New insights into the nutritional management of newborn infants derived from studies of metabolic and endocrine inter-relations during the adaptation to post-natal life

By Albert Aynsley-Green, *Department of Child Health, University of Newcastle upon Tyne, Framlington Place, Newcastle upon Tyne NE2 4HH*

Until the moment that the umbilical cord is cut at birth the human organism has been fed largely by the transplacental transfer of nutrients into the umbilical vein, with the enteral assimilation of amniotic liquor providing only a minor component. Maternal metabolism has had the central role in regulating fetal metabolism through controlling the delivery of substrates across the placenta. However, as soon as the cord is cut the infant has to be metabolically independent, and has to achieve metabolic homeostasis unaided, whilst adapting from intra-uterine intravenous nutrition to extra-uterine enteral feeding with milk.

The survival and growth of the newborn infant in the hostile extra-uterine environment depend crucially on successful adaptive changes occurring in a number of the body's physiological systems. Events occurring in the cardiovascular and respiratory systems are evident from external inspection immediately after birth, but other occult adaptive changes at least as complex in nature, and as important in terms of survival, occur during the process of adaptation to extra-uterine metabolism and nutrition. In this context two critical challenges confront every newborn infant, the first being the need to maintain normoglycaemia, the second the need to adapt to intermittent feeding and fasting.

We have suggested from collaborative work performed during the last 10 years that the adaptation to post-natal nutrition depends critically on the secretion of chemical messengers, including hormones and regulatory peptides released from specialized cells in the gut, together with those products of the more classical endocrine organs, the pancreas, thyroid, pituitary and adrenal gland. We have also suggested that it is important to examine the inter-relations of these concentrations with those of metabolic fuels in order to obtain a true perspective of the endocrine influences on metabolism and vice versa.

The present review will address three issues. The first is the control of blood glucose concentrations, the second is the effects of milk feeding in healthy full-term and preterm infants and the third is a consideration of how serious neonatal illness may affect these processes. The implications for nutritional management based on a knowledge of these inter-relations will be presented.

Before considering these issues further it is important to consider some practical problems relating to the performance of clinical studies of this nature. The first problem is ethical. All the results presented from our own studies were obtained from protocols which had the approval of the appropriate hospital ethical committees, and consent for the obtaining of blood and urine samples from the infants was obtained from their parents. Further details of the experimental protocols are to be found in the references cited. However, it is clearly unacceptable to obtain multiple blood samples from healthy babies purely for experimental purposes. This difficulty was overcome ethically by adopting a cross-sectional design in which only one blood sample was drawn from any individual baby, with the timing of the blood sample being arranged to coincide with the need for a sample for routine screening or monitoring purposes. In studies where repeated blood samples were drawn from sick infants, a total volume of not more than

Table 1. *Metabolic and endocrine variables*

(a) Blood

Glucose	Insulin	Aldosterone	Gastrin
Lactate	Glucagon	Cortisol	PP
Pyruvate	Adrenaline	Cortisone	Secretin
Alanine	Noradrenaline	11-Deoxycortisol	GIP
Glycerol	Growth hormone	11-Deoxycorticosterone	CCK
Triglycerides	Prolactin	17-Hydroxyprogesterone	Motilin
FFA	Thyroxine	Progesterone	Neurotensin
Acetoacetate		Dehydroepiandrosterone	Enteroglucagon
Hydroxybutyrate		Corticosterone	VIP
Amino acids			PYY
Carnitines			

(b) Urine

Creatinine	Organic acids
3-Methylhistidine	Octonyl carnitine

FFA, free fatty acids; PP, pancreatic polypeptide; GIP, gastric inhibitory polypeptide; CCK, cholecystokinin; VIP, vasoactive intestinal polypeptide; PYY, peptide tyrosine tyrosine.

5% of the baby's total blood volume was removed for research purposes, the timing of sampling again being related to clinical needs.

The second methodological problem follows from the previously stated consider-ations, namely the need to develop microanalytical assays which allow the measurement of a wide variety of metabolic and endocrine variables in microlitre quantities of blood or plasma. Table 1 lists all the substances which have been measured through specially developed microanalytical techniques in our own laboratories and in those of our collaborators. The power of these new methods is illustrated by the fact that by using centrifugal analysis a complete profile of metabolic fuels can be obtained from only 40 µl blood.

