50\,mg.dl^{-1}$ after 48 hours of age. SGA babies were not considered as a specific group. Hypoglycaemia among low-birth-weight babies was defined as $<20\,mg.dl^{-1}$. These values dominated opinion over the management of neonatal hypoglycaemia for many years. Furthermore, the acceptance of a lower threshold concentration for smaller babies has only been challenged relatively recently.

Early feeding was commonly discouraged in the 1960s when Cornblath & Reisner carried out their study (*97*). More recently Srinivasan et al. published plasma[c] glucose concentrations for 344 healthy full-term, AGA infants, calculating the mean and 95% CI from a mixture of serial and cross-sectional data (*101*). The lower estimate of 95% CI for cord samples was $3.3\,mmol.l^{-1}$, falling to $1.4\,mmol.l^{-1}$ ($26\,mg.dl^{-1}$) at 1 hour of age; after 2 hours it exceeded $2.3\,mmol.l^{-1}$ ($42\,mg.dl^{-1}$). The applicability of even these data to the normal, breastfed, newborn baby is, however, questionable.

Heck & Erenburg carried out longitudinal measurements of serum glucose concentration in 64 breastfed and 50 bottle-fed term infants during the first 48 hours of life (*102*). Both groups appear to have been fed first at 2 hours of age and then at scheduled 3–4 hour intervals. An unspecified number of the breastfed infants were given water or formula supplements (though not before blood sampling). Fifth centile blood glucose concentrations for the combined breastfed and bottle-fed groups were lowest at 6–12 hours of age ($1.9\,mmol.l^{-1}$), rising to $2.7\,mmol.l^{-1}$ at 48 hours of age. Values $<2.2\,mmol.l^{-1}$ were obtained for 16% of the study sample. Interestingly, the mean serum glucose concentration of

[c] Usually 15–20% higher than blood glucose concentrations (see Section 5.1.4).

bottle-fed babies was 0.22 mmol.l^{-1} lower than that of the breastfed at 5–6 hours of age. This statistically significant difference may have been attributable to higher postprandial insulin levels in the bottle-fed babies (*37*).

Hawdon et al., in the study discussed above (*36*), determined cross-sectionally a number of metabolic substrates, among healthy, term, demand-breastfed and bottle-fed infants. Few details on the management of breastfeeding in the study infants were supplied, however, with the only information being that they were demand-fed. No supplements of water or formula were given to the infants (J.M. Hawdon, personal communication, 1995). Wide variation in both blood glucose concentrations and those of other substrates prompted the authors to highlight a final problem in defining hypoglycaemia for the purpose of clinical management: "Factors other than absolute blood glucose concentration are important in the neonatal period and, while guidelines are important for clinical management, rigid definitions of hypoglycaemia are inadequate and should be avoided. The influence of gestational age, feeding practices and counterregulatory ability... must be considered in the interpretation of neonatal metabolic data."

In summary, changing care practices account for the wide variety of threshold plasma and blood glucose concentrations used in the past to define hypoglycaemia statistically. There are very few data on breastfed babies. More recent studies of the part played by substrates other than glucose in perinatal metabolic adaptation suggest that the quest to identify a safe blood glucose level by defining a normal range is not appropriate.

4.2. Metabolic definition

If glucose is viewed as the primary metabolic fuel, does the glucose concentration at which the counterregulatory response becomes activated indicate a safe value? At present such a value cannot be identified from the limited published data; few studies have measured concentrations of metabolic substrates other than glucose, and variability in the concentration of some, for example, ketone bodies, appears even greater than that of glucose.

Metabolic studies nevertheless make one essential contribution to the definition of hypoglycaemia. Counterregulatory responses differ significantly between term and preterm infants (*36*), suggesting that the threshold for a "safe" blood glucose concentration in the preterm infant is higher than that for a term infant, and not lower as implied by earlier data (*97*).

4.3. Neurophysiological definition

If the ultimate goal of identifying and treating hypoglycaemia is the maintenance of normal cerebral metabolism, can a threshold blood glucose concentration associated with disturbed neurophysiological function be identified?

Koh et al. studied the latency of the auditory evoked response waveform (AEPs) among 17 children, some of whom were spontaneously hypoglycaemic, while others were undergoing insulin-induced hypoglycaemia stress testing (*103*). Abnormalities were identified in some children when their blood glucose concentration fell below 2.6 mmol.l^{-1} but generalization to the healthy newborn is very difficult. First, only five of the subjects were newborn babies, second, the infants were relatively hypoketonaemic and consequently deprived of alternative cerebral fuels (see Section 3.3), unlike the healthy breastfed infant. It is also important to note that the electrophysiological abnormalities identified were not permanent.

Other workers have failed to observe an effect of hypoglycaemia on AEPs in the newborn (*104*). Furthermore, Pryds et al. were unable to identify abnormalities of either the amplitude-integrated EEG signal or of single flash visual evoked potentials (VEPs) among nine hypoglycaemic preterm infants (mean gestational age, 30.8 weeks; range, 26–34 weeks) (*90*). Blood glucose concentrations at the time of the study ranged from <0.5 mmol.l^{-1} (five infants) to 1.5 mmol.l^{-1}.

In summary in can be stated that current published evidence correlating neurophysiological disturbance with blood glucose concentration is equivocal and based on too few observations to set a safe threshold for either term or preterm infants.

4.4. Neurodevelopmental definition

The majority of studies examining neurodevelopmental prognosis after symptomatic or asymptomatic hypoglycaemia have compared control subjects with infants whose blood glucose concentration fell below a defined value. (see Section 1.2). Using a different approach, Lucas et al. correlated plasma glucose concentration with outcome in a large study of 661 preterm infants weighing <1850 g at birth (*18*). Bayley motor and mental developmental scores ascertained blind at 18 months of age were regressed upon lowest recorded glucose concentrations between 0.5 mmol.l^{-1} and 4.0 mmol.l^{-1}, adjusting for sex, gestational age, birth weight, days of ventilation, and other identifiable perinatal and social risk factors. The maximum regression coefficient for plasma glucose concentration

and Bayley scores was observed at a threshold value of 2.5 mmol.l^{-1} but no correlation with outcome was evident for plasma glucose concentrations >4.0 mmol.l^{-1}; the scores were also significantly correlated with the logarithm of number of days on which plasma glucose levels <2.6 mmol.l^{-1} were recorded. Frequent moderate hypoglycaemia (plasma glucose <2.6 mmol.l^{-1}) was more strongly associated with developmental deficit than more severe but less frequent hypoglycaemia. Large differences were seen between euglycaemic infants and those whose plasma glucose fell below 2.6 mmol.l^{-1} on five or more, not necessarily consecutive, days. Mean (standard error) scores in these respective groups for the Bayley motor developmental index were 96.1 (1.3) versus 84.4 (3.2) ($P < 0.001$) and 102.0 (1.5) versus 85.6 (3.7) ($P < 0.005$) for mental development. Furthermore, the risk of neurodevelopmental impairment (cerebral palsy or a Bayley motor/mental development score <70) for infants whose plasma glucose fell below 2.6 mmol.l^{-1} on 5 days or more was 3.5 (95% CI, 1.3–9.4; $P < 0.02$) relative to the risk for those in whom hypoglycaemia was not recorded.

This study is notable for its large sample size and unparalleled statistical power. Nevertheless, it has a number of limitations as a guide to "safe" plasma glucose concentrations. First, it applies only to preterm infants, and there is increasing evidence that the immature counterregulatory response of this group might make them more vulnerable to effects of hypoglycaemia (Section 2.4.1). Second, it is important to reiterate (see Section 1.3) that evidence of an association between hypoglycaemia and neurodevelopmental outcome in studies of this type may not reflect causation. Hypoglycaemia may merely have acted as a proxy for other unidentified risk factors not entered into the multiple regression model. It cannot be assumed that maintenance of a plasma glucose concentration >2.5 mmol.l^{-1} would have prevented neurodevelopmental sequelae.

4.5. Summary

There are insufficient data to define a normal range for blood glucose values in healthy term breastfed babies. The few studies that have examined this problem have not given detailed descriptions of breastfeeding management. Even if a normal range of blood glucose concentrations could be set, it would not establish a threshold blood glucose level at which to initiate treatment in the asymptomatic term baby, because the concentrations of alternative cerebral fuels (particularly ketone bodies, fatty acids, and lactate) are not known. Glucose concentration is only one piece in a complex metabolic jigsaw and its significance cannot be determined in isolation.

