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Hypoglycaemia of the Newborn

Review of the Literature

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Hypoglycaemia of the Newborn
Recommendations for Prevention and Management

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

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

3. Healthy term newborns do not develop "symptomatic" hypoglycaemia as a result of simple underfeeding. If an infant develops signs suggesting hypoglycaemia (see point 17), look for an underlying condition. Detection and treatment of the cause is as important as correction of the blood glucose level.

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

5. 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.

6. Breastfeeding should continue on demand. Healthy term newborns 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 newborns 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.

7. Newborns at risk of hypoglycaemia include those who are preterm and/or small for gestational age (SGA), those who suffered intrapartum asphyxia or who are sick, and those born to diabetic mothers.

8. In newborns at risk, hypoglycaemia is most likely to occur in the first 24 hours of life, as the infant adapts to extrauterine life. Hypoglycaemia which 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 3 of main document). Reference should be made to standard texts.

9. For newborns at risk, breastmilk 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.

10. At-risk newborns who have a gestational age of 32 weeks or more or who weigh more than 1500 g at birth, may be able to breastfeed sufficiently to satisfy their nutritional needs (but see also point 12). If healthy, they should be given the opportunity to breastfeed within 1 hour of birth like term babies.

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

12. At-risk newborns **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 breastmilk (EBM), or if necessary an appropriate breastmilk 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 texts" for details of the feeding of newborns 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]

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

14. For newborns 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 /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, EBM or an appropriate breastmilk substitute can be given by cup or gavage.
- The blood glucose measurement 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.
- Breastfeeding should continue.

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

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

17. For management of "symptomatic hypoglycaemia," when intravenous treatment is indicated and feasible, give 10% glucose intravenously. Monitor the blood glucose, and adjust the rate of infusion accordingly. Continue normal feeding as soon as possible.

18. 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 contra-indicated. Enteral treatment is otherwise preferable.

Further details about the above procedures will be found in the main document - *"Hypoglycaemia of the Newborn: A Review of the Literature" (WHO/CHD/97.1) (WHO/MSM/97.1).*

Definition of terms

Exclusive breastfeeding: An infant is given no food or drink, including water, other than breastmilk, (except any medicinal drops or syrups which may be indicated).

Preterm: Born before 37 completed weeks of gestation.

Small for gestational age (SGA): Birth weight below the 10th percentile for infants of the same gestational age in the same population.

Very low birth weight: Birth weight less than 1500 grams.

Hypoglycaemia of the Newborn
Executive Summary

1. The term "hypoglycaemia" refers to a low blood glucose concentration. Neonatal hypoglycaemia is not a medical condition in itself, but a feature of illness or of failure to adapt from the fetal state of continuous transplacental glucose consumption to the extrauterine pattern of intermittent nutrient supply. It is more likely to occur in conditions where infants become cold, or where initiation of feeding is delayed.

2. Metabolic adaptation at birth involves mobilisation of glycogen reserves (*glycogenolysis*), hepatic synthesis of glucose from other substrates (*gluconeogenesis*), and production of alternative cerebral fuels such as ketone bodies. The processes which ensure availability of glucose and other fuels are collectively described as *counterregulation*. They are activated principally by glucagon and adrenaline. The concentration of glucose in the blood is only one piece in a complex metabolic jigsaw and cannot be interpreted in isolation. **(Section 2.2; Section 3.2)**

3. A "normal range" for blood glucose values in the newborn has not been properly defined. Values are influenced by birth weight, gestational age, feeding method and postnatal age. Few studies have been made of breastfed infants and they do not define feeding patterns or milk intake. **(Section 4.1)**

4. There is controversy over the definition of a "safe" blood glucose concentration, i.e. a value below which there is risk of long-term neurodevelopmental impairment. Hypoglycaemia associated with abnormal clinical signs (*symptomatic hypoglycaemia*) has a poor short- and long-term outcome but evidence of risk in the absence of clinical signs (*asymptomatic hypoglycaemia)* is inconclusive. This is to be expected as maintenance of cerebral function depends as much on ability to mobilise alternative fuels (e.g. ketones) as on blood glucose concentration. **(Chapter 1; Chapter 3)**

5. It follows that the anticipated maturity of the counterregulatory response and the presence or absence of symptoms are as influential as the blood glucose concentration in deciding whether to treat. A rigid definition of hypoglycaemia relevant to all clinical situations cannot be made.

6. There is no evidence that low blood glucose concentrations among healthy breastfed term babies are detrimental to outcome. Healthy term babies who are breastfed on demand require no food or drink other than breastmilk. **(Section 6.2.1)**

7. All infants should be fed as soon as possible after birth. Those who are healthy and mature enough to suckle should be offered a breastfeed. There is some evidence that breastmilk promotes ketogenesis more vigorously than formula. **(Section 2.3)**

8. Screening for hypoglycaemia using glucose-oxidase based reagent strips has poor sensitivity and specificity. It is preferable to make occasional pre-feed laboratory measurements of blood glucose in infants at risk. Screening healthy, breastfed, term infants

for hypoglycaemia is furthermore inappropriate because a normal range of blood glucose values has not been defined. **(Section 4.1; Section 5.1.6)**

9. Some evidence suggests that preterm babies and babies who are small for gestational age show a constrained counterregulatory response to hypoglycaemia. Detection and treatment of hypoglycaemia in these groups is therefore important. Other groups of infants at risk of early hypoglycaemia are those who are infected, who have suffered intrapartum asphyxia and who are infants of diabetic mothers. Supplementary feeding may be required both to prevent and treat hypoglycaemia in these groups. Hypoglycaemia which recurs or persists longer than 48-72 hours of age suggests an underlying medical condition (e.g. inborn error of metabolism or endocrine disorder). **(Section 2.3; Chapter 6; Chapter 7)**

10. Infants at risk of hypoglycaemia and who are mature enough to suckle should be breastfed on demand. A blood glucose estimation should be made before a feed at around 4-6 hours of age. Current evidence suggests that supplementary feeding should be considered if the value falls below 2.6 mmol l^{-1} though there is no conclusive evidence that brief exposure to lower levels is harmful in asymptomatic infants. A blood glucose measurement should be repeated 1 hour after feeding. If the blood glucose value still lies below 2.6 mmol l^{-1}, treatment with an intravenous glucose infusion is necessary. **(Section 6.2; Section 7.1)**

11. Infants too immature to suckle should be given supplementary feeds either by cup or by gavage. Breastmilk or formula is preferable to dextrose water as it has greater energy density and contains fat which promotes ketogenesis and reduces glucose oxidation. The volume of milk administered should be 60 ml kg^{-1} d^{-1} on the first day, 90 ml kg^{-1} d^{-1} on the second day, 120 ml kg^{-1} d^{-1} on the third and 150 ml kg^{-1} d^{-1} on the fourth. Infants in stable condition without respiratory distress may tolerate larger volumes, starting with 100 ml kg^{-1} d^{-1} on the first day. Blood glucose concentration should be measured at 4-6 hours of age. **(Section 6.2)**

12. Sick infants who have clinical features which contraindicate enteral feeding (e.g cardiorespiratory instability; abdominal distension) should receive an intravenous infusion of 10% dextrose, commencing at 60 ml kg^{-1} d^{-1}. This quantity of glucose (4 mg kg^{-1} min^{-1}) will maintain normoglycaemia in the majority of infants of appropriate weight for gestational age. The infusion rate should be adjusted according to blood glucose concentration. **(Section 6.2; Section 7.1)**

13. Screening and supplementary feeding are inappropriate for infants who are healthy but large for gestational age, unless known to be infants of diabetic mothers. **(Section 5.3; Section 5.4; Section 6.2.5)**

Hypoglycaemia of the Newborn
Review of the Literature

1. HISTORICAL BACKGROUND

The term "hypoglycaemia" refers to a reduction in the glucose concentration of circulating blood. It is almost a century since it was first described in children and over fifty years since it was recognised in newborn and older infants (Hartmann & Jaudon, 1937). Given the numerous advances which have since 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 in the form of bedside glucose monitoring have exacerbated rather than eased the problem by facilitating screening for an ill-characterised clinical entity.

1.1 Patterns of hypoglycaemia

The vulnerability of premature infants and those of diabetic mothers to hypoglycaemia was recognised early in the history of neonatal medicine (e.g. Miller & Ross, 1940; Norval, 1950; McQuarrie, 1954; Farquhar, 1954). The transient nature of hypoglycaemia and apparent infrequency of clinical manifestations led many to assume that low blood glucose concentrations among these groups were innocuous and "physiological", in contrast to hypoglycaemia caused by metabolic and endocrine disease. However, in 1959 Cornblath *et al* described eight, 2-day old infants born to mothers with pre-eclamptic toxaemia in whom symptoms (apnoea, cyanosis, coma and convulsions) were associated with reduced blood glucose concentrations (1-24 mg dl^{-1})[1]. They described a clinical response to the infusion of intravenous glucose and drew attention to the "self-limited but quite refractory" course of hypoglycaemia. The outcome of this small group of infants was poor. Five were normal when followed-up at two weeks to eleven months but one died and two had persisting neurological abnormalities. Further descriptions of neurological sequelae associated with *symptomatic hypoglycaemia* (i.e. that associated with clinical signs[2] which resolve at increased blood glucose concentration) in the newborn followed.

