Metabolic and endocrine interrelations in the human fetus and neonate

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The efficient utilization of food in the human adult depends upon the integration of the functions of several physiological systems. Thus, food has to be propelled through the gut, and this requires coordination of gut motor activities to ensure the orderly transit of the foodstuffs through the different regions of the alimentary tract. The passage of food leads to local trauma, necessitating a continuous process of regeneration of the gut mucosa. Digestive secretions have to be introduced into the gut lumen at the appropriate times, and coordinated with this is redistribution of intestinal blood flow to carry the products of digestion and absorption through the visceral and systemic circulations. The influx of nutrients leads to changes in metabolic hormone secretion to ensure postprandial metabolic homeostasis, and this in turn has to be integrated with other adaptive metabolic changes as the individual enters into the interprandial starvation period.

It is obvious that the integration and coordination of these different aspects requires a complex regulatory system, and it is equally obvious that many factors are likely to be involved. However, recent evidence has accumulated to suggest that the secretion of hormones and regulatory peptides from peptide-producing cells in the gut and pancreas as well as from the pituitary, thyroid and adrenal glands (1-3), has a key role to play in this process.

Until the early 1960’s it was taught that the gastrointestinal endocrine system secreted only three hormones, namely, secretin, gastrin, and cholecystokinin-pancreozymin. Secretin was the first hormone to be described by Bayliss and Starling in 1902, and their hypothesis that it had a key role in the regulation of pancreatic exocrine secretion has been well substantiated since then. Despite the fact that gastrin and cholecystokinin had been identified as early as 1906 and 1928 respectively, relatively little progress was made in the field of gastrointestinal endocrinology for the next 40 years, largely because of methodological difficulties in the identification and characterization of peptides produced from cells dispersed throughout the gastrointestinal tract. However, during the last 10 years or so there has been an explosion of knowledge on the manufacture, secretion and regulation of peptides secreted by the gut, and it is clear that all of the aspects of utilization of food reviewed above can be influenced by these substances. Table 1 shows some of the peptides and their principal actions, together with hormones from the pancreas, pituitary, adrenal and thyroid gland which are involved in the regulation of food utilization.

There is an immediate problem with terminology since the peptides exert their effects in at least three different ways. Some substances act as true circulating hormones, and this is exemplified best by the “classical” hormones—glucagon, insulin, growth hormone, cortisol and thyroxine. However, some gut peptides are also secreted into the blood stream and act on the target tissue distally. The anatomical localization of the cells secreting these hormones in the adult is shown in Figure 1. Other peptides, for example somatostatin, act as paracrine substances, which means that the peptide-secreting cell acts locally to influence the activity of surrounding cells. Thus, Larsson (1), has shown that the somatostatin cell appears to have long cell processes which extend to influence cells some distance from the main body of the cell manufacturing the peptide. Finally, other peptides, for example, VIP, act as neurocrine substances—in other words act as

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neurotransmitters, the peptides being produced by nerve endings (1). For these reasons it is better to refer to the products of these groups of peptide-producing cells collectively as “regulatory peptides.”

**TABLE 1**
Regulatory peptides and hormones involved in food utilization

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrin</td>
<td>Gastric acid secretion, growth of the gut</td>
</tr>
<tr>
<td>Secretin</td>
<td>Pancreatic exocrine secretion</td>
</tr>
<tr>
<td>Cholecystokinin</td>
<td>Gall bladder contractility</td>
</tr>
<tr>
<td>GIP</td>
<td>Modulation of insulin secretion</td>
</tr>
<tr>
<td>VIP</td>
<td>Intestinal secretions; blood flow</td>
</tr>
<tr>
<td>Motilin</td>
<td>Intestinal tract and Gastric motility</td>
</tr>
<tr>
<td>Neurotensin</td>
<td>Glucose homeostasis</td>
</tr>
<tr>
<td>Enteroglucagon</td>
<td>Gut growth, gut transit time</td>
</tr>
<tr>
<td>Glucagon</td>
<td>Pancreatic growth, exocrine function, intestinal absorption</td>
</tr>
<tr>
<td>Insulin</td>
<td>Insular hormone release; intestinal absorption</td>
</tr>
<tr>
<td>Pancreatic Polypeptide</td>
<td>Pancreatic growth, exocrine function, intestinal absorption</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>Insular hormone release; intestinal absorption</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>Fuel utilization</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Gut enzyme activity</td>
</tr>
<tr>
<td>Thyroxine, T3</td>
<td>Gut development; hormone receptor activity; metabolic rate</td>
</tr>
</tbody>
</table>

![FIG 1. Anatomical localization in the adult of cells secreting gut hormones.](image)

![FIG 2. Hypothesis to explain regulation of postnatal nutritional adaptation.](image)

Enteral Feeding

- Gut Hormone Secretion
- which induces
  - Gut Growth
  - Mucosal Development and Intestinal Secretions
  - Gut Motility
  - Development of the Entero-Insular Axis

and influences

Pancreatic Endocrine Function and Hepatic Metabolism
Maternal and fetal plasma glucose concentrations (n=19, mean ± SEM)

Maternal Fetal

p < 0.001

FIG 3. Concentrations of blood glucose in human maternal and fetal circulations at 18-21 weeks of gestation.

the measurement of circulating and local concentrations of the peptides, and on their physiological and pharmacological affects. Recent reviews are to be found relating to studies in the human adult and in the experimental animal (4, 5, 6). Whilst measurement of circulating levels of peptides may not reflect accurately events occurring within the gut mucosa, it is a useful starting point in attempting to determine the role of the individual peptides.