In the case of symptomatic term babies and preterm babies there is more room for caution. Limited data suggest both that ketogenesis is constrained in preterm infants (see Section 2.4 and Section 4.2) and that a plasma glucose concentration <2.6 mmol.l^{-1} in this group is associated with adverse neurodevelopmental outcome (see Section 4.4). The neurodevelopmental outcome of symptomatic term babies with hypoglycaemia is also worse than for those who are asymptomatic. While these associations are not evidence of a causative link, it seems wise to adopt a cautious approach in the presence of symptoms and rapidly institute treatment to increase the blood glucose concentration regardless of a measured value, since no definite threshold can be set.

5. Screening for hypoglycaemia

The development of reagent strip blood glucose tests in the 1970s facilitated the practice of screening for hypoglycaemia in newborn infants. How reliable are these tests, and how justifiable is screening?

5.1. Methods for determining blood/plasma glucose concentration

5.1.1. Reductiometric methods. Traditional methods for determining blood glucose depended on the reducing property of glucose. An example is given by the ferricyanide method, which can be adapted for use on an autoanalyser. These methods determine total reducing sugar concentrations; the difference between these values and glucose concentrations is generally unimportant at high glucose concentrations but becomes clinically significant at low blood glucose concentrations. A preliminary sample dialysis step in the fully automated ferricyanide method circumvents this difficulty. Enzymatic methods have largely superseded reductiometric methods in clinical practice where precise determination of blood or plasma glucose concentrations is required (*105*).

5.1.2. Glucose oxidase method. Glucose oxidase catalyses the oxidation of glucose to yield glucuronic acid and hydrogen peroxide. The concentration of hydrogen peroxide liberated is measured using a peroxidase step coupled to a coloured oxygen acceptor or an electrode (*105*). These reactions form the basis of both the reagent strip and benchtop glucose electrode methods; their limitations are described in more detail in Sections 5.1.6 and 5.1.7.

5.1.3. Hexokinase method. Hexokinase catalyses the phosphorylation of glucose by ATP. Glucose-6-

phosphate is then reduced by glucose dehydrogenase yielding NADPH/H^+, which can be determined using a suitable spectrophotometric indicator. This method is precise and highly specific for glucose (*105*).

5.1.4. Precision and sources of error in the determination of blood and plasma glucose concentrations. Requirements for the ideal method of determining glucose concentrations in clinical practice are as follows: accuracy, precision, and rapid processing of small samples without the need for preparatory steps. The method must also be sufficiently simple for medical and nursing personnel to carry out without extensive laboratory skills. The methods developed and used most extensively over the last 20 years for cotside monitoring of blood and plasma glucose concentrations include paper reagent strips and glucose electrodes; both depend on the glucose oxidase reaction (see Section 5.1.2). Another more recently developed method (the HemoCue photometer, see Section 5.1.8) employs glucose dehydrogenase to reduce NAD, but measures indicator colour change using transmission spectrophotometry rather than the reflectance technique employed with paper strip methods.

5.1.5. Properties of the sample and sources of error. Arterial blood has a slightly higher glucose concentration than venous. The magnitude of this difference varies with tissue glucose demands and is greatest under anaerobic conditions. Capillary sampling is unreliable if peripheral blood flow is reduced. Samples must always be free-flowing, as squeezing the heel causes haemolysis which interferes with the assay unless deproteinization is performed (see below). Contamination by the alcohol used for skin preparation leads to erroneously high values (*106*, *107*). The sample should either be analysed immediately or deproteinized (e.g. using perchloric acid) and chilled — glycolysis otherwise continues. Commercially available sodium-fluoride-coated tubes do not always ensure a fluoride concentration sufficient to inhibit glycolysis (*108*).

One of the greatest problems with neonatal samples is that the erythrocyte volume fraction may vary from <40% to >70%. Red cells contain less water than an equivalent volume of plasma (though the glucose concentration in red cell water is the same as that in the plasma). Plasma glucose concentration is therefore higher than that of whole blood, on average by about 18% (*69*). Furthermore, all methods employing paper reagent strips are subject to an intrinsic erythrocyte volume fraction bias — the higher the erythrocyte volume fraction, the lower the result. Possible reasons for this include discolouration of the test-pad and resistance to wiping or washing before reading. Also the higher sample viscosity impedes diffusion of plasma into the test-pad of the strip. Preparation of a plasma sample, e.g. in a heparinized microhaematocrit tube, overcomes this problem (*109*).

Bilirubin, uric acid, and haemolysis also interfere with strip methods based on glucose oxidase/peroxidase. Bilirubin inhibits both steps of the assay leading to falsely low values (*110*); haemolysis also produces falsely low values. This may be attributable to the presence of haemoglobin or to release of reduced glutathione, which competes with the chromogen for hydrogen peroxide released in the assay. Interference by haemolysates, uric acid, and bilirubin can be prevented by deproteinization of the sample.

5.1.6. Paper strips. These were initially developed for monitoring blood glucose concentration in diabetes and not intended for detection of hypoglycaemia. Care must be taken to avoid contamination by alcohol skin-cleansers, to cover the whole surface of the test-pad, and to time the reaction precisely before wiping the strip. Even when these precautions are adopted, all paper-strip methods tend to underestimate systematically the mean of a series of determinations in the range of glucose concentrations relevant to the diagnosis of neonatal hypoglycaemia (<2.6 mmol.l^{-1}; ca. <50 mg.dl^{-1}) and are imprecise, typically giving values only to within ±0.5 mmol.l^{-1}, even when coupled with a reflectance metering system (e.g. Reflolux, Boehringer Mannheim, Mannheim, Germany).

Several commercially available systems are available and have been evaluated for neonatal use including Dextrostix (Ames Co., Slough, England) (*111*, *112*), BM-test-Glycemie 1-44 (Boehringer Mannheim, Mannheim, Germany) (*10*, *112*, *113*), and Chemstrip bG (Boehringer Mannheim, Mannheim, Germany) (*109*, *114*). Most studies have compared methods using linear correlation analysis (e.g. *109*, *112*, *115–119*) but a more informative comparison of two methods is obtained by plotting the difference between the results obtained with each method separately against the average of the two (*120*); this approach describes more clearly inaccuracy (systematic difference between methods) and imprecision (random variation of results about the mean).

Four studies have carried out such a comparison. The first compared blood glucose determinations made using the BM-test-Glycemie 1-44 strip and Reflolux reflectance meter with autoanalyser measurements across the range of blood glucose concentrations 0.8–2.8 mmol.l^{-1}. The 95% CI (precision) across this range was approxi-

mately 0.5 mmol.l^{-1}, and there was a small systematic difference of 0.05 mmol.l^{-1} at all concentrations. Anderson et al. compared the BM-test-Glycemie 1-44 strip with the Yellow Springs Instruments (YSI (UK), Farnborough, Hants, England) glucose electrode system (*10*). The former test gave results on average 0.37 mmol.l^{-1} lower than those obtained with the glucose electrode over the concentration range 1–5 mmol.l^{-1}; the confidence limits were not reported.

A third study (*113*) examined the effectiveness of paper-strip systems in screening for neonatal hypoglycaemia (see Section 5.2), defined as a blood glucose concentration of <2.0 mmol.l^{-1} detected at the cotside with the BM-test-Glycemie 1-44 (Table 4); the Kodak Ektachem (Eastman Kodak Company, Rochester, NY, USA) system was used as a comparative laboratory reference. The mean BM-test-Glycemie values underestimated the mean Kodak Ektachem values by as much as 1.5 mmol.l^{-1} at a BM-test-Glycemie glucose concentration of 1 mmol.l^{-1} but were comparable at 3.5 mmol.l^{-1}. At all concentrations there was a wide scatter of results, such that the laboratory blood glucose at a BM-test-Glycemie value of 2.0 mmol.l^{-1} could have lain in the range 1.4–4.3 mmol.l^{-1} on 95% of occasions. Hameed et al. similarly compared venous and capillary sample BM-test-Glycemie reflectance estimates with laboratory values obtained using the hexokinase technique and observed a tendency for the mean BM-test-Glycemie value to underestimate with a wide scatter of individual values (95% CI ca. ±1.6 mmol.l^{-1}).