Concern arose that hypoglycaemia *without* associated clinical signs[2] (*asymptomatic hypoglycaemia*) might also lead to neurodevelopmental sequelae. This led to an attempt to define hypoglycaemia statistically as a blood glucose concentration more

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

[2] It is technically 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 the manuscript as these terms have become widely adopted in the literature.

than 2 standard deviations below the mean for populations of well full-term and low birth weight infants. This, and the introduction in the early 1970's of reagent strip glucose assays (e.g. *Dextrostix*™) for cotside screening of newborns at risk, led to clinical classifications of neonatal hypoglycaemia (e.g. Fluge, 1974; Gutberlet & Cornblath, 1975). Gutberlet & Cornblath estimated the prevalence of hypoglycaemia (defined as serum glucose concentration <30 mg 100 ml^{-1}) as 4.4 per 1000 total inborn live births, 15.5 per 1000 low birth weight infants. Lubchenco & Bard (1971) arrived at much higher estimates: 11.4% of all nursery admissions and 20.3% of those premature or low birth weight had blood sugar <30 mg 100 ml^{-1} if screened before feeding at 6 hours of age.

Estimating the exact frequency of asymptomatic hypoglycaemia obviously begs the question of numerical definition. This is addressed in Section 4 but it is worth noting at this juncture that transitional hypoglycaemia is a common problem observed in both industrialised and less-developed countries. Formal studies in the latter are few. However, Anderson *et al* (1993) observed that 38% of uncomplicated term infants born in Kathmandu, Nepal showed a blood glucose concentration of <2.6 mmol l^{-1} during the first 50 hours of life. An approach aimed first at the prevention of hypoglycaemia, second at its reliable detection in newborns at risk and third at appropriate treatment which will not be deleterious to breastfeeding is thus of global importance.

1.2 "Symptomatic" and "asymptomatic" hypoglycaemia

Despite clinical characterisation of neonatal hypoglycaemia on the basis of blood glucose concentration, controversy existed as to whether hypoglycaemia, particularly in the absence of clinical signs, *caused* or was merely *associated with* neurodevelopmental sequelae. Long-term neurological sequelae were identified in up to 35% of those with symptomatic hypoglycaemia and 20% of those with asymptomatic hypoglycaemia (Haworth & Vidyasagar, 1971; Haworth & McRae, 1965); though others could find no relationship (Griffiths & Bryant, 1971).

In a large retrospective case-control study Koivisto (1972) and colleagues followed 151 cases of neonatal hypoglycaemia (defined as a blood glucose concentration of <30 mg dl^{-1}) for up to four years. The control series consisted of 56 concurrently treated asymptomatic newborns with no hypoglycaemia or neonatal disease. Ninety-four per cent of 66 asymptomatic hypoglycaemia subjects and 95% of controls were classified as developmentally normal at follow-up. Among the 85 who had suffered symptomatic hypoglycaemia, only 50% of those presenting with convulsions (8 infants) and 88% of those with non-convulsive symptoms were developmentally normal. This study therefore identified no important neurodevelopmental abnormalities in infants with *asymptomatic* hypoglycaemia. The authors stressed the tendency of symptomatic hypoglycaemia to present later in the clinical course than asymptomatic. Similar conclusions were drawn in a recently published Indian follow-up study of 107 cases of asymptomatic or symptomatic neonatal hypoglycaemia (Singh *et al*, 1991).

Pildes *et al* (1974) studied the effect of treatment on prognosis in a prospective study of 39 cases. 41 controls were selected 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 to 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 infants (cases 72.2%, controls 28.8%). This emphasises the weakness of case-control methodology in studying whether hypoglycaemia itself affects outcome or is merely a proxy for other risk factors. Sinclair (Cornblath *et al* 1990) has recently pointed out that all studies to date have been too flawed to demonstrate definitive correlation between hypoglycaemia and developmental outcome. A randomised 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 infants that are small for gestational age (SGA) may be at greater risk of sequelae (Lucas *et al*, 1988) because of metabolic immaturity (Section 2). Second, it seems likely that infants who develop symptomatic hypoglycaemia were hypoglycaemic but asymptomatic at an earlier stage of their clinical course. Rigorous, dichotomous classification of symptomatic and asymptomatic hypoglycaemia is thus philosophically difficult.

2. GLUCOSE HOMEOSTASIS AND METABOLIC ADAPTATION AT BIRTH

2.1 The fetal nutritional and metabolic environment

Glucose, amino acids and lactate are the principal energy substrates during fetal life, 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}), which is 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 adiposity of the newborn. Fat oxidation is believed quantitatively less important than amino acid/glucose oxidation, and rates of ketone body production are low during fetal life (Hay, 1991). The fetal endocrine *milieu* is dominated by insulin. Insulin 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 the mother's. 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 speculated 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 (Hales & Barker, 1992). 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 deposition of fat in adipose tissue. In this way, energy stores are laid down in preparation for birth.

Table 1
Metabolic effects of insulin
(+ indicates stimulation, - indicates inhibition)

Glucose uptake into muscle	+
Glucose uptake into adipose tissue	+
Release of amino acids from muscle	-
Release of fatty acids from adipose tissue	-
Gluconeogenesis	-
Ketogenesis	-

2.2 The regulation of blood glucose concentration after birth

Normally blood glucose concentration is regulated within a much narrower range than other metabolic fuels, varying only two to three-fold. By comparison ketone body and non-esterified fatty acid concentrations may vary ten to one hundred-fold under different physiological conditions. This tight control of blood glucose concentration during both the fed (or *postprandial*) and fasted (or *postabsorptive*) states is accomplished by balancing the utilisation of glucose in tissues with endogenous glucose 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 glycogen breakdown (*glycogenolysis*) or is synthesised from glycerol, lactate, pyruvate and glucogenic amino acid precursors, of which alanine is quantitatively 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 may be synthesised 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 which regulate glucose metabolism. These fall into two groups: *insulin* and the so-called *counterregulatory hormones* (Tables 1 & 2).

Table 2
Counterregulatory hormones

Glucagon
Catecholamines
Cortisol
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. Certain regulatory steps are subject to substrate and/or endocrine activation and inhibition. They are: pyruvate dehydrogenase, pyruvate carboxylase, phosphoenolpyruvate carboxykinase (PEPCK), pyruvate kinase and fructose-1,6-biphosphatase. The precise details of activation/inhibition at each of these steps are complicated (for review see Gerich, 1993) but for the purpose of this discussion it is sufficient to note that **the overall effect of insulin is to *inhibit* gluconeogenesis, whilst glucagon directly *activates* it**. Apart from the insulin/glucagon ratio, intracellular accumulation of precursors (e.g. pyruvate), acetyl CoA concentration and $NADH/NAD^+$ ratio are regulatory influences. Fat and fatty acids are not themselves converted to glucose. However, fat oxidation promotes gluconeogenesis by increasing intracellular acetyl CoA concentration and $NADH/NAD^+$ ratio. Adrenaline indirectly stimulates gluconeogenesis by stimulating peripheral mobilisation of non-esterified 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, inductive proof of this hormone's key role in perinatal metabolic and cardio-respiratory adaptation.

2.2.3 *Peripheral glucose utilisation.* 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 (G6P) through the action of hexokinase. When cells oxidise fat cytoplasmic glucose-6-phosphate (G6P) 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 utilisation.* In recent years it has been possible to measure rates of glucose production in newborn infants using stable (non-radioactive) isotopes of glucose labelled with deuterium (^2H) or ^{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, as some ^{13}C is recycled through the Cori cycle. Using $6,6^2H_2$ glucose, Bier *et al* (1977) estimated the rate of glucose production in infants over 1 day old as 4.3-8.5 mg kg^{-1} min^{-1}. In contrast, Kalhan *et al* (1976) obtained a figure of 3.8-4.9 mg kg^{-1} min^{-1} using 1-^{13}C glucose in 2 hour old infants. Gluconeogenesis is certainly demonstrable on the second day of life in healthy term newborns. Denne & Kalhan (1986) used D-[U-^{13}C]-glucose to measure glucose production rates on the second day of life in infants starved for 9 hours. They estimated the proportion of glucose manufactured from re-cycled glucose (measured from ^{13}C-1 enrichment) as approximately 36% or 1.87± 0.74 mg kg^{-1} min^{-1} of the total glucose production rate of 5.02± 0.41 mg kg^{-1} min^{-1}.

Subsequent studies using $6,6^2H_2$ glucose have found comparable glucose production rates in appropriate weight for gestational age (AGA) preterm and term infants (mean± s.d.: 3.5± 0.4 mg kg^{-1} min^{-1} and 3.5± 0.3 mg kg^{-1} min^{-1} respectively). In the same experiment small for gestational age (SGA) infants showed higher rates

of glucose production (4.3± 1.0 mg kg^{-1} min^{-1}). It has been suggested that this reflects the higher brain: body mass ratio of SGA babies (Kalhan *et al*, 1986) and that glucose requirements correlate more closely with brain than body weight (Bier *et al*, 1977).