In order to appreciate the potential and unique importance of regulatory peptides and hormones in the human neonate, it is necessary to consider first the changes which occur after the umbilical cord is cut at birth. With this act, the fetus, hitherto dependent upon its mother, is transformed into a free living individual child. Important changes in the structure and function of several physiological systems have to occur immediately after birth to enable the infant to adapt to its new circumstance. Some of these changes, for instance those of the cardiovascular and respiratory systems, can be detected with the naked eye. Other changes, however, which are of equal significance for the survival of the infant, occur unseen, and these relate to changes in the endocrine system and in intermediary metabolism as well as in gut function.

Concentrations of blood lactate and pyruvate in maternal vein (MV), umbilical vein (UV) and umbilical artery (UA) (n=10, mean ± SEM, *p<0.05 MV versus UV and MV versus UA)

Total blood ketone body concentrations in maternal vein (MV), umbilical vein (UV) and umbilical artery (UA) (n=10, mean ± SEM, *p<0.05 MV versus UV and MV versus UA)

FIG 4. Concentrations of a) blood lactate and pyruvate and b) total ketone bodies in human maternal vein (MV) fetal umbilical vein (UV) and umbilical artery (UA) at fetoscopy at 18-21 weeks gestation.
In utero, the fetus exists in a comfortable environment receiving a continuous intravenous supply of nutrients across the placenta, with maternal metabolism primarily controlling the supply of substrates. Once the umbilical cord is cut, the infant is confronted with a number of important challenges, the most immediate being the need to regulate the blood glucose concentration. Changes in the endocrine pancreas lead to a postnatal surge of glucagon (7) and this causes an immediate release of glucose from stored glycogen, as well as influencing the enzymes involved in gluconeogenesis. However, the body reserves of stored nutrients are limited, and the infant must adapt to a totally new form of nutrition—namely, enteral feeding with milk—in order to survive. The fact that the healthy infant born at term seems to adapt through this transition period without any apparent difficulty suggests that the gut and its regulatory mechanisms involved in the utilization of food are prepared for postnatal feeding before birth. The observation that prematurely born infants can also adapt satisfactorily to enteral feeding, suggests further that postnatal adaptation can be induced by environmental factors up to three months “too soon” in biological terms.

Some aspects of the development of the fetal intestine have been reviewed recently (8, 9), and there are also a number of excellent studies documenting histological and functional changes in the gut in postnatal experimental animals as well as in man (8, 10). From these studies, it has been shown that changes occur within days of birth in the secretion of acid from the stomach (11), together with the changes in gut motility which are necessary to accommodate the large volumes of milk which are introduced into the gut. Changes in enzyme secretion also occur (9), together with modification of the absorption of nutrients (12). Changes in
the responsiveness of the endocrine pancreas develop (13), and this lends to modifications in hepatic metabolism.

It is likely that several factors are involved in determining these changes, such factors including hormones and growth stimulating peptides in human milk, direct stimulation of mucosal development by the presence of food in the gut, and changes induced by alteration of intestinal secretions and bacterial colonization. However, we have suggested that the secretion of peptides has a key influence in regulating the postnatal adaptation to enteral feeding. Our hypothesis, constructed some 10 years ago, is illustrated in Figure 2.

In order to investigate this hypothesis, we measured, through an extensive collaborative project with Professor SR Bloom and others, the circulating concentrations of 18 hormones, 17 amino acids and 6 metabolic fuels in different groups of human infants ranging from the fetus at 18–21 weeks of gestation, through to the infant at 9 months after birth. The following sections are intended as a brief review of some of our more important studies and conclusions, together with a survey of studies by others where appropriate.

Buchan, et al (14), have documented the appearance of gut regulatory peptides in the human fetal intestine as early as 8–10 weeks after conception, and have also emphasized the changing molecular form of the peptides with advancing gestation. These observations, with further data from Larsson, et al, who have shown the appearance and disappearance of certain regulatory peptides in different regions of the gut during development (15), lead to the suggestion that these peptides may have a key role as local inducing agents regulating the growth and functional development of the fetal intestine.

Most of the data relating to measurements of circulating concentrations of fuels and a limited number of hormones in the fetus and mother have been derived from studies with experimental animals, and there are few data on these variables in the human situation. The limited information on the human fetus that is available has been derived primarily from either the cord blood of term and preterm infants at delivery, or at termination of pregnancy by hysterotomy (16, 17). We performed recently a study in collaboration with Mr IZ MacKenzie, in which, with ethical approval, maternal blood samples, umbilical artery, and umbilical vein samples together with aliquots of amniotic fluid were withdrawn at fetoscopy prior to termination of pregnancy for social reasons at 18–21 weeks of gestation, the mothers being conscious, although sedated (18, 19, 20).