Reagent strip methods are therefore prone to many errors when used to screen for neonatal hypoglycaemia; the mean of a series of measurements may be underestimated by as much as 0.5–1.0 mmol.l^{-1}. *Consequently, treatment should not be initiated on the basis of results obtained with these tests alone.*

5.1.7. Glucose electrode systems. One study examined the reliability of a YSI glucose electrode-based analyser (Yellow Springs Instruments, Model 23A) used by nurses in a clinical setting (*121*). The device measures the plasma glucose concentration in a 25-µl sample of whole uncentrifuged blood. An *in vitro* study found good linear agreement (r = 0.99) over the concentration range 0–100 mg.dl^{-1} (0–5.6 mmol.l^{-1}) between the YSI results and those obtained using a laboratory glucose oxidase method. The regression equation was given by:

$$\text{YSI blood glucose}\left(\text{mg.dl}^{-1}\right) = 0.95 \times \text{laboratory value} + 0.76\ \text{mg.dl}^{-1}$$

The standard error of the estimate (n = 49) was 3.0 mg.dl^{-1} (0.17 mmol.l^{-1}), significantly better than the agreement obtained between the YSI and reagent strip methods (Glucometer II, Chemstrip bG, Dextrostix, Glucostix) for which the standard error of the estimate lay in the range 15–20 mg.dl^{-1}. Interference from bilirubin is negligible at the concentrations encountered in practice, and sample haematocrit does not affect the assay (*119*). Fully automated systems are available but expensive (ca. US$ 15000) compared to reflectance meters. Once purchased, the running costs of the YSI equate closely to the cost of disposable reagent strips.

5.1.8. Other bedside systems. The HemoCue β-glucose photometer (HemoCue AB, Angelholm, Sweden) is an optical method utilizing disposable cuvettes, which determines whole blood glucose using small (5 µl) samples. Blood is haemolysed in the cuvette and the NADH formed by enzymatic glucose oxidation reduces methylthiazolyldiphenyl tetrazolium to produce a formazan dye, whose concentration is determined spectrophotometrically. Only one study has evaluated application of the HemoCue approach to neonatal samples (*122*). Furthermore, its reliability for detection of hypoglycaemia cannot be established since too few observations were in the range of importance (<3 mmol.l^{-1}) and results were expressed only in terms of statistical correlation rather than limits of agreement (see Section 5.1.7). Also, the cost per test is high compared with reagent strip or electrode methods. Cuvette storage temperature and room temperature variation can introduce errors, although these are more significant at high than at low glucose concentrations. A recent study conducted in Nepal found that HaemoCue tended to overestimate blood glucose concentrations of neonatal samples and was unsuitable for the detection of hypoglycaemia (<2 mmol.l^{-1}) (*123*).

5.2. Effectiveness of screening based on reagent strip methods

Table 4 summarizes the effectiveness of screening based on data from two published studies. The discrepancy in estimated positive predictive value between studies probably reflects different incidences of hypoglycaemia. In one study the proportion of true positives was 21% of all tests (*114*), while in the other it was <10% (*113*). In general, the lower the incidence of a condition, the greater the likelihood of a false positive diagnosis being made by a screening test and the poorer its positive predictive value (*124*). Sensitivity and specificity values are unaf-

Table 4: **Effectiveness of screening for neonatal hypoglycaemia using reagent strip methods**

	Definition of hypoglycaemia:[a]	
	<2.0 mmol.l^{-1}	<1.9 mmol.l^{-1}
Sensitivity[b]	82%	86%
Specificity[c]	70%	78%
Positive predictive value[d]	0.18	0.52
Negative predictive value[e]	0.98	0.95

[a] Hypoglycaemia defined as <2.0 mmol.l^{-1} using BM test Glycemie/Reflolux system (*113*) or as <1.9 mmol.l^{-1} using Chemstrip bG with visual matching (*114*).
[b] Sensitivity = true positives/(true positives + false negatives).
[c] Specificity = true negatives/(true negatives + false positives).
[d] Positive predictive value = true positives/(true positives + false positives).
[e] Negative predictive value = true negatives/(true negatives + false negatives).

fected by the incidence of a condition and the estimates in these two studies, (sensitivity: 82% and 86%; and specificity: 70% and 78%) were comparable. Using an average specificity value of 74% it can be calculated that approximately 1 in 4 normoglycaemic babies tested would have been erroneously classified as hypoglycaemic. A third study (*125*, not shown in Table 4) using the BM-test-Glycemie 20–800 and the Reflolux meter gave similar estimates: sensitivity, 88%; and specificity, 81%.

In summary, these studies show that reagent strip screening detects only about 85% of true cases of hypoglycaemia and 75% of babies who are truly normoglycaemic. Thus, *reagent strip tests are unsuitable for diagnosing neonatal hypoglycaemia and should not be used. Less frequent but more accurate laboratory or ward-based glucose electrode measurements among babies at risk are preferable* (see Section 6).

5.3. Incidence of hypoglycaemia

Estimates of the incidence of hypoglycaemia clearly vary with the definition chosen, the population studied (postnatal age, gestation, weight for gestational age), and the pattern of care.

Sexson examined the effect of the diagnostic threshold for hypoglycaemia on its incidence among 232 newborn babies born to low-risk mothers in the USA (*99*). No information about feeding regimens was given. A total of 72% (168) had one or more risk factors for hypoglycaemia as defined by Cornblath & Schwartz (*100*). Screening for hypoglycaemia was carried out using Dextrostix, a practice likely to overestimate the true incidence (see Section 5.1.6, and Section 5.2), although low values were confirmed by laboratory analysis. Hypoglycaemia was defined as a blood glucose value of <2.2 mmol.l^{-1} (<40 mg.dl^{-1}). None of the 64 infants without a risk factor was hypoglycaemic when tested at 5 hours of age (before the first feed), but 28.6% of the 168 infants with a risk factor became hypoglycaemic within the first 12 hours of life. The mean blood glucose level of the hypoglycaemic infants was 1.5 mmol.l^{-1} (range, 0–2.1 mmol.l^{-1}) and the mean age at diagnosis was 3.4 hours (range, 0.5–12 hours). The overall incidence of hypoglycaemia in the whole sample of 232 babies was 20.6% but it is difficult to set this in context since no data were given on birth weight or gestational age. Nevertheless, had the definition proposed by Cornblath et al. (<1.7 mmol.l^{-1}) been used, only 8.1% would have been labelled hypoglycaemic (*17*).

Holtrop studied the incidence of hypoglycaemia in large-for-gestational-age (LGA) and SGA newborns in the USA, identified as having birth weight >90th or <10th centile, respectively (*126*). The definition of hypoglycaemia chosen was that suggested by Srinivasan et al. (*101*): a serum glucose concentration of <35 mg.dl^{-1} at <3 hours of age; <40 mg.dl^{-1} at 3–24 hours of age; and <45 mg.dl^{-1} at >24 horus of age. Hypoglycaemia was detected in 8.1% (24/298) of LGA infants and 14.7% (30/204) of SGA infants; and in all but three SGA infants it occurred in the first 10 hours of life. Although data on mean birth weight and gestation were given, no information about feeding regimens was presented.

A study of 164 SGA babies in the United Kingdom detected hypoglycaemia (defined as Dextrostix value <1.4 mmol.l^{-1}) in only 3/104 with birth weight >2.3 centile and 6/60 with birth weight <2.3 centile (*127*). Only one of the nine infants was symptomatic, being described as "jittery". Hawdon et al., in a review, quote incidences of "hypoglycaemia"[d] in term infants in the range 0–8% and 3–15% in preterm infants (*36*).

Information on the incidence of neonatal hypoglycaemia in developing countries is very limited. Anderson et al. conducted a cross-sectional study of 226 full-term, uncomplicated newborns in a hospital in Kathmandu, Nepal (*10*). Hypoglycaemia, defined as a blood glucose level <2.6 mmol.l^{-1} during the first 50 hours of life (*103*), was present in 38%, while 7% had a blood glucose concentration <2.0 mmol.l^{-1}. Low birth weight and hypothermia were associated with hypoglycaemia, which was

[d] Hypoglycaemia was defined as <30 mg.dl^{-1} (1.6 mmol.l^{-1}) in term infants aged <48 hours; and <40 mg.dl^{-1} among those aged ≥48 hours. Hypoglycaemia in preterm infants was defined as <20 mg.dl^{-1} (1.1 mmol.l^{-1}).

present in 55% of those weighing <2500 g and 32% of those >2500 g. Similarly, 57% of those with a rectal temperature of <35.5 °C at the time of sampling were hypoglycaemic, compared with 32% of those who were not. More than half the babies studied received prelacteal feeds (sugar water) and many mothers delayed initiating breastfeeding for over 24 hours, discarding colostrum. The authors hypothesized that these were important etiological factors but did not correlate systematically these practices with hypoglycaemia.

5.4. Is screening for hypoglycaemia necessary?

The term "screening" is used here to denote scheduled measurement of blood glucose in asymptomatic infants.

Term infants. Screening for hypoglycaemia in healthy term infants is flawed for two principal reasons; first, no diagnostic blood glucose concentration can be set (Section 4); second, no reliable cotside methodology is available: reagent strip methods greatly overestimate the true frequency of hypoglycaemia in this population (Section 5.2) and are likely to lead to unnecessary investigation and treatment.