Infusion of glucose into adults suppresses endogenous glucose production both through a direct effect of glucose concentration and through enhancement of insulin secretion (see 2.2.2 above). 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 (Cowett *et al* 1983; Sunehag *et al*, 1994). This probably demonstrates variable expression of the counterregulatory response in hypoglycaemic and stressed newborns.

2.2.5 *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 non-esterified 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 endocrine events believed to trigger the release of glucose and the mobilisation of fat from peripheral stores are an increase in adrenaline 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 (Ktorza *et al*, 1985). Whether insulin concentration does actually fall is still debated. Hawdon *et al* (1992) were unable to confirm this in a cross-sectional study of healthy term and preterm neonates of appropriate weight for gestation. A methodological problem is the cross reaction between insulin, proinsulin, and other propeptides in radioimmunoassays. Using highly specific assays Hawdon *et al* (1995) found that insulin: glucose ratios remain high in healthy preterm infants whilst proinsulin and 32-33 split proinsulin account for 34-70% of the total insulin/insulin pro-peptide concentration. Healthy term infants have not been studied to date. Much remains to be learnt about the maturation of insulin and insulin pro-peptide 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 in which early starvation was fashionable and feeding (usually with formula) was postponed for hours or days after birth (Beard *et al*, 1966; Melichar *et al*, 1967; Persson & Gentz, 1966; Stanley *et al*, 1979; Anday *et al*, 1981). Principal findings of these studies were, first, that blood glucose concentration falls with the duration of starvation and, second, 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* (1966) 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. Mean blood glucose concentration at 72 hours was 40 mg dl^{-1} (2.2 mmol l^{-1}) in the fasted term infants, as compared to 68 mg dl^{-1} (3.8 mmol l^{-1}) in the "early-fed" group. 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, as compared to only 4% (1 infant) among the early-fed group; though no complications were noted. The fasted group also showed a reduced increment in blood glucose concentration on injection of glucagon and adrenaline, suggesting a relative reduction in their glycogen stores. Free fatty acid concentrations nevertheless rose in the fasted infants and over 50% of the fasted healthy premature infants showed ketonuria by 48-72 hours of age. Persson & Gentz (1966) similarly noted increases in free fatty acid, glycerol and ketone body levels among fasted term infants. The highest values were noted in babies with the lowest blood glucose concentrations. 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 (Stanley *et al*, 1979; Anday *et al*, 1981). Moreover it is important to emphasise that the "premature" babies of thirty years ago were probably more mature as a group than preterm infants of today whose adaptive capacity may be even less well developed.

More recently Hawdon *et al* (1992) conducted a cross-sectional study of *whole blood* glucose concentration among 156 healthy term babies. This work is of importance for many reasons. Firstly, infants were *demand-fed*. Secondly, breastfed babies were studied (46% of the sample). Thirdly, metabolic substrates other than glucose (glycerol, lactate, pyruvate, alanine, non-esterified fatty acids, ketone bodies) were measured. Finally, infants were studied throughout the first week and not only in the first eight hours (Stanley *et al*, 1979) to three days (Beard *et al*, 1966; Anday *et al*, 1981). It was shown convincingly that although healthy term breastfed babies had significantly lower blood glucose concentrations than those who were bottle-fed (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. A statistically significant negative correlation between [log] ketone body and blood glucose concentration was measured at 2-3 days of age, but not within the first 24 hours or after 3 days. Lucas *et al* (1981) also found breastfed babies to have significantly higher ketone body concentrations than formula-fed babies studied on the sixth day of life.

In summary, blood glucose concentration falls in babies who are not fed. But healthy term babies of appropriate weight for gestation (AGA) mobilise alternative

metabolic substrates (free fatty acids and ketone bodies) in response. Breastfed babies as a group have lower blood glucose concentrations (referred to later 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 breastmilk 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.* It has been acknowledged for many years that blood glucose concentrations of preterm infants tend to be lower than those of term infants. This was considered "physiological" though there is no evidence that preterm infants are more resistant to the effects of hypoglycaemia than term infants.

Reasons for the preterm infant's propensity to hypoglycaemia are many. 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, mobilisation and oxidation of fat reduces glucose uptake and oxidation (Section 2.2.3).

Second, recent evidence indicates that preterm infants show 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 (Deshpande *et al*, 1994). This phenomenon is unexplained though it is possible that the greater protein intake of preterm infants, necessary to match their faster growth potential, is an insulinogenic stimulus. It has been known for some years that insulin secretion in term infants (as reflected by C-peptide excretion) is modified by dietary protein intake and related to plasma valine: glycine ratio (Ginsburg *et al*, 1985).

Third, it is likely that gluconeogenic pathways are less mature than in term infants. For example, expression of microsomal glucose-6-phosphatase was reduced in liver necropsy samples obtained from preterm infants up to 1 year of age and ranging between 24-36 weeks of gestation at birth. This enzyme catalyses the final step of both glycogenolysis and gluconeogenesis (Hume & Burchell, 1993).

Given the increased risk of hypoglycaemia associated with preterm birth, some recent research has focused on the adequacy of the counterregulatory response. Hawdon *et al* (1993) studied 62 clinically stable preterm babies (median gestation 31 weeks, range 25-36 weeks; median birth weight 1760 g, range 830-3203 g). 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 36 weeks of gestation a dramatic increase in ketogenic potential appeared, but this cross-sectional observational study does not make clear whether this is a

developmental event, or whether it simply reflects differences in the clinical management of babies <36 weeks of gestation. It may be recalled (see Section 2.3) that Beard *et al* (1966) observed ketonuria in over 50% of premature infants after prolonged fasting (48-72 hours). However, blood ketone concentrations were not measured.

In summary, preterm infants show an increased incidence of hypoglycaemia and a reduced capacity to mobilise 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 (SGA) infants.* This group has long been recognised to be at increased risk of neonatal hypoglycaemia (Cornblath *et al*, 1959). More recently hypoglycaemia has been detected during fetal life among infants small for gestational age at birth. Factors which may account for this include 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* (1986) noted SGA infants in the basal (fasting) state on the first day of life to have significantly higher rates of endogenous glucose production (4.25 ± 0.98 mg kg^{-1} min^{-1}) than appropriate weight for gestational age (AGA) infants (3.53 ± 0.32 mg kg^{-1} min^{-1}; $p < 0.03$). It was suggested that this reflected the greater brain weight of SGA infants relative to AGA infants. Several studies have shown that SGA infants, when compared to AGA infants, have increased plasma concentrations of glucogenic substrate (Lindblad, 1970; Lindblad *et al* 1970; Haymond *et al*, 1974; Mestyan *et al*, 1975). Amongst the glucogenic substrates, alanine and lactate levels particularly were increased. When alanine is infused into SGA infants it disappears more slowly than in normal, AGA full-term newborns (Mestyan *et al*, 1975) and has less effect on blood glucose concentrations (Sann *et al*, 1978). 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 phosphoenolpyruvate carboxykinase (PEPCK) (Haymond *et al*, 1974). Hawdon & Ward Platt (1993), in a longitudinal 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 fourth 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. This seems 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, ketone body concentrations of SGA and AGA infants do not appear to differ; though by 24 hours of age (Haymond *et al*, 1974), and throughout the first postnatal week (Hawdon & Ward Platt, 1993) ketone body levels of both term and preterm SGA infants remain low relative to those seen in AGA infants at equivalent blood glucose concentrations. Whether this reflects an inability of the SGA infant to

mount a ketogenic response, or just more aggressive attention to nutritional management and prevention of hypoglycaemia among the infants studied, is open to debate. In the studies of Hawdon & Ward Platt (1993) fewer SGA than AGA infants had a blood glucose concentration <3 mmol l^{-1}.

There is some evidence that SGA infants with abnormal metabolic adaptation are those in whom Doppler studies identify abnormal end diastolic flow velocities (EDV) in the umbilical artery. Hawdon *et al* (1992) found that a group of 11 fetuses with absent EDV showed lower blood glucose and free fatty acid concentrations in the first six 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 668-2020 g *vs.* 1903 g, 859-2296 g); though the difference did not attain statistical significance ($p = 0.065$).

Endocrine adaptation in SGA babies has also been studied by several authors. Most have shown no differences between AGA and SGA infants in insulin and glucagon concentrations, though 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 (LeDune, 1972; Collins & Leonard, 1984; Collins *et al*, 1990). A prospective study of SGA infants admitted to a single neonatal unit over one year found that 10 of 27 became hypoglycaemic and that half of them had inappropriately high plasma insulin concentration at the time of hypoglycaemia (Collins *et al*, 1990). Although the assay used did not discriminate insulin from its propeptides, and hence may have overestimated the "true" insulin concentration (Hawdon *et al*, 1995), low plasma free fatty acid concentrations and high glucose requirements (exceeding 10 mg kg^{-1} min^{-1} in two 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 aetiology of hypoglycaemia in SGA infants as does hyperinsulinism (Mehta, 1991). Mestyan *et al* (1976) studied this possibility by infusing glucagon into normoglycaemic and hypoglycaemic SGA infants. Only the former group responded by showing a reduction in concentration of glucogenic amino acids. 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. The most common are sepsis and perinatal asphyxia, but it is also seen 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 mobilisation 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. It is also seen 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 may be idiopathic.