The regulation of blood glucose concentrations after birth

An overview of the control of blood glucose concentrations has been presented recently (Aynsley-Green & Soltesz, 1985) in which the differences between the regulation of blood glucose concentrations in the fetus, the neonate and the adult are considered. Glucose is an essential fuel for the human newborn infant. Apart from other obligatory glucose-consuming organs (erythrocytes, renal and cardiac tissue), glucose is the most important substrate for brain metabolism, and a continuous supply of this fuel is essential for normal neurological function. Due to the large size of the neonatal brain in relation to body-weight, cerebral glucose consumption is particularly high, thus increas-ing considerably the overall neonatal glucose requirement. At delivery, the constant supply of glucose received from the mother ceases abruptly, and the neonate has to face an immediate metabolic crisis, namely the need to maintain normoglycaemia and to meet the high glucose demand.

The normal infant born at term shows an immediate fall in blood glucose concen-trations during the first 4–6 h (Cornblath & Reisner, 1965), from values close to maternal levels to about 2·5 mmol/l, suggesting that one or more of the mechanisms required for fasting adaptation are not fully active at birth. During the first hours after birth the

maintenance of normal blood glucose levels is dependent on adequate stores of glycogen, a functional glycogenolytic enzyme system, normally functioning gluconeogenic enzymes, an adequate supply of endogenous gluconeogenic substrates, and finally, and of greatest importance in triggering these counter-regulatory processes, the integrated secretion of metabolic hormones. Anything which interferes with any of these processes is likely to lead to the development of hypoglycaemia.

We have shown that the first feed of milk given to the full-term human infant causes an increase in blood glucose concentrations of the order of 1·0–1·5 mmol/l (Aynsley-Green *et al.* 1977). Although no changes are seen in the concentration of blood glucose after the first feed of milk in preterm infants (Lucas *et al.* 1978), nonetheless, in healthy preterm infants who are given regular feeds of milk from birth, demonstrable feed-induced cyclic increments in blood glucose concentrations are evident within 2–3 d of delivery (Lucas *et al.* 1980*d*).

These observations suggest that the full-term infant at birth and the preterm infant within 2–3 d of birth are both capable of digesting milk and absorbing the products to cause a cyclic increase in blood glucose concentrations, thereby maintaining normoglycaemia. However, infants who are unable to tolerate milk feeding from birth are at high risk from the development of hypoglycaemia.

It is well known that hypoglycaemia can occur in the absence of symptoms in human neonates, and this has led to three controversies, namely, the definition of hypoglycaemia, the acute effects of asymptomatic hypoglycaemia, and finally, the long-term consequences of hypoglycaemia.

We have shown (Koh *et al.* 1988*a*) that there is an extraordinarily wide variation in the recommendations for the definition of hypoglycaemia, not only amongst standard textbooks of paediatrics but also amongst practising neonatologists in charge of intensive care nurseries. There is a persistence of the belief that the brain of the neonate is more resistant to the effects of hypoglycaemia than the adult, and that the brain of prematurely born and small-for-date infants is even more resistant to hypoglycaemia and, thus, can tolerate lower levels of blood glucose. By the use of the measurement of auditory-brainstem-evoked potentials and somatosensory-evoked potentials we have demonstrated (Koh *et al.* 1988*b*) that asymptomatic hypoglycaemia is associated with profound neural dysfunction in neonates and children. Moreover, transient periods of asymptomatic hypoglycaemia may be associated with prolonged periods of dysfunction before the latency of the evoked potentials returns to normal values. We have demonstrated that we have been unable to document abnormal neural function at blood glucose concentrations equal to or above 2·6 mmol/l, and this has led to our recent recommendation that the definition of hypoglycaemia should be a blood glucose concentration below 2·6 mmol/l at all ages in early life. We have emphasized, however, that the threshold for hypoglycaemic neural dysfunction may well vary from infant to infant, and may also be influenced by additional factors such as polycythaemia or birth asphyxia or hypoxia. Clearly, further work is necessary to identify more precisely the relation of blood glucose concentrations to neural function under different clinical circumstances in the neonatal nursery, but the previously mentioned evidence suggests that neonatologists should not be complacent about the presence of low blood glucose concentrations, particularly in premature or in small-for-date infants.