Preterm infants. Limited available data give cause for concern that infants of gestational age <37 weeks have an immature counterregulatory response to hypoglycaemia (see Section 2.3 and Section 2.4). It seems desirable in this group to maintain plasma glucose concentration >2.6 mmol.l^{-1} (*18*); in achieving this aim, prevention (see Section 6) by early enteral feeding (or provision of intravenous glucose for those unable to feed) is more important than frequent blood glucose testing. Daily or twice daily laboratory determinations are preferable to frequent but inaccurate reagent strip measurements. Such determinations should be sufficient in most cases to tailor feeding regimens to the individual infant's requirement.

Small-for-gestational-age infants. Care should be taken in the diagnosis of SGA (see Section 6.2.3), since not all such infants are at risk of hypoglycaemia. Infants <3rd percentile (birth weight <2 SD of the mean for gestation) (*71*, *127*) and those who are disproportionate (increased head circumference: body weight ratio) or with abnormal umbilical artery Doppler flow velocity profiles in fetal life (*47*) are probably most vulnerable. Polycythaemia is an additional risk factor that is easily excluded (Section 6.1). Excessively frequent blood sampling is not necessary to identify those at risk; reliable laboratory measurements of cord blood glucose and blood glucose at 4–6 hours of age (before the second feed) are preferable (*46*).

Large-for-gestational-age term infants. Infants with organic hyperinsulinism are typically large at birth, and this association has led to screening of those whose birth weight exceeds the 90th percentile for gestational age. Occasionally, large size for gestational age (LGA) is associated with hitherto undetected maternal gestational diabetes. But the majority of LGA infants are simply large, normal healthy infants (see Section 2.4.4). As in AGA infants (*36*), their blood glucose concentrations may fall below 2 mmol.l^{-1}, usually within the first 8 hours of life (*126*). There is no evidence that transient hypoglycaemia in this group has a detrimental outcome. Consequently, reagent-strip screening, supplementary feeding, and treatment of transient, mild hypoglycaemia in the absence of symptoms are inappropriate.

Infants of diabetic mothers. Most of these infants display transient hyperinsulinism and are consequently at risk of hypoketonaemic hypoglycaemia. Screening should be undertaken for at least the first 24 hours of life and blood glucose concentration maintained at >2.6 mmol.l^{-1}. Testing may be discontinued once satisfactory blood glucose concentrations are maintained without supplementary feeds or intravenous therapy.

6. Prevention

6.1. Peripartum factors

6.1.1. Intrapartum factors. Although many intrapartum factors that predispose to neonatal hypoglycaemia are unavoidable (e.g. use of β-sympathomimetics to suppress preterm labour and Caesarean section) some are avoidable, including excessive maternal glucose infusion during labour. Restriction to <10 g.h^{-1} should not have a significant effect on either the cord blood insulin concentration or the incidence of hypoglycaemia (see Section 2.4.4).

6.1.2. Early postpartum management. The baby should be dried immediately after birth to reduce evaporative heat loss, which increases energy demands. Skin-to-skin contact between the mother and her baby as soon as possible after delivery is important in maintaining core temperature (*128*). Early enteral feeding should have the highest priority in healthy infants, whether term or preterm (*129*, *130*).

6.1.3. Neonatal risk factors. Factors that increase the risk of neonatal hypoglycaemia were discussed in Section 2.4. Feeding regimens for categories of babies at risk are suggested in Section 6.2. Polycythaemia (packed cell volume >0.65) may be associated with hypoglycaemia in some babies, particularly those who are small for gestational age and infants of diabetic mothers. The management of neonatal polycythaemia is controversial; some authorities recommend partial dilutional exchange with 5% albumin in infants who are "symptomatic", including those who are hypoglycaemic (*131*), but there is no consistent evidence of short- or long-term benefit in those who are well (*132*).

6.2. Feeding regimens

The most effective method of preventing hypoglycaemia is feeding with milk as soon as possible after delivery. Prolonged fasting is associated with a progressive fall in mean blood glucose in both term and preterm infants and in those appropriate or small for gestational age (*31*). Breast milk is preferred to formula because it appears to promote ketogenesis (*36*). Furthermore, there is some evidence that early blood glucose values in term babies fed formula are lower than those in babies who are breastfed (*102*); this may reflect the insulinogenic effect of protein in formula (*37*) (see Section 4.1).

6.2.1. Term infants. There is no justification for giving healthy term infants 10% dextrose water or any other form of prelacteal feeds; although the practice was once routine, particularly in nurseries in the USA, it is outdated. Dextrose water is of lower energy density than milk, which contains fat, and the practice of feeding dextrose water presumably arose through concern about aspiration of the first feed, but there is no evidence that aspiration of colostrum is any more harmful than that of dextrose or water.

In some parts of the world, notably India, prelacteal feeding and withholding of colostrum is common. In an Indian Council of Medical Research collaborative study, only 32% of mothers suckled their baby within the first 24 hours and only 13% in the first 8 hours of life. An alternative to breast milk, such as honey or sugar water, was offered by 71% of mothers (*10*). Such practices seem very likely to increase the incidence of neonatal hypoglycaemia, although no intervention studies appear to have documented this.

6.2.2. Preterm infants. Over 30 years ago two studies in the United Kingdom documented that "early" feeding with expressed breast milk reduced the incidence of hypoglycaemia (blood glucose $<20\,mg.dl^{-1}$) in preterm infants (*129*, *130*). In the 1940s and 1950s preterm infants were starved for the first 24 hours of life in order to reduce the incidence of aspiration. Smallpeice & Davies showed that nasogastric-tube feeding of small infants (birth weight, 1–2 kg) using graded volumes of milk was safe and reduced the frequency of hypoglycaemia, jaundice, and dehydration compared with historical controls (*129*). The feeding schedule they adopted, commencing with $60\,ml.kg^{-1}.d^{-1}$ and increasing daily in steps of $30\,ml.kg^{-1}.d^{-1}$ to $150\,ml.kg^{-1}.d^{-1}$ on the fourth day of life, is still widely recommended in standard neonatal textbooks, though it has never been systematically evaluated. Wharton & Bower found that this practice halved the incidence of asymptomatic hypoglycaemia (immediate-fed group, 5/44; late-fed group, 10/54) and abolished symptomatic hypoglycaemia (immediate-fed, 0/44; late-fed 4/54) although it was associated with an increased risk of mortality, often involving aspiration.

An alternative approach may be to provide $100\,ml.kg^{-1}.d^{-1}$ breast milk on the first day, $75\,ml.kg^{-1}.d^{-1}$ on the second day, and $50\,ml.kg^{-1}.d^{-1}$ on the third day as the volume of breast milk obtained by suckling increases (JM Hawdon & M Ward Platt, personal communications, 1996). Concern about the relationship between high early feed volume and necrotizing enterocolitis may be unjustified, since it is based on case–control data (*133*, *134*) and retrospectively controlled studies (*135*, *136*). It was not supported by a single, small randomized controlled trial (*137*). Moreover, studies examining feed volume have not adequately controlled for the protective effect of human milk (*138*, *139*).

Preterm infants with features of respiratory distress (tachypnoea, grunting, recession) should not be enterally fed but should be treated with intravenous glucose (see Section 6.4) until respiratory rate begins to fall. Feeding tubes should always be passed via the mouth in infants recovering from respiratory distress, since nasogastric tubes increase airway impedance and may precipitate apnoea (*140*). Alternatively, infants may be cup-fed (*141*). Initially, small aliquots of feed should be offered hourly and intervals increased to 30 hourly, as tolerated.

Healthy preterm infants of 32–36 weeks' gestational age. Sustained coordination of suckling and swallowing is present from about 32 weeks of gestation (*142*) and many such infants may be allowed an opportunity to suckle. The ability of small babies to feed at the breast is often underestimated. Pearce & Buchanan reported that 12 of 17 very low birth weight babies consecutively admitted to a neonatal unit started breastfeeding at a mean weight of 1.324 ± 0.099 kg and a mean age of 11 days (*143*); 10 were

fully breastfed at a mean age of 27 days at 1.600 ± 0.139 kg weight.

The breast should be offered as soon as possible after birth and at 3-hourly intervals thereafter. There is little point in persisting if the infant is sleepy, undemanding, and unwilling to attach or suckle. Total requirements may not be obtained directly and supplementary feeds should be given after breastfeeds during the early days of life. The volume of supplement should be reduced as suckling improves and birth weight is regained (see guidelines in Section 6.2.2). Feeds should be offered by cup or gavage in preference to a bottle. Expressed breast milk is the food of choice but formula is preferable to dextrose water if it is not available.