The macrosomic infant of the diabetic mother (IDM) has a characteristic habitus. Whereas the infant who is simply large for dates has proportionate increases in both brain size and abdominal circumference, the macrosomic IDM has increased muscle, fat and liver mass as might be predicted from the known effects of insulin (Table 1). Thus, in fetal life the IDM has an increase in abdominal circumference: head circumference ratio (Fraser, 1994). For many years fetal hyperinsulinism has been ascribed to maternal, and consequent fetal, hyperglycaemia (Pedersen *et al*, 1954). More recently it has been speculated that other factors, including amino acid concentrations, must operate as mid-trimester human pancreatic tissue shows little insulin response to glucose concentration *in vitro* (Milner *et al*, 1972). The risk of hypoglycaemia in the neonatal period (Farquhar, 1956) may be reduced by careful control of maternal blood glucose concentration during pregnancy but is still greater in IDM 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 (Kalhan *et al*, 1977). A reduced postnatal glucagon surge appears to accompany the hyperinsulinism (Williams *et al*, 1979).

Some aspects of obstetric management may result in transient hyperinsulinism and hypoglycaemia among otherwise normal infants. Lucas *et al* (1980) found that intravenous infusion of >10 g glucose h^{-1} during labour was associated with significantly increased cord blood insulin concentration. Subsequent randomised trials investigating the effect on blood glucose concentrations and incidence of hypoglycaemia in the newborn have been reviewed by DiGiacomo & Hay (1992). When mothers were infused with >25 g glucose h^{-1} in the 2 hours prior to delivery there was a 17% mean increase (95% CI 5, 30) in the incidence of hypoglycaemia (blood glucose <2.2 mmol l^{-1}). Blood glucose in the baby was a mean 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 baby even when <25 g glucose h^{-1} had been infused (mean 0.4 mmol l^{-1}, 95% CI 0, 0.8), though the incidence of hypoglycaemia was not significantly different (mean odds ratio 2.6, 95% CI 0.61, 11.34).

Both prolonged oral (Epstein *et al*, 1979), and short-term intravenous, administration of β-agonists (Procianoy & Pinheiro, 1982) used to suppress preterm labour have 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 (Thomas *et al*, 1977).

Epstein *et al* (1979) noted transient hypoglycaemia in the baby, but Jouppila *et al* (1980) noted an *increase* in the baby's blood glucose concentration when fenoterol was administered briefly to suppress uterine contractions before caesarian section.

2.4.5 *Persistent hyperinsulinism, endocrine disorders and inborn errors of metabolism.* Neonatal hypoglycaemia which persists or recurs after the first few days of life should raise the diagnostic possibility of an endocrine disorder or inborn error of metabolism (Table 3).

Among the more common endocrine disorders are adrenocortical insufficiency, hypopituitarism, and the "B-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 the IDM in the absence of features of gestational diabetes mellitus in the mother. Infants with congenital or acquired glucagon deficiency also show severe and protracted hypoglycaemia (Vidnes & Oysaeter 1977, Kollee et al 1978, Gotlin & Silver 1970), illustrating well the importance of this hormone in perinatal adaptation.

Inborn errors of metabolism which may present as hypoglycaemia in the neonatal period include glycogen storage diseases, defects of β-oxidation (dicarboxylic aciduria), defects of gluconeogenesis (e.g fructose-1,6-diphosphatase deficiency), and some defects of amino acid metabolism.

The diagnosis and treatment of these conditions is beyond the scope of this work, and the reader is, therefore, referred to recent review articles (Saudubray *et al*, 1990; Aynsley-Green, 1991; Fernandes & Berger, 1993; Cornblath & Schwartz, 1993).

Table 3
Causes of recurrent and persistent neonatal hypoglycaemia
(Cornblath & Schwartz, 1993)

Endocrine deficiency
- Hypopituitarism
- Growth hormone deficiency
- Glucagon deficiency
- Cortisol deficiency /ACTH unresponsiveness

Hyperinsulinism
- Beckwith-Wiedemann syndrome
- B 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

3. EFFECTS OF HYPOGLYCAEMIA ON THE CENTRAL NERVOUS SYSTEM

Despite the lack of clinical evidence in human infants that hypoglycaemia is *causal* in inducing sequelae of symptomatic hypoglycaemia (Section1), evidence from animal studies and *post mortem* 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 which 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 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 (reviewed by Auer & Siesjo, 1988; Auer & Siesjo, 1993).

It is now clear that 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 for pre-treatment with *n*-methyl-d-aspartate (*N*MDA) antagonist drugs (notably dizocilpine maleate) has been found protective in both cell culture and animal models (reviewed by Papagapiou & Auer, 1990; Auer & Siesjo, 1993).

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 utilised. The primary candidates are lactate and ketone bodies. Lactate reverses stupor associated with insulin induced hypoglycaemia in suckling-weaning mice (Thurston *et al*, 1983) and has been shown to serve as a cerebral fuel in other species of newborn animals (Young *et al*, 1991). Insulin-induced hypoglycaemia (blood glucose <0.5 mmol l^{-1}) in newborn dogs was accompanied by a more than 50% fall in cerebral metabolic rate for glucose (CMR_{gluc}), and a more than 15-fold rise in cerebral metabolic rate for lactate (CMR_{lac}) which became the predominant metabolic fuel in this hypoketonaemic situation (Hernandez *et al*, 1980). Recent studies in hypoglycaemic, diabetic, human adults have also demonstrated that the brain consumes lactate (Amiel, 1994). 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) (Fernandes *et al*, 1984).

The newborn's capacity to promote ketogenesis in the face of "suckling hypoglycaemia" has been described previously (Section 2.3). Newborn term infants rapidly increase ketone body flux to rates observed in adults, but only after several

days of fasting, flux (i.e. rate of ketone body turnover) being correlated with plasma ketone body concentration (Bougneres *et al*, 1986). Furthermore, free fatty acid, glycerol (Persson & Gentz, 1966) and ketone body concentrations (Hawdon *et al*, 1992) are inversely related to blood glucose concentration. Extensive evidence from animal species (Dombrowski *et al*, 1989; Nehlig *et al*, 1993), including primates (Levitsky *et al*, 1977), demonstrates that ketone bodies are important cerebral energy substrates. Owen *et al* (1967) first demonstrated that the human brain consumes ketones. They catheterised the cerebral vessels of three adults and found that ketone bodies became the predominant cerebral fuel with prolonged (5-6 weeks) starvation. Similar catheterisation studies in infants (mean age 5 months) undergoing elective surgery demonstrated higher rates of ketone body uptake than those measured in adults (Settergren *et al*, 1976). Enzyme systems necessary for the metabolism of ketones are present in human fetal brain (Patel *et al*, 1975) and uptake of ketone bodies has been demonstrated in perfused brain obtained from fetuses aborted at 12-21 weeks of gestation (Adam *et al*, 1975). Kraus *et al* (1974) 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. 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 (LCBF) is well matched to the local cerebral metabolic rate for glucose (CMR_{glu}). In newborn dogs total cerebral blood flow was conserved even at blood glucose concentrations <0.5 mmol l^{-1} (Hernandez *et al*, 1980). However, the developmental time course of the mechanisms responsible may vary from species to species (reviewed by Nehlig, 1993) and extrapolation to human neonates must be cautious. Pryds *et al* (1988, 1990) identified increased plasma adrenaline concentrations and cerebral blood flow (measured using ^{133}Xe) in preterm infants whose blood glucose fell below 1.7 mmol l^{-1}. In further studies a fall in cerebral blood volume (measured using near infra-red spectroscopy) accompanied restoration of normal blood glucose concentration in hypoglycaemic preterm infants (Skov & Pryds, 1992). The authors speculated that the speed 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 newborn 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 future clinical role in cerebral protection.

4. DEFINITION OF HYPOGLYCAEMIA

Confusion about the definition of "neonatal hypoglycaemia" was well documented by Koh *et al* (1988) who surveyed paediatric textbooks and the opinion of consultant paediatricians in the United Kingdom (Table 4). Subsequent review articles have restated the controversy (Cornblath *et al*, 1990; Aynsley-Green, 1991; Ward Platt, 1991; Ward Platt & Hawdon, 1993; Schwartz, 1991; Cornblath & Schwartz, 1993).

Table 4
Some definitions of neonatal hypoglycaemia

	Textbooks	Paediatricians
Term AGA	< 1.7 (< 1.0 - 2.5)	< 2.0 (< 1.0 - < 4.0)
Preterm or SGA	< 1.1 (< 1.0 - 2.5)	< 1.1 (< 1.0 - < 4.0)

Table shows modal value (range in parentheses) for blood glucose concentration (mmol l^{-1}) defined as neonatal hypoglycaemia by paediatric textbooks or practising paediatricians (Koh *et al*, 1988).

Approaches to defining abnormally low blood glucose concentration have included: statistical (4.1), metabolic (4.2), neurophysiological (4.3), neurodevelopmental (4.4).