Powerful evidence to support this contention is to be found in the study of Lucas *et al.* (1988), in which analysis of a detailed multicentre study on 661 preterm infants showed that hypoglycaemia (plasma glucose less than 2·6 mmol/l) occurred in 67% of infants, with 25% of cases experiencing hypoglycaemia on three to thirty-seven separate days. Of particular significance is their observation that the number of days on which hypo-

glycaemia occurred at this level was strongly related to reduced mental or motor development scores at 18-months-corrected age, even after adjusting for a wide range of factors known to influence development. When such hypoglycaemia was recorded on five or more separate days, 18-months-adjusted mental and motor developmental scores were reduced by 14 and 13 points respectively, and the incidence of neurodevelopmental impairment (cerebral palsy or developmental delay) was increased by a factor of 3·5. These findings, as the authors comment, suggest that moderate hypoglycaemia, frequently ignored in the light of published recommendations, might well have serious neurodevelopmental consequences and a reappraisal of current management is urgently required.

The practical implication of these recent findings is that nutritionists should direct nutritional management to the maintenance of normoglycaemia during the first postnatal days. In view of the delay which occurs before there is full adaptation to enteral milk feeding in preterm infants, the logical consequence of this statement is a recommendation that glucose support must be given to all preterm infants and to all but the healthiest of full-term babies.

The adaptation to enteral feeding

The hypothesis, suggested by Bayliss & Starling in 1902, that the gut secreted a 'chemical messenger' into the bloodstream to affect the exocrine secretion of the pancreas, is the foundation stone on which the science of endocrinology is based. Despite the fact that a gut hormone was the first endocrine messenger to be described, little progress was made during the next 50 years in the field of gastrointestinal endocrinology, until newer methods became available for the isolation, purification and characterization of peptide substances secreted by specialized gut cells. During the last decade an explosion of knowledge has occurred on the manufacture, secretion and effects of a large number of peptides secreted by the gut and the pancreas, and it is clear that they, together with hormones secreted by the thyroid, adrenal and pituitary glands, are intimately involved in the regulation of food utilization. This includes the control of intestinal motility, of intestinal secretions, digestion and absorption, and of post-prandial fuel homeostasis. Some of these substances act as true circulating hormones; some act as paracrine substances, whilst others act in a neurocrine capacity as neurotransmitters. The reader is referred to Bloom & Long (1982) and to Creutzfeldt (1980) for further information concerning assay methods and for a general background to the subject.

Aspects of the development of the fetal intestine have been described. Buchan et al. (1981) and Larsson (1980) have documented the appearance of gut regulatory peptides in the human fetal intestine by 10 weeks after conception, and have emphasized the change in molecular form of the peptides and the changing anatomical distribution of these cells with advancing gestation. More recently, we have defined the metabolic and endocrine milieu of the human fetus at 18–21 weeks of gestation by measuring fetal arterio-venous and amniotic levels of fuels, hormones and regulatory peptides (for review, see Aynsley-Green, 1988). There are also a number of excellent studies documenting histological and functional changes in the gut in post-natal experimental animals as well as in man (Grand et al. 1976; Lebenthal, 1982). From such studies it is known that within days of birth dramatic changes occur in the growth of the gut and in the secretion of acid from the stomach, together with changes in gut motility to cope with the large volumes of milk introduced into the gut. Changes in enzyme secretion also occur, together with modifications in the absorption of nutrients; changes in the responsiveness of the endocrine pancreas also develop, and this leads to modifications in hepatic metabolism (Gentz et al. 1971).