Healthy preterm infants under 32 weeks' gestational age. The majority of such infants will not suckle effectively and require gavage feeding, although cup-feeding is possible from 30 weeks of gestation (*141*). If required, a gastric tube should be passed orally and not nasally (*140*). On the first day 60 $ml.kg^{-1}.d^{-1}$ should be given, divided into hourly aliquots. If facilities for intravenous therapy are available, a 10% glucose infusion should be initiated as soon as possible after birth (see Section 6.4). Absolute contraindications to feeding include bile-stained gastric aspirate and abdominal distension, most commonly attributable to ileus. Feeds should be stopped and intravenous 10% glucose infusion commenced (or parenteral nutrition when available). Enteral feeding may be recommenced when signs resolve, assuming that necrotizing enterocolitis has been excluded. This and other conditions associated with ileus (e.g. sepsis, respiratory disease) should be treated according to standard procedures.

Most infants of <28 weeks' gestation show immature patterns of bowel motility, although early feeding hastens adaptation to the pattern seen in more mature babies (*144*). A randomized controlled study of babies <1850 g birth weight found human milk feeds were more rapidly tolerated than formula feeds (*145*).

Management of the mother. If the baby is unable to suckle, mothers should express their breast milk as soon as possible after delivery and continue to do so on at least 3-hourly intervals, even at night. All milk expressed should be given to the baby. If the baby is capable of suckling but appears unable to obtain his/her total requirements the mother should express *after* each feed. A randomized controlled study has shown that skin-to-skin contact ("kangaroo care") increases the duration of lactation among mothers of very small preterm infants (*146*).

6.2.3. Small-for-gestational-age infants. *Identifying SGA babies.* Usually SGA babies are defined as those whose birth weight is below the 10th centile for gestational age, which ignores the strong effect of maternal height and weight on birth weight. The mean birth weights at term of babies born to mothers of height 1.47 m (4 feet 10 inches) or 1.78 m (5 feet 10 inches) differ by approximately 500 g. If the extremes of mid-pregnancy weight are also taken into account, the difference approaches 1 kg (*147*). A study in the United Kingdom estimated that 28% of infants conventionally classified as SGA were of appropriate weight when maternal race, height, weight, and parity were taken into account (*148*). Similarly, 24% of babies conventionally classified as AGA were really SGA. Ideally, birth weight should be adjusted at least for the effect of maternal height, parity, and mid-pregnancy weight before babies are labelled SGA (*147*).

As the endogenous glucose production rate and glucose requirements correlate more closely with brain weight than body weight, those SGA babies at greatest risk of hypoglycaemia are probably those of disproportionate appearance with high OFC:MAC (head circumference:mid-arm circumference) or OFC:body weight ratios. Unfortunately there are insufficient data at present to establish a sufficiently precise threshold for identifying an at-risk population. Moreover, the calculation of such an index from two independent parameters doubles the potential for measurement error.

Management of SGA infants. The reasons for the increased incidence of hypoglycaemia among SGA infants were discussed in Section 2.4: counter-regulatory response and ketogenesis are blunted relative to AGA infants, but they appear to mature on feeding. Consequently, early feeding is believed to be as important in this group as in preterm infants of normal weight. Glucose production rates in SGA infants are higher than in AGA infants (see Section 2.2.4). Enteral feeding in healthy SGA infants should therefore start at 90 $ml.kg^{-1}.d^{-1}$ as 3-hourly feeds on the first day and increase in 30 $ml.kg^{-1}$ steps daily.

In a study carried out in Cambridge, England, of 269 infants weighing 1.8–2.5 kg who were provided with 60 $ml.kg^{-1}.d^{-1}$ of milk on the first day (increasing by aliquots of 30 $ml.kg^{-1}.d^{-1}$) only five developed hypoglycaemia (Dextrostix value <25 $mg.dl^{-1}$.). All were asymptomatic; 55% of the infants made some attempt to breastfeed at discharge. A further study in Cambridge of 164 infants below the 5th centile birth weight at ≥37 weeks who were fed according to this regimen reported only nine cases of

hypoglycaemia,[e] most of which involved infants <2 SD below the mean birth weight for gestation (*149*). Eight of the nine were asymptomatic and one was described as "jittery".

There are no properly controlled studies of the incidence of hypoglycaemia among small (SGA and preterm) babies exclusively breastfed on demand or breastfed with supplements. These are urgently needed to uncover the incidence and outcome of hypoglycaemia, the incidence of adverse effects associated with formula supplementation, and the size of any negative effect on breastfeeding. Another area worthy of study might be the role of simple anthropometry (e.g. head circumference:arm circumference/length ratios) in identifying more precisely those small for gestational age infants at risk.

6.2.4. Infants of diabetic mothers. These infants display transient hyperinsulinism. The risk is greatest among those who are macrosomic (see Section 2.4). Hypoglycaemia is not likely to occur after the first 24 hours of life and affected infants should be breastfed as soon as possible after birth and thereafter on demand. If a pre-feed blood glucose estimation at 3 hours of age is normal, it is unlikely that supplements will be required; however, if the plasma glucose is <2.6 mmol.l^{-1} at this age, supplementary feeds (90 ml.kg^{-1}.d^{-1}) should be instituted for the first 24–48 hours of life, bearing in mind that the ability of these infants to withstand hypoglycaemia can be compromised by hypoketonaemia. It is reassuring to note that most studies have found neurodevelopmental outcome among infants of diabetic mothers to be similar to that of controls, provided that hypoglycaemia was appropriately treated.

6.2.5. Large-for-gestational-age infants. LGA is usually defined as birth weight <90th centile for gestational age. Infants with persistent hyperinsulinism (e.g. attributable to islet cell dysregulation syndrome) are typically LGA, as are those born to mothers with unrecognized gestational diabetes. Metabolic adaptation has not been studied so intensively in LGA infants as a group as it has been, for example, in SGA or preterm infants. The incidence of hypoglycaemia[f] in a study in the USA of LGA infants was 8.1%, but no details of feeding regimens were given (*126*). In the same study 14.7% of SGA infants were hypoglycaemic using the same criteria. Hypoglycaemia in LGA infants was early (mean age, 2.9 hours) and no cases occurred in infants over 8 hours of age. Persistent organic hyperinsulinism in otherwise healthy infants is very rare and it is doubtful that screening and supplementary feeding of breastfed LGA infants is justified.

6.3. Additives for milk feeds

The effectiveness of supplementing feeds with carbohydrate was investigated in a randomized controlled trial involving 130 full-term, LGA infants in India (*150*).[g] Infants were admitted to a nursery for the first 24 hours of life and fed standard formula, either alone or supplemented with 5 g powdered "sugar" per 100 ml. Both groups were fed 80 ml.kg^{-1}.24 h^{-1} by bottle or gastric tube, making the average glucose supply of the two groups 5 mg.kg^{-1}.min^{-1} and 7.8 mg.kg^{-1}.min^{-1}, respectively. The blood glucose concentrations (determined on an autoanalyser) of the two groups at 12 hours of age were 53.3 ± 7.1 and 71.6 ± 6.5 mg.dl^{-1}, respectively. Moreover, significantly fewer infants in the supplemented group (4.6%) than in the control group (16.9%) had a blood glucose <30 mg.dl^{-1} (relative risk, 4.2; 95% CI-2.88–5.44; $P < 0.05$).

Unfortunately this study does not address the question as to whether the higher blood glucose concentration in the supplemented group was beneficial to outcome. Moreover, the incidence of hypoglycaemia in both groups is likely to be spuriously high since Dextrostix was used to detect cases (see Section 5.1.6 and Section 5.2). There is an additional question about the safety of increasing feed osmolality by adding sugar. In this study the supplemented feed contained 363 mosmol.l^{-1} compared with 290 mosmol.l^{-1} in the standard feed. Abdominal distension was not noted but "10.8% of babies on fortified feeds did not relish the taste compared with 4.8% on standard milk."

Further studies of outcome and safety are required before this practice can be endorsed.

Supplementation of enteral feeds with fat may have a role in preventing hypoglycaemia (*151*). There is evidence that oral administration of lipid (as a medium chain triglyceride) increases blood glucose concentration in unfed preterm and SGA babies (*152*, *153*). Excessive use of fat supplements may, nevertheless, precipitate diarrhoea and there is the additional possibility of precipitating severe illness in those rare infants who have defective β-oxidation pathways.

[e] See footnote *d*, p. 275.