4.1 Statistical definition

In general terms a "low" value for any normally distributed biochemical variable is defined as a value below 2 standard deviations from 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 Chapter 5. Second, early feeding schedules have a prominent effect on blood glucose concentrations but have changed a great deal since early studies (Cornblath & Reisner, 1965; Chance & Bower, 1966; Lubchenco & Bard, 1971; Fluge, 1974). Even now they vary greatly from hospital to hospital and few breastfed infants have been studied (Hawdon *et al*, 1992; Anderson *et al*, 1993). Third, there is a problem in defining what is meant by a "normal healthy term baby" in this context; in one study (Sexson, 1984) 72% of inborn babies had one or more of the "risk factors" for hypoglycaemia set out by Cornblath & Schwartz (1976). 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 (Hawdon *et al*, 1992).

Cornblath & Reisner (1965) first published data on blood glucose concentrations in normal newborns. They found that 95% of values among term infants were >30 mg dl^{-1} and 98.4% of values in "premature" infants >20 mg dl^{-1}. They defined hypoglycaemia in "full-size" term infants as a blood glucose value below 30 mg dl^{-1} in the first 48 hours and below 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 era of this study (Cornblath & Reisner, 1965). Srinivasan *et al* (1986) have more recently published *plasma*[3] glucose concentrations of 344 healthy full-term, appropriate weight for gestational age (AGA) infants. Mean and 95% confidence intervals (95% CI) were calculated from a mixture of serial and cross-sectional data. 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 one hour of age. After two 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 questionable for the early care of the infants studied is described as follows:

> "All neonates were admitted to an observation nursery where weight, temperature and other vital signs were recorded. The infant was placed under a servo-controlled radiant warmer to maintain skin temperature at 36.5°C. Skin care and bath were given after stabilisation of core temperature. All infants were fed 20 calories/oz formula at 3 to 4 hours of age; after feeding, the infants were transferred to their respective nurseries and fed every 4 hours; 10-15% of the infants were breastfed."

Heck & Erenburg (1987) made longitudinal measurements of serum glucose concentration in 64 breastfed and 50 bottle-fed term infants during the first 48 hours of life. 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. Values <2.2 mmol l^{-1} were obtained in 16% of the sample studied. Interestingly the mean serum glucose concentration of 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 (Lucas *et al*, 1981).

Data published by Hawdon *et al* (1992) have been discussed in a previous section (2.3). These authors measured cross-sectionally a number of metabolic substrates, not just glucose, among healthy, term, demand-breastfed and bottle-fed infants. The paper provides limited information about the management of breastfeeding in the

[3] Usually 15-20% higher than blood glucose concentrations.
Section 5.1.5.

infants studied, stating only that the infants were "demand-fed". No supplements of water or formula were given (JM Hawdon, personal communication). 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 figure 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 point about the definition of hypoglycaemia. Counterregulatory responses differ significantly between term and preterm infants (Hawdon *et al*, 1992), 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 (Cornblath & Reisner, 1965).

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* (1988) studied latency of the auditory evoked response waveform (AEP's) among 17 children, some of whom were spontaneously hypoglycaemic whilst others were undergoing insulin-induced hypoglycaemia stress testing. Abnormalities were identified in some when blood glucose concentration fell below 2.6 mmol l^{-1} but generalisation to the healthy newborn is very difficult for two reasons. First, only five of the subjects were newborn babies. Second, the infants were relatively hypoketonaemic and consequently deprived of alternative cerebral

fuels (Section 3.3) unlike the healthy breastfed infant. It is also important to note that the electrophysiological abnormalities identified were not permanent.

Others have failed to observe an effect of hypoglycaemia on AEP's in the newborn (Greisen & Pryds, 1989). Furthermore, Pryds *et al* (1988) were unable to identify abnormalities of either the amplitude-integrated EEG signal or of single flash visual evoked potentials (VEP's) among nine hypoglycaemic preterm infants (mean gestational age 30.8 weeks, range 26-34 weeks). Blood glucose concentrations at the time of study ranged from <0.5 mmol l^{-1} (five infants) to 1.5 mmol l^{-1}.

In summary, 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 in whom blood glucose concentration fell below a defined value (Section 1.2). Using a different approach Lucas *et al* (1988) correlated plasma glucose concentration with outcome in a large study of 661 preterm infants weighing <1850 g at birth. Bayley motor and mental developmental scores ascertained blindly at 18 months of age were regressed upon lowest recorded glucose concentrations between 0.5 and 4.0 mmol l^{-1} adjusting for sex, gestational age, birth weight, days of ventilation and other identifiable perinatal and social risk factors. 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}. Scores were also significantly correlated with 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 in whom plasma glucose fell below 2.6 mmol l^{-1} on five or more, not necessarily consecutive, days. Mean (SE) scores in these respective groups for the Bayley motor developmental index were 96.1 (1.3) *v* 84.4 (3.2) ($p<0.001$) and 102.0 (1.5) *v* 85.6 (3.7) ($p<0.005$) for mental development. Furthermore, the risk of neurodevelopmental impairment (defined as cerebral palsy or Bayley motor/mental development score <70) for infants whose plasma glucose fell below 2.6 mmol l^{-1} on five 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 (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 which 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 concentrations of alternative cerebral fuels (particularly ketone bodies, fatty acids and lactate) remain unknown. 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 (Section 2.4; Section 4.2) and that presence of a plasma glucose concentration <2.6 mmol l^{-1} in this group is associated with adverse neurodevelopmental outcome (Section 4.4). The neurodevelopmental outcome of symptomatic term babies with hypoglycaemia is also worse than in those who are asymptomatic. Whilst 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, as no definite threshold can be set.

5. SCREENING

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

5.1 Methods for measuring blood/plasma glucose concentration

5.1.1 *Reductiometric methods.* Traditional methods for measurement of blood glucose depended on the reducing property of glucose. An example is the ferricyanide method which can be adapted for use on an Autoanalyser. These methods measure total reducing sugar concentrations. The difference between total reducing sugar 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 problem. Enzymatic methods (Bergmeyer, 1974) have largely superseded reductiometric methods in clinical practice where precise measurement of blood or plasma glucose concentrations is required.

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 (Bergmeyer, 1974). These reactions form the basis of both reagent strip and benchtop glucose electrode methods. The limitations of these systems are described in more detail below (Sections 5.1.6, 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 measured using a suitable spectrophotometric indicator system. This method is precise and highly specific for glucose (Bergmeyer, 1974).

5.1.4 *Precision and sources of error in the determination of blood & plasma glucose concentrations.* Requirements for the ideal method for measurement of glucose concentrations in clinical practice are: 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 undertake it without extensive training in laboratory skills. Methods developed and used most extensively in the last two decades for cotside monitoring of blood and plasma glucose concentrations include paper reagent strips and glucose electrodes. Both depend on the glucose oxidase reaction (Section 5.1.2). Another more recently developed method (the HemoCue photometer, Section 5.1.8) employs glucose dehydrogenase to reduce NAD but measures indicator colour change by transmission spectrophotometry rather than the reflectance technology 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 will be greatest under anaerobic conditions. Capillary

sampling is unreliable if peripheral blood flow is reduced. Samples must be always be free-flowing as squeezing the heel causes haemolysis which interferes with the assay unless deproteinisation is performed (see below). Contamination by alcohol used for skin preparation leads to erroneously high values (Grazaitis & Sexson 1980; Togari *et al*, 1987). The sample should either be analysed immediately or deproteinised (for example 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 (Joosten *et al*, 1991).

One of the greatest problems with neonatal samples is that haematocrit 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% (Aynsley-Green, 1991). Furthermore, all methods employing paper reagent strips are subject to an intrinsic haematocrit bias; the higher the haematocrit value, the lower the result. Possible reasons 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 heparinised micro-haematocrit tube, overcomes this problem (Kaplan *et al*, 1989).

Bilirubin, uric acid, and haemolysis also interfere with glucose oxidase-peroxidase based strip methods. Bilirubin inhibits both steps of the assay leading to falsely low values (Fox & Redstone 1976). Haemolysis also produces falsely low values. This may be attributable to 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 deproteinisation 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 tend to under-estimate systematically the mean of a series of measurements in the range of glucose concentrations relevant to the diagnosis of neonatal hypoglycaemia (<2.6 mmol l^{-1}; approx < 50 mg dl^{-1}) and are imprecise, typically giving values only to within $\pm$ 0.5 mmol l^{-1} even when coupled with a reflectance metering system (e.g *Reflolux*).

Several commercially available systems are available and have been evaluated for neonatal use including *Dextrostix* (Ames Co.) (Chantler *et al*, 1967; Wilkins & Kalra, 1982), *BM-test-glycemie 1-44* (Wilkins & Kalra, 1982; Reynolds & Davies, 1993; Anderson *et al*, 1993), and *Chemstrip bG* (Boehringer Mannheim) (Holtrop *et al*, 1990; Kaplan *et al*, 1989). Most studies have compared methods using linear correlation analysis (e.g Kaplan *et al*, 1989; Wilkins & Kalra, 1982; Perelman *et al*, 1982; Hererra & Hsiang, 1983; Hay & Osberg, 1983; Lin *et al*, 1989; Hameed *et al*, 1995) but a more informative means of comparing two methods of measurement is to plot the difference between results obtained by each method against the average of the two (Bland & Altman, 1986). This describes more clearly

inaccuracy (*systematic* difference between methods) and imprecision (*random variation* of results about the mean).