After the preparation of the fetal gut for post-natal feeding, the first feed is an event of considerable physiological significance, since it is the first time that the alimentary tract is challenged by the new foodstuff, milk. As indicated previously, we have shown (Aynsley-Green *et al.* 1977) that the first feed of milk in term neonates caused an immediate increase in blood glucose, implying that the first feed had been at least partly digested and absorbed. Significant increases in plasma insulin, growth hormone, gastrin and enteroglucagon also occurred, without any change in the concentrations of plasma pancreatic glucagon or of plasma gastric inhibitory peptide (GIP). These results indicate that the full-term infant is prepared for enteral feeding and within hours of birth demonstrates post-prandial changes in intermediary metabolism, together with changes in the secretion of hormones from the gut, pancreas and pituitary. It is possible that these changes may well trigger the development of the gut and its growth. We have also documented impressive differences between breast-fed and formula-fed infants on the sixth post-natal day (Lucas *et al.* 1980*b*, 1981). At this age there was a greater insulin response to the feed in formula-fed infants than in breast-fed infants, and this appears to be related to differences in GIP secretion. There are also differences in the responses of the motor hormones of the gut, with much more powerful and dramatic changes occurring in motilin and neurotensin, together with a tendency to greater growth hormone secretion. These differences may be important in the genesis of well known clinical phenomena, including the greater number of bowel actions per day seen in formula-fed infants, and the greater rate of weight gain in such infants compared with breast-fed babies. Plasma cortisol concentrations show a definite feed-related cycle on the sixth day in both breast-fed and formula-fed infants (Aynsley-Green, 1988), whilst plasma prolactin concentrations are massive in the infant compared with the adult, and, unlike adults who demonstrate post-prandial surges of prolactin, newborn full-term babies demonstrate a tendency to a post-prandial fall in concentration. It is also worth emphasizing that plasma thyroxine concentrations are high in the infant at this age compared with the adult, but not unexpectedly there is no difference between the concentrations in the breast-fed or the formula-fed group, nor is there any post-prandial increase in thyroxine in any of these babies (Aynsley-Green, 1988).

Collectively, these studies confirm the post-natal development of hormonal and metabolic responses to feeding in the infant at term, the responses being profoundly affected by the composition of the feed, differences which are evident in the case of full-term infants even as early as the first feed (Aynsley-Green *et al.* 1979).

More recently we have demonstrated (Salmenperä *et al.* 1988) that metabolic and endocrine differences still exist between infants who have been formula-fed and those exclusively breast-fed until 9 months of age.

These findings raise interesting questions concerning the effects of subtle metabolic and endocrine differences which are directly related to neonatal nutrition on long-term outcome. Is it possible, for example, that feeding responses immediately after birth could 'programme' the pattern of satiety and feeding habit and, eventually, the development of obesity and adult disease?

In contrast to the changes summarized above, which occur in full-term infants, we have published a series of papers documenting the development of post-natal circulating hormone concentrations in preterm infants (reviewed by Aynsley-Green, 1988), and conclusions from these studies are illustrated in the following paragraphs.

The first point concerns the induction of post-natal surges of peptides in infants receiving regular boluses of milk into the stomach by gavage feeding. All peptides measured demonstrate a marked increase in their preprandial circulating concentrations within 2·5 d after delivery, and these concentrations are very high when compared with

adult fasting concentrations; no similar increments are seen in infants who had never been fed enterally, and who had received only intravenous fluids during the first 6 d after birth. These findings suggest that it is food itself which, when introduced into the gut in the form of milk, is a powerful stimulus to the secretion of gut hormones (Lucas *et al.* 1978, 1983). Very small amounts of milk appear to be able to induce these surges (Lucas *et al.* 1986), raising the fascinating possibility of regarding milk to be a pharmacological agent rather than solely as a nutrient. Recent evidence suggests that the concept of 'minimal enteral feeding' may be very important indeed in maintaining the drive to post-natal gut development, and we have recommended that seriously ill infants unable to tolerate full enteral feeding should, whenever possible, receive small subnutritional quantities of milk in order to maintain the post-natal endocrine surges. That this is beneficial is supported by recent evidence (Dunn *et al.* 1988).

The second point relates to the development of cyclic post-prandial responses to milk. As stated previously, no change in the circulating concentration of any metabolite or hormone measured occurred after the first bolus feed. However, the regular provision of milk into the stomach, in the form of boluses, rapidly induces a definite cyclic response to the feed which is evident as early as 2·5 d after birth with reference to the concentrations of glucose, insulin, gastrin, secretin, motilin, neurotensin and growth hormone (Adrian *et al.* 1983; Lucas *et al.* 1980*a,c*, 1982). In infants receiving milk by continuous infusion into the stomach, a similar increase in peptides to the levels documented in preprandial blood samples in bolus-fed infants is seen, suggesting that food, no matter how it is given into the gut, triggers the secretion of peptides.