[f] Defined here as serum glucose concentration <35 mg.dl^{-1} at <3 hours of age; <40 mg.dl^{-1} at 3–24 hours of age; and <45 mg.dl^{-1} at >24 hours of age.

[g] Defined as birth weight >90th centile on local Indian charts.

6.4. Infants who cannot be fed

Immediate enteral feeding is contraindicated in some situations, for example, in the presence of cardiorespiratory distress, congenital malformations of the gastrointestinal tract, ileus, and extreme prematurity (gestational age <28 weeks). Glucose infusion should be commenced at a rate approximating the endogenous rate of hepatic glucose production as follows:[h]

— full-term infant, appropriate weight for gestational age: 3–5 $mg.kg^{-1}.min^{-1}$;

— preterm infant, appropriate weight for gestational age: 4–6 $mg.kg^{-1}.min^{-1}$; and

— small-for-gestational-age infant: 6–8 $mg.kg^{-1}.min^{-1}$.

The use of bolus or "minibolus" glucose injections in the *treatment* of documented hypoglycaemia is controversial (see Section 7.2) but there is agreement that they are unnecessary when initiating glucose infusion to prevent hypoglycaemia in babies who cannot be fed enterally. It is undesirable to curtail abruptly intravenous infusions of glucose. The concentration of glucose infused into a peripheral vein should not exceed 10%; if glucose requirements exceed this, insertion of a central intravenous line may be necessary, though intravenous glucagon injection (200 $\mu g.kg^{-1}$) may be an alternative (see Section 7.3.1, *154*).

7. Treatment

The occurrence of hypoglycaemia should prompt consideration of the cause. It is particularly important to note that term breastfed babies do not develop symptomatic hypoglycaemia as a result of simple underfeeding. Presence of hypoglycaemia in this group is likely to be a manifestation of underlying illness, for example, sepsis. Detection and treatment of the cause is as important as is correction of the blood glucose concentration.

7.1. Enteral feeding

Moderate, asymptomatic hypoglycaemia should first be treated by adjusting the enteral feeding regimen. If this approach fails, intravenous therapy should be instituted when facilities are available (see Section 7.2).

[h] 60 $ml.kg^{-1}.24h^{-1}$ of 10% dextrose supplies 4.2 mg glucose $kg^{-1}.min^{-1}$. It should be noted, however, that strictly, 10% dextrose solution contains 9.3 g of glucose in the unhydrated form but is assumed to contain 10 g for most clinical purposes.

7.1.1. Oral dextrose water or milk? Some authorities recommend oral feeding of 10% dextrose water 10 $ml.kg^{-1}$ (*71*). Others (*46*, *69*) point out that milk (10 $ml.kg^{-1}$) is more energy dense (100 ml of breast milk contains 292.9 kJ; 100 ml of 10% dextrose contains 167.4 kJ) and that the fat component is theoretically beneficial; fat will both promote ketogenesis and reduce uptake of glucose into cells (Section 2.2.3 and Section 2.3). Whether glucose or milk is given, a blood glucose measurement should be repeated preferably within the hour. Frequent feeds and preprandial blood glucose measurements (at least every 3 hours) should continue.

7.1.2. Lipids. Studies of hypoglycaemic infants and of preterm and SGA infants have shown that feeding lipids produces an increase in blood glucose and nonesterified fatty acid concentrations (*152*, *153*) (Section 2.2.3 and Section 2.3). Hawdon et al. administered 5 $ml.kg^{-1}$ medium chain triglyceride (MCT) intragastrically and detected small but significant increases in blood glucose concentrations, together with a highly variable change in the glucose production rate (*155*). Variability was attributed to differences in absorption (though this was not measured). Although the glycaemic effect of administering 200 $\mu g.kg^{-1}$ glucagon was greater than the effect of giving 5 $ml.kg^{-1}$ MCT, ketogenesis was promoted more effectively with the latter and such a change might be of equal importance to the glycaemic effect, in view of the probable importance of ketone bodies as a cerebral fuel (see Section 3.2).

7.1.3. Concentrated dextrose gel. There have been anecdotal reports of the use of Hypostop, a 40% dextrose gel, in the treatment of neonatal hypoglycaemia. In an uncontrolled study Hypostop (0.5 $ml.kg^{-1}$) was massaged into the buccal mucosa after drying the latter with a gauze swab. A total of 67% of term infants are said to have responded with a rise in blood glucose concentration of $\geq$0.5 $mmol.l^{-1}$ (*156*). In the absence of controlled studies we cannot recommend this practice to be effective and have concerns that it may defer implementation of more appropriate therapy aimed at correction of hypoglycaemia and treatment of its cause.

7.2. Intravenous treatment

If facilities are available, intravenous treatment should be used under any of the following circumstances:

— enteral treatment has failed (see Section 7.1);

— hypoglycaemia is severe (<1.1 $mmol.l^{-1}$); and

— the baby is unwell or has signs that may be attributable to hypoglyaemia ("symptomatic" hypoglycaemia).

The place of a priming glucose "bolus" (2.5–3.0 ml of 10% dextrose $kg^{-1}.min^{-1}$ administered at a rate of $1 ml.min^{-1}$) before glucose infusion is controversial. Some authorities (*71*, *157*, *158*) recommend it but others have argued that the rate of glucose entry in such circumstances exceeds uptake (*154*), provoking "rebound hypoglycaemia" through enhancement of insulin secretion and inhibition of glucagon secretion. Moreover, excessively rapid administration of glucose has the potential to cause hyperosmolar cerebral oedema, as described in older children (*159*). Any bolus given *must* be followed by a continuous infusion of glucose, initially providing 4–8 $mg.kg^{-1}.min^{-1}$. There is no place for treatment with intermittent glucose boluses alone.

In the USA it is common practice to give a $2 ml.kg^{-1}$ "minibolus" of 10% dextrose intravenously before starting a continuous infusion, repeating the bolus after 1 hour if the blood glucose concentration is still low (J.E. McGowan, personal communication, 1995). In a study using historical controls Lilien et al. showed that blood glucose concentration was restored more rapidly in this way than by continuous infusion of glucose ($8 mg.kg^{-1}.min^{-1}$) alone (*157*). Only one infant became transiently hyperglycaemic. Hawdon et al. recommended using a $3 ml.kg^{-1}$ solution of 10% dextrose priming bolus for *symptomatic* infants (*158*), relying upon slower correction by continuous infusion alone (at least $5 mg.kg^{-1}.min^{-1}$) in infants who are hypoglycaemic but otherwise well (*95*).

The rate of infusion may require adjustment until the plasma glucose concentration is corrected and stabilized. Requirements exceeding 10–12 $mg.kg^{-1}.min^{-1}$, or dependence after 5–7 days of age, suggest that a cause requiring further investigation and treatment may be present (see Section 2.4.5 and Table 2).

Glucose infusions should not be discontinued abruptly. The rate of infusion should be gradually reduced *pari passu*, increasing the volume of enteral feed (steps of $1 ml.kg^{-1}.h^{-1}$ have been recommended). Extravasation at drip sites needs urgent attention both to ensure continued glucose supply and to prevent tissue damage; glucose solutions are an irritant and concentrations exceeding 10% should not be infused into peripheral veins. A central line may be needed if glucose requirements exceed 10.5 $mg.kg^{-1}.min^{-1}$ ($150 ml.kg^{-1}.d^{-1}$ of 10% dextrose). Glucagon administration (200 μg) may be an alternative if central line insertion is not possible.

7.3. Drugs

7.3.1. Glucagon. Mehta et al. described four term infants who presented with symptomatic hypoglycaemia in association with "normal" insulin concentrations (*16*). Studies using 6,6-dideuteroglucose as a tracer indicated a reduced rate of hepatic glucose production. Glucagon injection (200 $\mu g.kg^{-1}$ intravenously) led to a rapid and persistent increase in the rate of hepatic glucose production with restoration of plasma glucose concentration. Hawdon et al. also described rapid increases in both plasma glucose concentration, total glucogenic substrate, and glucose production rate after an intravenous bolus of 200 $\mu g.kg^{-1}$ glucagon among 10/11 hypoglycaemic term and preterm infants (*155*). In an uncontrolled study, Carter et al. described a response to continuous intravenous infusion of glucagon among 20/25 hypoglycaemic SGA infants whose blood glucose concentration had remained $<2.0 mmol.l^{-1}$ despite infusion of 6.5 $mg.kg^{-1}.min^{-1}$ glucose (*161*). The initial dose employed was 0.5 $mg.d^{-1}$, increased if necessary to 20 $mg.d^{-1}$. In some respects these results are surprising, since SGA infants may be resistant to glucagon, probably as a result of delay in maturation of gluconeogenic pathways (see Section 2.2 and Section 2.4) (*52*).

