

important in those centres that provide services outside the National Health Service as some of these higher multiple births will require intensive care in inadequately funded health service cots. Perhaps a start could be made if there were agreement that an insurance policy should be taken out by those involved in these forms of treatment to cover the cost of neonatal intensive care should this be required as the result of a higher multiple birth.

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Development of intestinal motility

Normal intestinal motility is essential for the orderly movement of nutrients from one specialised part of the gastrointestinal tract to the next. Disturbances will result in abdominal distension and vomiting when the transit of luminal contents slows down, and in diarrhoea when it speeds up. Under both circumstances the normal digestion and absorption of nutrients and the excretion of waste products will be compromised. In preterm infants, immature intestinal motility is one of the main causes of the 'physiological ileus' that often occurs.¹

Control of intestinal motility

Patterns of normal intestinal motor activity have been described for most sections of the gastrointestinal tract and it is clear that a hierarchy of controls is responsible for determining the contractile behaviour of the gut.² At the lowest level the smooth muscle cells exhibit spontaneous rhythmic electrical activity which determines the timing and frequency of contractile activity. This is further modulated by the action of the enteric nervous system and by the influences of a range of humoral substances that are loosely referred to as 'gut hormones'. The enteric nervous system is essential for the coordination of motor activity, while the gut hormones modulate the tone and excitability of the smooth muscle cells. The sympathetic and parasympathetic limbs of the autonomic nervous system link the enteric nervous system to the nuclei of the brain stem and to higher levels within the central nervous system. The enteric nervous system is complex, containing a similar number of neurones to the spinal cord, and although central connections exist one should think of the enteric nervous system as an autonomous unit that is modulated rather than controlled by the central nervous system.

The cells that ultimately form the enteric nerves migrate from the neural crest during the first trimester, and after colonisation of the gut they undergo a prolonged period of maturation that is in part determined by the microenvironment in which they find themselves.³ Evidence from animal

studies suggests that these enteric neurones remain 'plastic' and open to environmental influences until a relatively late stage in their development.⁴ Histological and ultrastructural studies show the presence of enteric nerves and smooth muscle cells within the wall of the human intestine during the second trimester, and by 22 weeks' gestation the small intestine is 'histologically mature'.⁵ From clinical experience, however, we know that the intestines of preterm infants are often intolerant of enteral feeds, indicating that immaturity in the development of motor control is often a limiting factor in our ability to feed by the enteral route.¹ Our present understanding of the development of these controls is outlined below.

Sucking and swallowing

The actions of sucking and swallowing a feed rely on the integration of control between a larger number of cranial nerve nuclei and are clearly dependent on the maturation of brain stem function. Swallowing has been observed in utero as early as 16 weeks' gestation and from studies using red blood cells tagged with ⁵¹Cr injected into the amniotic fluid we know that the volume of fluid swallowed increases from 13 ml/day at 20 weeks to 450 ml/day at full term.⁶ It must be remembered, however, that the fetus is immersed in a bath of amniotic fluid and does not have to coordinate swallowing with either sucking or the protection of the airway. In preterm infants sucking movements are generally feeble but by 34-35 weeks' gestation a mature nutritive sucking pattern has developed.^{7 8}

Gryboski was the first to outline the normal patterns of oesophageal motility in both term and preterm infants.⁹ In adults a swallow initiates relaxation of the upper oesophageal sphincter so that food can be carried along the length of the oesophagus by a primary peristaltic wave to the lower sphincter, which then relaxes to allow its passage into the stomach.¹⁰ While this pattern is present in full term infants who suck effectively, the motility of the oesophageal body in preterm infants is characterised by poorly propagated, low

pressure biphasic contractions.⁹ These will be inefficient at clearing refluxing fluids from the oesophagus and are in many ways similar to the disordered activity that is commonly seen in children with cerebral palsy.¹¹

The lower oesophageal sphincter has an important role in preventing the regurgitation of fluid from the stomach and in preterm infants the pressure gradient between the fundus of the stomach and the lower oesophagus is reduced. With increasing maturity this pressure gradually rises as a result of the increased contractile activity of the intrinsic smooth muscle of the sphincter and the extrinsic diaphragmatic muscle, and of the increasing length of the intra-abdominal oesophagus.¹² In small preterm infants chronic respiratory disease that leads to increases in intra-abdominal pressure, and drugs such as theophylline that lower sphincter pressure,¹³ will conspire to increase greatly the risks of reflux and aspiration. The apparent late development of nutritive sucking acts to protect the oropharynx and oesophagus at a time when controls may not have adequately developed to cope with the passage of fluids.