Four studies have examined the problem in this way. One (Aynsley-Green, 1991) compared blood glucose measurements made using the *BM 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% confidence limits (precision) across this range approximated 0.5 mmol l^{-1}, and there was a small systematic difference of 0.05 mmol l^{-1} at all concentrations. Anderson *et al* (1993) compared *BM* strip with the *Yellow Springs Instruments* glucose electrode system. *BM glycemie test* gave results on average 0.37 mmol l^{-1} lower than those obtained with the glucose electrode in the range of concentrations 1-5 mmol l^{-1}. Confidence limits were not given.

A third study (Reynolds & Davies, 1993) examined the effectiveness of paper strip systems in screening for neonatal hypoglycaemia (see 5.2 below), defined as a blood glucose concentration of <2.0 mmol l^{-1} detected at the cotside with the *BM glycemie 1-44 test* (Table 5). The *Kodak Ektachem* system was used as a comparative laboratory reference. Mean *BM glycemie test* values understimated mean *Kodak Ektachem* values by as much as 1.5 mmol l^{-1} at a *BM* 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* value of 2.0 mmol l^{-1} could have been between 1.4 and 4.3 mmol l^{-1} on 95% of occasions. Hameed *et al* (1995) similarly compared venous and capillary sample *BM*-test reflectance estimates with laboratory values obtained by the hexokinase technique and observed a tendency for the mean *BM*-test value to underestimate with a wide scatter of individual values (95% CI approximately ± 1.6 mmol l^{-1}).

In summary, reagent strip methods are 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 (Conrad *et al*, 1989) examined the reliability of a glucose electrode based analyser (YSI) (*Yellow Springs Instruments*, Model 23A) used by nurses in a clinical setting. The device measures plasma glucose concentration on a whole blood uncentrifuged 25µl sample. An *in vitro* study found good linear agreement (r = 0.99) over the range 0-100 mg dl^{-1} (0 - 5.6 mmol l^{-1}) between YSI results and those obtained using a laboratory glucose oxidase method. The regression equation was:

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

Standard error of the estimate (n=49) was 3.0 mg dl^{-1} (0.17 mmol l^{-1}), significantly better than agreement obtained between YSI and reagent strip methods (*Glucometer II, Chemstrip bG, Dextrostix, Glucostix*) for which standard error of the estimate ranged between 15-20 mg dl^{-1}. Interference from bilirubin is negligible

at concentrations encountered in practice, and sample haematocrit does not affect the assay. Fully automated systems are available but expensive (approx $15,000) 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 (*Hemo-Cue AB*, Angelholm, Sweden) is an optical method measuring whole blood glucose on small (5μl) samples utilising disposable cuvettes. Blood is haemolysed in the cuvette and NADH formed by enzymatic glucose oxidation reduces methylthiazolyldiphenyl tetrazolium to produce a formazan dye, the concentration of which is determined spectrophotometrically. Only one study has evaluated application to neonatal samples (Vadsadi & Jacobs, 1993). Furthermore, its reliability for detection of hypoglycaemia cannot be established because 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 comments in Section 5.1.7). Moreover, the cost per test is high when compared with reagent strip or electrode systems. Cuvette storage temperature and room temperature variation can introduce errors, though these are more significant at high than at low glucose concentrations. A recent study (Ellis *et al*, 1996) 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}).

5.2 Effectiveness of screening based on reagent strip methods

Table 5 summarises data on the effectiveness of screening from two published studies. A positive predictive value (PPV) of 0.18 or 0.52 implies that a reagent strip measurement predicted true hypoglycaemia (i.e. confirmed by laboratory measurement) on only 18 or 52% of occasions. The discrepancy between studies in estimated positive predictive value probably reflects different incidence of hypoglycaemia. In one (Holtrop *et al*, 1990) the proportion of true positives was 21% of all tests, in the other (Reynolds & Davies, 1993) it was <10%. 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 (Hall & Michel, 1995). Sensitivity and specificity values are unaffected by the incidence of a condition and estimates in these two studies, of 82% and 86% for sensitivity, and 70% and 78% for specificity, 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 (Ho *et al*, 1991; not shown in Table 5) using *BM-test Glycemie 20-800* and the *Reflolux* meter gave similar estimates: sensitivity 88% and specificity 81%.

Table 5
Effectiveness of screening for neonatal hypoglycaemia using reagent strip methods

Definition:	<2.0 mmol l^{-1}	<1.9 mmol l^{-1}
Sensitivity	82%	86%
Specificity	70%	78%
Positive predictive value	0.18	0.52
Negative predictive value.....	0.98	0.95

Hypoglycaemia defined as <2.0 mmol l^{-1} using *BM glycemie /Reflolux* system (Reynolds & Davies, 1993) or as <1.9 mmol l^{-1} using *Chemstrip BG* with visual matching (Holtrop *et al*, 1990).

Sensitivity = true positives / [true positives + false negatives]
Specificity = true negatives / [true negatives + false positives]
Positive predictive value = true positives / [true positives + false positives]
Negative predictive value = true negatives / [true negatives + false negatives]

In summary, these studies show that reagent strip screening detects only about 85% of true cases of hypoglycaemia and 75% of babies 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** (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 (1984) examined the effect of the diagnostic threshold for hypoglycaemia on incidence of the condition among 232 newborn babies born to low-risk mothers in the USA. No information about feeding regimens was given. 72% (168) had one or more risk factors for hypoglycaemia as defined by Cornblath & Schwartz (1976). *Dextrostix* were used to screen for hypoglycaemia, a practice likely to overestimate the true incidence (Section 5.1.6; Section 5.2), though 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 the age of 5 hours (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 of the hypoglycaemic infants was 1.5 mmol l^{-1} (range 0-2.1 mmol l^{-1}) and the mean age at diagnosis 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 as 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.

Holtrop (1993) studied the incidence of hypoglycaemia in LGA and SGA American newborns, identified as having birth weight >90th or <10th centile respectively. The definition of hypoglycaemia chosen was that suggested by Srinivasan *et al* (1986): 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 hours of age. Hypoglycaemia was detected in 8.1% (24/298) of LGA infants and 14.7% (30/204) of SGA infants. In all but 3 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 British study of 164 SGA babies 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. Only one of the 9 infants was symptomatic, being described as "jittery". Hawdon *et al* (1992), reviewing the literature, quote incidences of "hypoglycaemia"[4] in term infants ranging between 0 and 8% and between 3 and 15% in preterm infants.

Information on the incidence of neonatal hypoglycaemia in developing countries is very limited. Anderson *et al* (1993) conducted a cross-sectional study of 226 full-term, uncomplicated newborns in a hospital in Kathmandu, Nepal. Hypoglycaemia, defined as a *blood* glucose value of <2.6 mmol l^{-1} during the first 50 hours of life (Koh *et al*, 1988), was present in 38%. Seven per cent had a blood glucose concentration <2.0 mmol l^{-1}. Low birth weight and hypothermia were associated with hypoglycaemia which was 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 to 32% of those who were not. More than half the babies studied received prelacteal feeds (sugar water) and many mothers delayed initiation of breastfeeding for over 24 hours, discarding colostrum. The authors speculated reasonably that these were important aetiological factors but did not seek systematically to correlate these practices with hypoglycaemia in their study.

5.4 Summary: 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

[4] Hypoglycaemia defined as <30 mg dl^{-1} (1.6 mmol l^{-1}) in term infants <48 hours old, <40 mg dl^{-1} if over 48 hours old. Hypoglycaemia in preterm infants defined as <20 mg dl^{-1} (1.1 mmol l^{-1}).

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 <37 weeks gestation have an immature counterregulatory response to hypoglycaemia (Section 2.3, Section 2.4). It seems desirable in this group to maintain plasma glucose concentration >2.6 mmol l^{-1} (Lucas *et al*, 1988). In achieving this aim, prevention (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 measurements are preferable to frequent but inaccurate reagent strip measurements. They should be sufficient in most cases to tailor feeding regimens to the individual infant's requirement.

Small for gestational age (SGA) infants. Care should be taken in the diagnosis of SGA (see Section 6.2.3). This group is very heterogeneous and not all are at risk of hypoglycaemia. Those <3rd percentile (birth weight <2 SD from the mean for gestation) (Jones & Roberton, 1986; Cornblath & Schwartz, 1993), and those who are disproportionate (increased head circumference: body weight ratio) or with abnormal umbilical artery Doppler flow velocity profiles in fetal life (Hawdon *et al*, 1992), are probably most vulnerable. Polycythaemia is an additional risk factor which 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 (Hawdon & Ward Platt, 1993).