The place of glucagon in the treatment of neonatal hypoglycaemia is controversial (*154*, *158*). Theoretically, a 200 $\mu g.kg^{-1}$ intravenous bolus effects enhancement of gluconeogenesis and ketogenesis (see Section 2.2), which persists for many hours though an effect has been claimed for doses in the range 3–300 $\mu g.kg^{-1}$. Side-effects of glucagon include vomiting, diarrhoea, and hypokalaemia; at high doses it may stimulate insulin release. Controlled studies of the relative efficacy of glucagon and the more conventional alternative of glucose infusion at concentrations $>6 mg.kg^{-1}.min^{-1}$ are needed. More information about dosage is also required.

7.3.2. Other drugs: diazoxide, somatostatin, and octreotide. These drugs play a specific part in the management of persistent hyperinsulinism and have no place in the management of transient hypoglycaemia associated with abnormal metabolic adaptation in preterm and SGA infants (*71*, *95*).

8. Research

The following questions require to be answered urgently in order to improve the prevention and management of hypoglycaemia of the newborn.

Does neonatal hypoglycaemia compromise neurodevelopmental outcome?
A question remains as to the effect of hypoglycaemia, particularly asymptomatic hypoglycaemia, on neurodevelopmental outcome (see Section 1 and Section 3). Randomized intervention studies in asymptomatic hypoglycaemia seem likely to be the only means of obtaining a definite answer. This approach would clearly be unethical in symptomatic hypoglycaemia.

What is the relationship between early breast milk intake and plasma concentrations of metabolic substrates?
The healthy, breastfed, term infant must represent a biochemical norm, yet data on blood glucose and other metabolic substrate concentrations are few. Most studies refer to infants who were fed formula or glucose water on a scheduled basis, often after early starvation. Moreover, those studies that do refer to breastfed infants provide no information about feed frequency and the extent of supplementary feeding, let alone measurements of breast milk intake. A detailed study of the relationship between feeding patterns, breast milk intake and substrate concentrations (including glucose) is urgently needed to characterize the normal pattern of metabolic adaptation. Such studies need to be performed in less developed as well as industrialized countries.

What is the incidence of neonatal hypoglycaemia in less developed countries?
Studies of the incidence of hypoglycaemia and its causes in less developed countries are urgently needed. The increased incidence of low birth weight makes such studies vital to formulation of recommendations for prevention and treatment.

What is a "safe" threshold blood glucose concentration for a preterm infant?
Several authorities have recommended treatment when blood glucose concentrations are $<2.6\,mmol.l^{-1}$. This level has three principal justifications: the counterregulatory response of preterm infants is blunted; there is evidence of neurophysiological dysfunction at this level; and there is evidence of subsequent neurodevelopmental delay in preterm infants exposed to hypoglycaemia of this severity. Each of these justifications can, however, be challenged (see Section 4).

Studies such as those carried out by Hawdon et al. have suggested that SGA and preterm infants are less able to mount a counterregulatory response than term infants (*36*, *47*, *162*). However, these studies were observational and could simply reflect the success of medical management in preventing hypoglycaemia rather than metabolic immaturity. Against such an explanation was the low ketone body concentration at blood glucose concentrations associated with a vigorous ketogenic response in healthy term infants. Early work nevertheless demonstrated ketonuria in fasted "premature" infants and it is controversial as to whether mild hypoglycaemia (plasma glucose $<2.6\,mmol.l^{-1}$) affects the latency of visual/auditory-evoked potentials in this group.

Intervention studies are needed to establish more precisely whether mild/moderate hypoglycaemia needs treatment in preterm infants. Using an intervention threshold of $2.6\,mmol.l^{-1}$, as suggested, may be unnecessary, particularly in more mature preterm infants (32–36 weeks' gestation) who are otherwise well.

What is the role of glucagon administration in prevention and treatment of neonatal hypoglycaemia?
Glucagon is effective in provoking glycogenolysis and gluconeogenesis in hypoglycaemic infants. There are no controlled studies comparing glucagon therapy with the conventional treatment — intravenous dextrose infusion. Dosage, efficacy, and safety of glucagon as an alternative to infusion of glucose (particularly where requirements exceed $10\,mg.kg.^{-1}.min^{-1}$) need to be established in randomized controlled studies.

Is breast milk more ketogenic than formula; if so, why?
Some workers have suggested that breast milk is specifically ketogenic (Section 2.3). It seems unclear whether this reflects active promotion of ketogenesis by a breast milk constituent or is simply a consequence of the trend towards slightly lower blood glucose levels among breastfed infants.

Role for determination of other substrates in clinical decision-making?
Much stress has been placed on the protective influence of alternative cerebral metabolic substrates in hypoglycaemia, yet these are rarely taken into account in clinical management. Should decisions on treatment be based not merely on blood glucose levels but on the simultaneous blood concentration of ketone bodies and other substrates, or the presence/absence of ketonuria?

Small-for-gestational-age babies?
Such babies are very important because they represent the largest group likely to be given supplements to prevent hypoglycaemia. Randomized trials of supplementary feeding of this group are needed urgently to establish the incidence and outcome of hypoglycaemia during exclusive breastfeeding and the adverse effects (including cessation of breast-

feeding) of early formula supplements (Section 6.2.3).

There is also a need to identify better anthropometric predictors of hypoglycaemia in SGA infants than weight for gestational age (Section 6.2.3).

Both these areas are of crucial importance in the management of SGA infants in less developed countries.

Recommendations for prevention and management of hypoglycaemia of the newborn

- Early and exclusive breastfeeding is safe to meet the nutritional needs of healthy term neonates worldwide.

- Healthy term neonates who are breastfeeding on demand need not have their blood glucose routinely checked, and need no supplementary foods or fluids.

- Healthy term neonates do not develop "symptomatic" hypoglycaemia as a result of simple underfeeding. If an infant develops signs suggesting hypoglycaemia, an underlying condition should be sought. Detection and treatment of the cause is as important as correction of the blood glucose level.

- Thermal protection (the maintenance of normal body temperature) in addition to breastfeeding is necessary to prevent hypoglycaemia.

- Breastfeeding should be initiated as soon as an infant is ready, preferably within 1 hour of birth. Immediately after birth the baby should be dried and held against the mother's chest with skin-to-skin contact to provide warmth and to facilitate the initiation of breastfeeding.

- Breastfeeding should continue on demand. Healthy term neonates show signs of readiness to feed when they are hungry, but the interval between feeds varies considerably, particularly in the first few days of life. There is no evidence that long interfeed intervals adversely affect healthy neonates who are kept warm and who are breastfed when they show signs of hunger. An infant who shows no signs of hunger or is unwilling to feed should be examined to exclude underlying illness.

- Neonates at risk of hypoglycaemia include those who are preterm and/or SGA, those who suffered intrapartum asphyxia or who are sick, and those born to diabetic mothers.

- In neonates at risk, hypoglycaemia is most likely to occur in the first 24 hours of life, as the infant adapts to extrauterine life. Hypoglycaemia that presents after the first day of life, or which persists or recurs, does not necessarily indicate inadequate feeding. It may indicate underlying disease such as infection, or a wide range of other conditions (see Table 2 main document). Reference should be made to standard textbooks.

- For neonates at risk, breast milk is the safest and nutritionally most appropriate food. However it may need to be supplemented with specific nutrients for some very low birth weight infants.

- At-risk neonates who have a gestational age of $\geq$32 weeks or who weigh >1500 g at birth may be able to breastfeed sufficiently to satisfy their nutritional needs. If healthy, they should be given the opportunity to breastfeed within 1 hour of birth, like term babies.

- At-risk neonates able to suckle sufficiently should continue to breastfeed when they show signs of hunger. However, they should not be allowed more than 3 hours between feeds. Normal body temperature should be carefully maintained.

- At-risk neonates *not* able to suckle adequately and obtain all the milk that they need from the breast, but well enough for oral feeds, can be fed expressed breast milk or if necessary an appropriate breast milk substitute, by cup or by gavage (orogastric or nasogastric tube feeding). Feeds should commence within 3 hours of birth and should continue at least 3 hourly thereafter.

Reference should be made to standard textbooks for details of the feeding of neonates who are less than 32 weeks' gestational age, or who are very low birth weight, who are sick or born to diabetic mothers, or who are unable to feed enterally.

- If reliable laboratory measurements are available, the blood glucose concentration of neonates at risk should be measured at around 4–6 hours after birth, before a feed. Measurements using glucose-oxidase-based reagent paper strips have poor sensitivity and specificity in neonates, and should not be relied upon as an alternative.