The stomach

In clinical practice it is easy to bypass the mouth and oesophagus and to deliver milk directly into the stomach through a nasogastric tube. It is, however, clear that the emptying of liquids from the stomach is not normal in preterm infants and feeds often have to be delivered directly into the jejunum before they will be tolerated. No systematic study of the ontogeny of gastric emptying has been carried out but in preterm infants (as in adults) the gastric emptying of liquids decreases as the energy density of the feed increases.¹⁴ This explains why infants may tolerate a half strength feed while a full formula feed results in gastric stasis, abdominal distention, and vomiting. It seems likely that in the immature gut this inhibitory feedback, which is mediated by both neural and humoral mechanisms, is set at a level of increased sensitivity. Manometric studies have shown that the pressures generated by spontaneous contractile activity in the gastric antrum increase with increasing gestational age,¹⁵ and results of interventional studies have suggested that non-nutritive sucking may increase enteral food tolerance, presumably through a vagally mediated reflex.¹⁶

The small intestine

The small intestine has clearly defined cyclical patterns of contractile activity when fasting,¹⁷ which in older children or adults are completely disrupted after a meal when they are replaced by more random mixing activity. Studies using implanted electromyographic electrodes to record small intestinal contractile activity in utero in fetal lambs have shown that, at a time equivalent to 28 weeks' gestation in humans, activity is random and of low amplitude with the progressive development of more organised propagative activity during subsequent weeks, until at full term a mature cyclical pattern has developed.¹⁸ In human preterm infants an identical developmental progression of fasting activity has been shown to occur with manometric recording.¹⁵ This preprogrammed pattern of development, which is almost certainly dependent on the maturation of neural connections within the enteric and central nervous system, has also been seen in cows and dogs. In dogs, which are neurologically immature at birth, fasting small intestinal motility is less well developed than in the more mature sheep, cows, or humans.¹⁹ These links between small intestinal motility and the integrity of the central nervous system are further supported by the observations that birth asphyxia and hydrocephalus reduce the rate of duodenal contrac-

tile activity in human preterm infants and by the similar cycle times during fasting motor activity and rapid eye movement sleep.²⁰

The motor response of the small intestine to food is not only a function of the volume and nutritional density of the food, but is also determined by the sensitivity of the gut to these stimuli. In preterm infants the length of time that the gut is exposed to food is an important determinant factor, implying that the humorally mediated postprandial motor response is upregulated by previous luminal nutrition.²¹ The idea that early feeding is beneficial to intestinal function is not new and gut hormone concentrations²² and brush border digestive function²³ are potentiated by luminal nutrients.

The colon

Little is known about the development of the motility of the colon in humans. The colon probably plays little part in the circulation of swallowed amniotic fluid. In utero, and for most newborns their first bowel motion occurs either during or within 48 hours of birth. In preterm infants slowing of colonic motility may result in constipation and this may lead by enteroenteral reflexes to delays in gastric emptying. Anecdotal observations have suggested that glycerine suppositories may indirectly increase enteral food tolerance by promoting rectal evacuation.

Conclusions

The development of motor activity at all levels within the gastrointestinal tract is broadly similar. After migrating from the neural crest to their final destination in the wall of the intestine, the cells that form the enteric nervous system undergo many months of maturation. Disruption of this migration or alterations to the environment of these cells may lead to loss of function with the development of motility disorders such as intestinal pseudo-obstruction or Hirschsprung's disease. In preterm infants this maturation is incomplete, and noxious stimuli such as sepsis or acidosis may disrupt the immature motor controls and lead to reduced contractile activity and intolerance of feeds. In addition to the development of intrinsic controls, the central nervous system and the circulating gut hormones have important roles in modulating intestinal motor activity. It is the integrity and normal development of these controls that is required before young infants are able to tolerate a full oral nutrient intake safely.

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