There is, however, a major difference in the endocrine milieu of the continuously fed infant compared with the bolus-fed infant, and this relates to the point discussed previously, namely the development of cyclic responses to feeding. The bolus-fed premature infant experiences major cyclic changes in hormones and metabolites that are not seen in the steady state circumstances of the continuously fed infant (Aynsley-Green *et al.* 1982).

The third point relates to the provision of different forms of milk for the premature infant. We have compared the development of preprandial hormone concentrations in two groups of healthy preterm infants who received from birth either regular feeds of human milk, or a proprietary milk formula specifically designed for the premature infant (Calvert *et al.* 1985). The results confirm the post-natal development of surges in motilin, neurotensin, GIP, enteroglucagon and pancreatic polypeptide and, for the first time, cholecystokinin. There are, however, some interesting differences between the two groups, namely, formula-fed infants have higher plasma GIP concentrations at about the second week after birth, whereas pancreatic polypeptide concentrations are higher in human milk-fed infants approximately 3 weeks after birth. The mechanism and significance of these differences are unclear, but they do suggest that not only the method of feeding, but also the composition of the feed, may influence the development of post-natal hormone concentrations of some of the peptides.

The interaction of environmental influences on the ontogeny of the gut seems to be well exemplified by the adaptation of the premature infant to post-natal feeding. It is quite clear that changes in hormone concentrations of a magnitude greater than those seen in term infants can be induced when the infant is born up to 3 months 'too soon' in biological terms. It is important to emphasize that both preterm infants and, to a lesser extent, the infant at term, have concentrations of peptides in response to feeding that are considerably above those seen in the adult. It is possible that this could relate to deficient plasma clearance mechanisms in the immature infant or, alternatively, result from the relatively large endocrine cell mass of the developing gut. A further possibility relates to

the fact that preterm and formula-fed infants have a feeding regimen imposed on them, so that within a few days of birth very large quantities of milk are introduced into their guts. Whatever the mechanism may be of the differences in absolute levels, it is possible that high concentrations of hormones and regulatory peptides are needed in both preterm and term neonates to induce receptor activity and hence their functional effects in target tissues.

The stimulation of post-natal endocrine surges in both preterm and term infants leads to the temptation to speculate that it is they which are involved in the physiological adaptive changes associated with the commencement of feeding after birth. Thus, it is possible that motilin and neurotensin stimulate changes in gastrointestinal motility; gastrin, enteroglucagon and cholecystokinin might, perhaps, have important roles in regulating the post-natal growth of the gut mucosa and the pancreas. GIP could be an important stimulus to insulin secretion, and could mediate changes in the entero-insular axis; pancreatic polypeptide may be involved in the development of gall bladder contractility and pancreatic exocrine secretion.

It is also worth emphasizing that the 'classical' hormones such as cortisol and thyroxine may well have essential roles in the adaptive process, more particularly since cortisol has been shown to influence the development of gut enzyme activity, whilst thyroxine may have a key role in regulating the development of insulin receptors on liver cell membranes.

What are the practical recommendations which arise from our results?

Our findings indicate that the method of administering feeds and the composition of feeds affect profoundly the endocrine milieu of the preterm infant. It is not possible to state from these findings whether one method or composition is to be preferred or recommended, and further work is needed to investigate the potential consequences. However, our findings question more severely the current policy of feeding routinely small premature infants entirely by the intravenous route. These infants are deprived not only of enteral milk, but also of the amniotic fluid they should be swallowing *in utero*. As indicated previously, we have postulated that 'minimal enteral feeding' may be beneficial in small infants who are unable to tolerate full volumes of enteral milk by helping to promote gut development and growth.

It is clear that much further work is needed to determine the control of the development of regulatory peptides and their functional significance *in utero* as well as in the immediate post-natal period. However, new insights into nutritional management can be obtained from the study of metabolic and endocrine relations, and it is suggested that the nutritional management of different groups of newborn infants might be improved by further studies on the somatic effects of the hormonal surges which have been documented. Similar studies might also throw further light on the aetiology of a wide variety of disorders which interfere with normal adaptation to post-natal nutrition, and it is not beyond the bounds of possibility that hormones themselves might be administered therapeutically to affect facets of gut adaptation. We have already demonstrated that motilin administration might be helpful in some children who develop pseudo-obstructive ileus (Aynsley-Green, 1984).