- For neonates at risk *who do not show abnormal clinical signs* ("asymptomatic"), the blood glucose concentration should preferably be maintained at or above 2.6 mmol.l^{-1} (47 mg per 100 ml).

If the blood glucose concentration is below 2.6 mmol.l^{-1}:

— the infant should be fed — this can be a breastfeed if the infant can suckle adequately; if not, expressed breast milk or an appropriate breast milk substitute can be given by cup or gavage;

— the blood glucose determination should be repeated preferably after 1 hour and certainly before the next feed 3 hours later; if it is still below 2.6 mmol.l^{-1}, treatment with intravenous glucose should be considered;

— if facilities for administering intravenous glucose are not readily available, a supplementary feed should be given by cup or gavage; and

— breastfeeding should continue.

• If reliable laboratory determinations of blood glucose are not available, neonates at risk should be kept warm and breastfed. If breastfeeding is not possible, they should be given supplements of expressed breast milk or an appropriate breast milk substitute by cup or gavage at least every 3 hours. The infant should continue to breastfeed as much as he or she is able.

• If a neonate is unwell or shows signs of hypoglycaemia (apnoea, cyanosis, jitteriness, or convulsions ("symptomatic hypoglycaemia")), the above guidelines are superseded. Blood glucose should be determined urgently, and if it is below 2.6 mmol.l^{-1}, intravenous glucose should be administered as soon as possible.

• For management of "symptomatic hypoglycaemia," when intravenous treatment is indicated and feasible, 10% glucose should be given intravenously. Blood glucose should be monitored and the rate of infusion adjusted accordingly. Normal feeding should be continued as soon as possible.

• If reliable blood glucose measurement is not possible, intravenous glucose should be reserved for the treatment of major complications associated with hypoglycaemia (e.g. convulsions) and for situations in which enteral feeds are contraindicated. Enteral treatment is otherwise preferable.

• Further details about the above-mentioned procedures can be found in the document *Hypoglycaemia of the newborn: review of the literature* (see footnote, p. 261).

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Résumé

Hypoglycémie du nouveau-né

L'hypoglycémie correspond à une faible concentration de glucose dans le sang. L'hypoglycémie néonatale n'est pas une maladie en soi mais c'est un signe de maladie ou de l'incapacité du nouveau-né à passer du stade foetal d'absorption transplacentaire continue de glucose au mode extra-utérin d'apport intermittent d'éléments nutritifs. L'hypoglycémie risque davantage de survenir lorsque le nouveau-né se refroidit ou qu'il n'est pas alimenté tout de suite.

L'adaptation métabolique à la naissance suppose la mobilisation des réserves de glycogène (*glycogénolyse*), la synthèse hépatique du glucose à partir d'autres substrats (*gluconéogenèse*) et la production d'autres éléments énergétiques cérébraux comme les corps cétoniques. Les processus qui assurent la libération du glucose et d'autres éléments énergétiques (*contre-régulation*) sont surtout activés par le glucagon et l'adrénaline. La concentration de glucose dans le sang n'est qu'un des aspects d'un puzzle métabolique complexe et ne saurait être interprétée isolément.

Il n'a pas vraiment été défini de "fourchette normale" pour les taux de glycémie chez le nouveau-né, qui sont influencés par le poids à la naissance, l'âge gestationnel, la méthode d'alimentation et l'âge postnatal. Les études sur les nouveau-nés nourris au sein sont rares et elles ne définissent pas les modes d'alimentation ni l'apport lacté.

La définition de ce qu'est une glycémie "sûre", c'est-à-dire un taux en dessous duquel il y a risque de perturbation du développement neurologique à long terme, ne fait pas l'unanimité. L'hypoglycémie associée à des signes cliniques anormaux (*hypoglycémie symptomatique*) a une issue défavorable à court comme à long terme, mais on ne peut pas tirer de conclusion quant au risque en l'absence de signes cliniques (*hypoglycémie asymptomatique*). Cela est logique puisque le maintien de la fonction cérébrale dépend tout autant de l'aptitude à mobiliser d'autres substrats énergétiques (par exemple, les corps cétoniques) que de la glycémie.

Il s'ensuit que la maturité escomptée de la réponse de contre-régulation et la présence ou l'absence de symptômes sont aussi importantes que la glycémie lorsqu'on doit décider de l'opportunité d'un traitement. Il n'y a pas de définition rigoureuse de l'hypoglycémie qui corresponde à toutes les situations cliniques.

Rien n'indique que de faibles concentrations sanguines de glucose chez des enfants nés à terme en bonne santé qui sont nourris au sein soient annonciatrices d'une issue défavorable. Les enfants nés à terme en bonne santé qui sont nourris au sein à la demande n'ont besoin que de lait maternel.

Tous les nouveau-nés doivent être nourris le plus tôt possible après la naissance. Il faut donner du lait maternel ou maternisé à tous ceux qui sont en bonne santé et assez matures pour pouvoir téter. Certains faits indiquent que le lait maternel favorise plus la cétogenèse que les préparations pour nourrissons.

Le dépistage de l'hypoglycémie à l'aide de bandelettes réactives à base de glucose-oxydase est peu sensible et peu spécifique. Il est préférable de procéder de temps à autre, avant l'alimentation, à la détermination en laboratoire de la glycémie chez les nouveau-nés à risque. De plus, il n'est pas opportun de procéder à ce dépistage chez les enfants nés à terme en bonne santé qui sont nourris au sein puisqu'il n'existe pas de fourchette normale pour les taux de glycémie.

Il semblerait que les prématurés et les enfants de petite taille pour leur âge gestationnel présentent une mauvaise réponse de contre-régulation à l'hypoglycémie. Il est donc important de déceler et soigner l'hypoglycémie parmi ces enfants. Parmi les autres groupes de nouveau-nés exposés au risque d'hypoglycémie précoce figurent les enfants atteints d'une infection, ceux qui ont souffert d'asphyxie pendant la naissance et ceux dont la mère est diabétique. Il faut parfois une alimentation de complément pour prévenir comme pour soigner l'hypoglycémie chez ces enfants. Une hypoglycémie récurrente ou qui persiste plus de 48 à 72 heures après la naissance est le signe d'une maladie sous-jacente (par exemple, anomalie innée du métabolisme ou trouble endocrinien).

Les nouveau-nés exposés au risque d'hypoglycémie qui sont assez matures pour téter doivent être nourris au sein à la demande. Il faut déterminer la glycémie avant de commencer à les alimenter 4 à 6 heures après la naissance. D'après les données actuelles, il faudrait envisager une alimentation de complément si le taux de glycémie tombe en deçà de 2,6 mmol.l^{-1}, encore que rien ne permette de conclure qu'une brève exposition à des taux inférieurs soit nuisible chez le nourrisson asymptomatique. Il faut répéter la détermination de la glycémie une heure après l'allaitement: si le taux reste en deçà de 2,6 mmol.l^{-1}, il faut assurer un traitement par administration intraveineuse de glucose.

Les nouveau-nés trop immatures pour téter doivent recevoir des aliments de complément à la tasse ou par gavage. Du lait maternel ou maternisé est préférable à une solution glucosée car il a une plus grande densité énergétique et contient des graisses qui favorisent la cétogenèse et diminuent l'oxydation du glucose. Il faut administrer 60 ml.kg^{-1}.j^{-1} le premier jour, 90 ml.kg^{-1}.j^{-1} le deuxième jour, 120 ml.kg^{-1}.j^{-1} le troisième jour et 150 ml.kg^{-1}.j^{-1} le quatrième jour. Les nourrissons dont l'état est stable et qui ne présentent pas de détresse respiratoire peuvent supporter des quantités plus importantes, en commençant par 100 ml.kg^{-1}.j^{-1} le premier jour. Il faut mesurer la glycémie 4 à 6 heures après la naissance.

Les enfants malades chez lesquels des signes cliniques sont une contre-indication à l'alimentation entérale (par exemple, instabilité cardio-respiratoire ou distension abdominale) doivent recevoir une perfusion de glucose à 10%, en commençant par 60 ml.kg^{-1}.j^{-1}. Cette quantité de glucose (4 mg.kg^{-1}.min^{-1}) maintient une glycémie normale chez la plupart des nourrissons de poids satisfaisant pour leur l'âge gestationnel. Le rythme de perfusion doit être adapté à la concentration sanguine de glucose.

Il n'est pas nécessaire de pratiquer de dépistage ou d'alimentation de complément chez les nouveau-nés en bonne santé mais de taille élevée pour leur âge gestationnel sauf si l'on sait que leur mère est diabétique.

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