Large for gestational age (LGA) term infants. Rare infants with organic hyperinsulinism are typically large at birth, and this association has led to screening of infants whose birth weight exceeds the 90th percentile for gestational age. Occasionally 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 (Hawdon *et al*, 1992), blood glucose concentrations may fall below 2 mmol l^{-1} in this group, usually within the first 8 hours of life (Holtrop, 1993). There is no evidence that transient hypoglycaemia in this group is detrimental to 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 the 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 predisposing to neonatal hypoglycaemia are unavoidable (e.g. β-sympathomimetics to suppress preterm labour, caesarean section) some are avoidable. One such is 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 (Section 2.4.4).

6.1.2 *Early postpartum management.* The baby should be dried immediately 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 are important in the maintenance of core temperature (van den Bosch & Bullough, 1990). Early enteral feeding should have the highest priority in healthy infants, whether term or preterm (Smallpeice & Davies, 1964; Wharton & Bower, 1965).

6.1.3 *Neonatal risk factors.* Section 2.4 discussed factors which increase the risk of neonatal hypoglycaemia. Feeding regimens for categories of babies at risk are suggested below (Section 6.2). Polycythaemia (packed cell volume, or PCV, of >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 polycythamia is controversial; some authorities (Glader & Naiman, 1991) recommend partial dilutional exchange with 5% albumin in infants who are "symptomatic" (including those who are hypoglycaemic) but there is no consistent evidence of short- or long-term benefit in those who are well (Doyle & Zipursky, 1992)..

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 (Beard *et al*, 1966). Breastmilk is preferred to formula because it appears to promote ketogenesis (Hawdon *et al*, 1992). Furthermore, there is some evidence that early blood glucose values in term babies fed formula are lower than those in babies breastfed (Heck & Erenburg, 1987). This may reflect the insulinogenic effect of protein in formula (Lucas *et al*, 1981) (Section 4.1).

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 North American nurseries, it is outdated. Dextrose water is of lower energy density than milk which contains fat. 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 aspiration of dextrose or water.

In some parts of the world, notably the Indian sub-continent, prelacteal feeding and withholding of colostrum is common. In an Indian Council of Medical Research collaborative study of infant feeding, only 32% of mothers suckled their baby within the first 24 hours and only 13% in the first 8 hours. Seventy-one per cent of mothers offered an alternative to breastmilk, such as honey or sugar water (Anderson *et al*, 1993). Such practices seem very likely to increase the incidence of neonatal hypoglycaemia though no intervention studies appear to have documented this.

6.2.2 *Preterm infants*. It is over thirty years since two British studies documented that "early" feeding with expressed breastmilk reduced the incidence of hypoglycaemia (blood glucose <20 mg dl^{-1}) in preterm infants (Smallpeice & Davies, 1964; Wharton & Bower, 1965). In the 1940's and 1950's preterm infants were starved for the first 24 hours of life in order to reduce the incidence of aspiration. Smallpeice & Davies (1964) 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 when compared with historical controls. 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 texts though has never been systematically evaluated. Wharton & Bower (1965) found that this practice halved the incidence of asymptomatic hypoglycaemia (immediate-fed group 5/44; late-fed group 10/54) and abolished symptomatic hypoglycaemia (0/44 immediate-fed; 4/54 late-fed) though was associated with an increased risk of mortality, often associated with aspiration.

An alternative may be to provide 100 ml kg^{-1} d^{-1} on the first day, 75 ml kg^{-1} d^{-1} on the second and 50 ml kg^{-1} d^{-1} on the third as the volume of breastmilk obtained by suckling increases (JM Hawdon, M Ward Platt; personal communications, 1996). Concern about the relationship between high early feed volume and necrotising enterocolitis may be unjustified, being based on case-control data (Anderson & Kliegman, 1991; McKeown *et al*, 1992) and retrospectively controlled studies (Brown & Sweet, 1978; Goldman, 1980). It was not supported by a single, small randomised controlled trial (Book *et al*, 1976). Studies examining feed volume moreover have not adequately controlled for the protective effect of human milk (Lucas & Cole, 1990; Beeby & Jeffery, 1992).

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 as nasogastric tubes increase airway impedance and may precipitate apnoea (Stocks, 1980). Alternatively infants may be cup-fed (Lang *et al*, 1994). Initially, small aliquots of feed should be offered hourly and intervals increased to 3-hourly as tolerated.

Healthy preterm infants 32-36 weeks of gestation. Sustained coordination of suckling and swallowing is present from about 32 weeks of gestation (Rennie,

1992) 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 (1979) 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 (mean, SD) and a mean age of 11 days. Ten were fully breastfed at a mean age of 27 days when they weighed 1.600 ± 0.139 kg.

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 6.2.2 above). Feeds should be offered by cup or gavage in preference to a bottle. Expressed breastmilk is the food of choice but formula is preferable to dextrose water if it is not available.

Healthy preterm infants under 32 weeks of gestation. The majority of these will not suckle effectively and require gavage feeding though cup-feeding is possible from 30 weeks of gestation (Lang *et al*, 1994). If required, a gastric tube should be passed orally and not nasally (Stocks, 1980). On the first day a volume of 60 ml kg^{-1} d^{-1} divided into hourly aliquots should be given. If facilities for intravenous therapy are available, a 10% glucose infusion should be initiated as soon as possible after birth 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 necrotising enterocolitis (NEC) has been excluded. NEC and other conditions associated with ileus (e.g. sepsis, respiratory disease) should be treated according to standard texts.

Most infants <28 weeks of gestation show immature patterns of bowel motility though early feeding has been shown to hasten adaptation to the pattern seen in more mature babies (Bissett *et al*, 1989). A randomised controlled study of babies <1850 g birth weight found human milk feeds more rapidly tolerated than formula feeds (Lucas, 1987).

Management of the mother. If the baby is unable to suckle, mothers should express their breastmilk as soon as possible after delivery and continue at least 3-hourly 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. Skin-to-skin contact ("kangaroo care") has been shown in a randomised controlled study to increase the duration of lactation among mothers of very small preterm infants (Whitelaw *et al*, 1988).

6.2.3 *Small for gestational age (SGA) infants*

Identifying SGA babies. Usually SGA babies are defined as those whose birth weight is below the 10th centile for gestational age. This crude classification ignores the strong effect of maternal height and weight on birth weight. There is a

difference of approximately 500 g between the mean birth weights at term of babies born to mothers of 4 feet 10 inches or 5 feet 10 inches. If the extremes of mid-pregnancy weight are also taken into account, the difference approaches 1 kg (Altman & Coles, 1980). A study of British babies (Gardosi *et al*, 1992) estimated that 28% of infants conventionally classified as SGA were of appropriate weight when maternal race, height, weight, and parity were taken into account. Similarly, 24% of babies conventionally classified as appropriate weight for gestational age (AGA) were truly SGA. Ideally, birth weight should be adjusted at least for the effect of maternal height, parity and mid-pregnancy weight (Altman & Coles, 1980) before babies are labelled SGA.

As the endogenous glucose production rate and glucose requirements correlate more closely with brain weight than body weight, the 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 ratio. Unfortunately there are insufficient data at present to establish a sufficiently precise threshold 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. Reasons for the increased incidence of hypoglycaemia among SGA infants were discussed in Section 2.4: counterregulatory response and ketogenesis are blunted by comparison with AGA infants but 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 (Section 2.2.4). We therefore commence enteral feeding in healthy SGA infants 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 Cambridge study (Whitby *et al*, 1982) 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 5 developed hypoglycaemia[5]. All were asymptomatic. 55% of the infants were "*..making some attempt to breast-feed at discharge.*" A further Cambridge study of 164 infants below the 5th centile birth weight at $\geq$ 37 weeks fed according to this regimen observed only 9 cases of hypoglycaemia (footnote[4]), most of which were in infants <2 standard deviations below mean birth weight for gestation. Eight of the 9 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

[5] *Dextrostix* value of <25 mg dl^{-1}.

circumference: arm circumference or length ratios) in identifying more precisely those small for gestational age infants at risk.

6.2.4 *Infant of the diabetic mother.* These infants display transient hyperinsulinism. The risk is greatest among those who are macrosomic (Section 2.4). Hypoglycaemia is not likely to occur after the first 24 hours of life. 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. But 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 similar to that of controls, provided that hypoglycaemia was appropriately treated.

6.2.5 *Large for gestational age (LGA) infants.* LGA is usually defined as birth weight >90th centile for gestational age. Infants with persistent hyperinsulinism (e.g. attributable to B-cell dysregulation syndrome) are typically LGA, as are those born to mothers with unrecognised 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[6] in an American study (Holtrop, 1993) of LGA infants was 8.1% but no details of feeding regimens were given. 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 old. 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 randomised controlled trial involving 130 full-term, LGA infants[7] (Singhal *et al*, 1991). 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} $24h^{-1}$ by bottle or gastric tube, making the average glucose supply of the two groups 5 or 7.8 mg kg^{-1} min^{-1} respectively. 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} recorded (Relative risk 4.2, 95% CI 2.88, 5.44, p <0.05).

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[6] 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, <45 mg dl^{-1} at >24 hours of age.

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

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 as *Dextrostix* were used to detect cases (Section 5.1.6; 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 mosm l^{-1} as opposed to 290 mosm l^{-1} in the standard feed. Abdominal distension was not noted but...