Nutritional implications of the metabolic and endocrine stress response to anaesthesia and surgery

During the last 20 years major advances have occurred in the intensive care of seriously ill newborn infants requiring surgery, and this had led to more preterm and more critically ill infants being subjected to major stress. Despite this, however, much of the currently accepted management in terms of anaesthesia and analgesia has evolved by

a process of empiricism rather than being based on scientific observations of the ability of infants to respond to surgical stress. Indeed, the need for anaesthesia at all has been questioned, and it is known that large numbers of seriously ill neonates are subjected to major surgery under anaesthesia which would be judged to be grossly inadequate by adult standards (Anand & Aynsley-Green, 1985; Anand et al. 1985a,b).

Until recently, the stress response of neonates to surgical trauma has not been studied in depth, despite the fact that the concept of a catabolic stress reaction assumes much greater significance in this age group. The normal baby exists in a precarious metabolic state as it adapts to the post-natal environment and to post-natal nutrition. Its body reserves of fat, protein and carbohydrate are limited at a time when it also has to meet the metabolic cost of rapid growth and organ maturation. From all this it would seem to be particularly disadvantageous, if not life threatening, for a seriously ill infant, particularly when born prematurely, to experience a severe and prolonged catabolic reaction to surgery.

In a recent series of papers we have documented that the human newborn infant is capable of mounting a very substantial catabolic stress response characterized by increases in the secretion of catecholamines, growth hormone and cortisol, and by the inhibition of insulin secretion. The metabolic consequences of the change in endocrine milieu result in hyperglycaemia and hyperlactacidaemia, with changes in plasma amino acid concentrations and in urinary 3-methyl histidine excretion indicating substantial protein breakdown.

In randomized controlled trials we have also shown that the magnitude of this stress response can be obtunded substantially by the administration of powerful opiate or inhalation anaesthetics. Documentary evidence was also provided to suggest that the clinical course post-operatively was much more stable in infants subjected to effective anaesthesia (Anand et al. 1987, 1988; Anand & Aynsley-Green, 1988).

These studies have raised important questions concerning the perception of pain by human newborn babies. There is a widely held belief amongst paediatric staff, including paediatric anaesthetists, that newborn infants do not feel pain (Anand & Aynsley-Green, 1985). Anand & Hickey (1987) have reviewed comprehensively the reasons why there is sound physiological evidence to suggest that all the pathways involved in the recognition and perception of pain are present by the middle of the second trimester of pregnancy. Our metabolic and endocrine findings support these observations, and we suggest that there are important practical applications of these findings.

First, although our studies were performed on the surgical neonate, it is well known that painful experiences are likely to be inflicted on infants receiving medical intensive care. Should not paediatric staff be much more concerned about the 'comfort' and relief of pain in all neonates? Without effective analgesia to decrease the catabolic drive it is unlikely that nutritional management will be effective. The diversion of precious calories to extra energy expenditure as a result of inadequate analgesia may lead to a decrease in somatic and cerebral brain growth.

Second, it is relevant to recognize that apparently innocuous nutritional management may have unforeseen consequences. This is well illustrated in our observation that infants subjected to surgery, with total parenteral nutrition being administered up to the moment of induction of anaesthesia, have a significantly greater hyperglycaemic response to the stress of anaesthesia than do infants not receiving intravenous amino acids. It is likely that the administration of amino acids leads to glucagon secretion which is further enhanced by anaesthesia (Anand & Aynsley-Green, 1985).

It is evident that much research still needs to be performed on the nutritional

management of infants and children experiencing painful or stressful circumstances in order to provide the optimum anabolic milieu.

Conspectus

This brief review indicates the value of examining metabolic and endocrine inter-relations in newborn infants, not only in order to obtain insights into the control of the process of adaptation to post-natal nutrition, but also to recognize that some aspects of current dogma may be based on an inadequate foundation. This aspect is best illustrated by current teaching in the context of hypoglycaemia in the newborn period. It is also clear that the metabolic and endocrine milieu of newborn infants is profoundly influenced by the mode of nutrition, the composition of the feeds and by the route of administration; additional influences arise as a result of the hitherto empirical approach to the management of pain, and these create further difficulties which have potentially important nutritional consequences.

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