> *"...10.8% of babies on fortified feeds did not relish the taste, as compared to 4.8% on standard milk."*

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

Fat supplementation of enteral feeds may have a role in *prevention* of hypoglycaemia (Sann *et al*, 1988). There is evidence that oral administration of lipid (as medium chain triglyceride) increases blood glucose concentration in unfed preterm and SGA babies (Sann *et al*, 1981, 1982). 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.

6.4 Infants who cannot be fed

Immediate enteral feeding is contraindicated in some situations, for example in the presence of cardio-respiratory distress, congenital malformations of the gastrointestinal tract, ileus, and extreme prematurity (gestation <28 weeks). Glucose infusion should be commenced at a rate approximating the endogenous rate of hepatic glucose production (Section 2.2.4), that is:

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}
Small for gestational age infant	6-8 mg kg^{-1} min^{-1}

Note: 60 ml kg^{-1} $24h^{-1}$ 10% dextrose supplies 4.2 mg glucose kg^{-1} min^{-1} (footnote[8])

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 enterally fed. It is undesirable to curtail abruptly intravenous infusions of glucose. The concentration of glucose infused into a peripheral vein

[8] Strictly, 10% dextrose solution contains 9.3 g glucose in the unhydrated form but is assumed to contain 10 g for most clinical purposes.

should not exceed 10%. If glucose requirements exceed the above, insertion of a central intravenous line may be necessary, though intravenous glucagon injection (200 μg kg^{-1}) may be an alternative (Section 7.3.1; Mehta, 1994).

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 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).

7.1.1 *Oral dextrose water or milk?* Some authorities recommend oral feeding of 10% dextrose water 10 ml kg^{-1} (Cornblath & Schwartz, 1993). Others (Aynsley-Green, 1991; Hawdon & Ward Platt, 1993) point out that milk (10 ml kg^{-1}) is more energy dense (100 ml breastmilk contains 70 kcal; 100 ml 10% dextrose contains 40 kcal) and that the fat component is theoretically beneficial; fat will both promote ketogenesis and reduce uptake of glucose into cells (Section 2.2.3; Section 2.3). Whether glucose or milk is given, a blood glucose measurement should be repeated preferably within the hour. Frequent feeds and pre-prandial blood glucose measurements (at least every 3 hours) should continue.

7.1.2 *Lipid.* Studies in hypoglycaemic infants and in preterm and SGA infants have shown that feeding lipid produces an increase in blood glucose, and non-esterified fatty acid concentrations (Sann *et al*, 1981, 1982) (Section 2.2.3; Section 2.3). Hawdon *et al* (1993) administered 5 ml kg^{-1} medium chain triglyceride (MCT) intragastrically and measured small but significant increases in blood glucose concentration, together with a highly variable change in the glucose production rate. Variability was attributed to differences in absorption (though this was not measured). Although the glycaemic effect of administering 200 μg kg^{-1} glucagon was greater than the effect of giving 5 ml kg^{-1} of MCT, ketogenesis was promoted more effectively with MCT and such a change might be of equal importance to glycaemic effect, given the probable importance of ketone bodies as a cerebral fuel (Section 3.2).

7.1.3 *Concentrated Dextrose Gel.* There have been anecdotal reports of the use of *"Hypostop"*, a 40% dextrose gel in treatment of neonatal hypoglycaemia. In an uncontrolled study 0.5 ml kg^{-1} *Hypostop* was massaged into the buccal mucosa after drying it with a gauze swab. Sixty seven per cent of term infants are said to

have responded with a rise in blood glucose concentration of $\geq$ 0.5 mmol l^{-1} (Bourchier *et al*, 1992). In the absence of controlled studies we cannot recommend this practice as effective and have concerns that it may defer implementation of more appropriate therapy aimed at correction of hypoglycaemia and treatment of the cause.

7.2 Intravenous treatment

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

A. Enteral treatment has failed (see Section 7.1)

B. Hypoglycaemia is severe (<1.1 mmol l^{-1})

C. The baby is unwell or has signs which may be attributable to hypoglycaemia ("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 (Lilien *et al*, 1980; Hawdon et al, 1994; Cornblath & Schwartz, 1993) recommend it but others have argued that the rate of glucose entry in such circumstances exceeds uptake (Mehta, 1994) provoking "rebound hypoglycaemia" through enhancement of insulin secretion and inhibition of glucagon secretion. Excessively rapid administration of glucose moreover has potential to cause hyperosmolar cerebral oedema, as described in older children (Shah *et al*, 1992). 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 United States 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 blood glucose concentration is still low (JE McGowan, personal communication, 1995). In a study using historical controls Lilien *et al* (1980) 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. Only one infant became transiently hyperglycaemic. Hawdon *et al* (1994) recommended using a 3 ml kg^{-1} 10% dextrose priming bolus for *symptomatic* infants, relying upon slower correction by continuous infusion alone (at least 5 mg kg^{-1} min^{-1}) in infants who are hypoglycaemic but otherwise well (Ward Platt & Hawdon, 1993).

The rate of infusion may require adjustment until plasma glucose concentration is corrected and stabilised. 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 (Section 2.4.5; Table 3).

Glucose infusions should not be discontinued abruptly. The rate of infusion should be gradually reduced *pari passu* with increase in 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 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* (1987) described four term infants who presented with symptomatic hypoglycaemia in association with "normal" insulin concentrations. Studies using the tracer 6,6-dideuteroglucose indicated a reduced rate of hepatic glucose production. Glucagon injection (200 mcg kg^{-1} i.v.) led to a rapid and persistent increase in hepatic glucose production rate with restoration of plasma glucose concentration. Hawdon *et al* (1993) also described rapid increases in both plasma glucose concentration, total glucogenic substrate and glucose production rate after an intravenous bolus of 200 μg kg^{-1} glucagon among 10/11 hypoglycaemic term and preterm infants. In an uncontrolled study Carter *et al* (1988) described a response to continuous intravenous infusion of glucagon among 20/25 hypoglycaemic SGA infants in whom blood glucose concentration had remained <2.0 mmol l^{-1} despite infusion of 6.5 mg kg^{-1} min^{-1} glucose. 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 as SGA infants may be resistant to glucagon, probably as a result of delay in maturation of gluconeogenic pathways (Section 2.2; Section 2.4) (Mestyan *et al*, 1976).

The place of glucagon in treatment of neonatal hypoglycaemia is controversial (Mehta, 1994; Hawdon *et al*, 1994). Theoretically, a 200 μg kg^{-1} intravenous bolus effects enhancement of gluconeogenesis and ketogenesis (Section 2.2) which persists for many hours though an effect has been claimed for doses ranging between 3-300 μg 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 >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 (see Ward Platt & Hawdon, 1993; Cornblath & Schwartz, 1993). Reference should be made to suitable texts.

8. RESEARCH

The following questions have been identified as those to which an answer is most needed, to improve prevention and management of hypoglycaemia of the newborn.

8.1 *Does neonatal hypoglycaemia compromise neurodevelopmental outcome?*

A question remains as to the effect of hypoglycaemia, particularly asymptomatic hypoglycaemia, on neurodevelopmental outcome (Section 1; Section 3). Randomised 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.

8.2 *What is the relationship between early breastmilk 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 which do refer to breastfed infants give no information about feed frequency and the extent of supplementary feeding, let alone measurements of breastmilk intake. A detailed study of the relationship between feeding patterns, breastmilk intake and substrate concentrations (including glucose) is urgently needed to characterise the normal pattern of metabolic adaptation. Such studies need to be performed in less developed as well as industrialised countries.

8.3 *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

8.4 *What is a "safe" threshold blood glucose concentration for a preterm infant?*

Several authorities have recommended treatment when blood glucose concentration is < 2.6 mmol l^{-1}. This figure has three principal justifications: first that the counterregulatory response of preterm infants is blunted, secondly that there is evidence of neurophysiological dysfunction at this level and, third, that there is evidence of subsequent neurodevelopmental delay in preterm infants exposed to hypoglycaemia of this severity. Each of these justifications can, however, be challenged (Section 4).

Studies such as those of Hawdon *et al* (1992) have suggested that SGA and preterm infants are less able to mount a counterregulatory response than term infants. 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 there remains controversy as to whether mild hypoglycaemia (plasma glucose <2.6 mmol l^{-1}) affects 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.

8.5 *What is the role of glucagon administration in prevention and treatment of neonatal hypoglycaemia?*

Glucagon has been shown to be 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 randomised controlled studies.

8.6 *Is breastmilk more ketogenic than formula; if so, why?*

Some authors have suggested that breastmilk is specifically ketogenic (Section 2.3). It seems unclear whether this reflects active promotion of ketogenesis by a breastmilk constituent or is simply a consequence of the trend towards slightly lower blood glucose levels among breastfed infants.

8.7 *Role for measurement 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?

8.8 *Small for gestational age (SGA) babies.*

These are very important because they represent the largest group likely to be given supplements to prevent hypoglycaemia. Randomised trials of supplementary feeding in this group are needed urgently to establish the incidence and outcome of hypoglycaemia during exclusive breastfeeding and the adverse effects (including cessation of breastfeeding) 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.

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