Figure 3 shows the concentrations of blood glucose in the maternal vein and fetal vessel, and this confirms previous studies showing a materno-fetal gradient for this substrate. An impressive materno-fetal gradient also exists for the concentrations of ketone bodies, but not for lactate or pyruvate (Fig 4). Of greater interest, however, from the point of view of development of the endocrine pancreas, are the differences in maternal and fetal amino
Maternal, fetal and amniotic fluid concentrations (mean ± sem) of Glucagon and Enteroglucagon

FIG 7. Concentrations of pancreatic glucagon and enteroglucagon in human maternal venous plasma (M) and in fetal umbilical vein (FV) and artery (FA) as well as in amniotic fluid (Am) at 18–21 weeks gestation.

Concentrations of 17 amino acids, in the maternal vein and umbilical vein, and it can be seen that there is a consistently higher concentration of all amino acids in the fetal circulation than in the mother. It should be noted in particular that the concentrations of insulinogenic amino acids, namely, alanine, arginine, and leucine are all substantially higher in the fetus. Despite this, however, the fetal concentrations of insulin are not increased (Fig 6).

Figure 7 shows the concentrations of glucagon and enteroglucagon in the maternal and fetal circulations as well as in amniotic fluid. There is no significant difference between the maternal and fetal concentrations of glucagon, although the amniotic fluid concentration is significantly lower than in the latter. Of greater interest, however, are the concentrations of enteroglucagon, since fetal levels of this hormone are markedly higher compared with the mother (undetectable concentrations are found in the amniotic fluid). Figure 8 shows the concentrations of gastrin, gastric inhibitory polypeptide and pancreatic polypeptide from these sampling sites. Gastrin concentrations are much higher in the maternal circulation than in the fetal circulation, as are the concentrations of pancreatic polypeptide. However, fetal concentrations of GIP are higher than those in the maternal circulation; the highest levels of this peptide are found in amniotic fluid.

This study shows for the first time the interrelation of a wide variety of hormones and metabolites in the fetal and maternal circulation at this stage of human gestation, and the observations raise several interesting questions. First, why are some hormones
present in lower concentrations in the fetus than in the mother, whereas others are present in higher concentrations? What is the significance of the very high amniotic concentration of GIP, and the absent concentration of enteroglucagon? From where do amniotic concentrations arise? Are the molecular forms of the hormones similar in mother, amniotic fluid, and fetus? It is known that the fetus swallows and can utilize the constituents of amniotic fluid (21) and, moreover, amniotic fluid is in continuous circulation with the fetal lung. Could these peptides have an important role to play as local inducing agents in the development of the fetal lung as well as the alimentary tract? Answers to these questions await further elucidation. Nonetheless whatever the precise significance of these particular observations, it is now evident that study of the ontogeny and control of the fetal secretion of hormones and regulatory peptides may well throw further light on the orderly sequence of development of the lung and gut, and may provide further insight into pathological development.

After preparation of the fetal gut for postnatal feeding, an important physiological event which occurs after birth is the first feed of milk. This seemed to us to be an event of considerable physiological significance, since it is the first time that the fetal alimentary tract is challenged by the new foodstuff. Six years ago we performed a study to investigate the metabolic and endocrine consequences of the very first feed in a group of term infants given human milk into the stomach at 4–6 hours of age by nasogastric tube (22).

This study showed that there was an immediate increase in blood glucose, implying that the first feed had been at least partially digested and absorbed. The rise in glucose
including sympathetic activity and the effect of counter-regulatory hormones consequent to the stress of delivery, and not necessarily due to the presence of food in the gut. It will be important to perform studies using stable isotopes to determine the origin of the increasing blood glucose level. Nonetheless, the increase in blood glucose was accompanied by a significant increase in plasma insulin, and this suggests that the latter is directly related to the former.

We also documented a significant change in plasma growth hormone and gastrin, together with entero-glucagon after the first feed, but interestingly, no change was evident in plasma pancreatic glucagon (22). Similarly, no change occurred in plasma GIP, and this could be of protective importance. Thus, in a study in which we gave ourselves the same volume of milk per kg bodyweight, we determined a higher insulin concentration after the feed than in the infant, and it is tempting to speculate that this could be related to differences in GIP secretion. Clearly, it would be disadvantageous for the neonate to experience an insulin surge after a feed at a time of glucose instability during the first hours after birth.

We concluded from this study that the infant born at term is prepared for enteral feeding and that within hours of birth demonstrable postprandial changes occur in intermediary metabolism together with changes in the secretion of hormones from the gut, pancreas and pituitary.

In contrast to the impressive changes in variables measured in the term infant, when we repeated the same study in infants born prematurely it was found that no change occurred after the first feed in the concentration of any metabolite or hormone that was

**TABLE 2**
Methods of feeding the preterm infant

<table>
<thead>
<tr>
<th>Method</th>
<th>Formulation</th>
<th>‘bolus’ or continuous infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Enteral—</td>
<td>by: Nasogastric tube</td>
<td></td>
</tr>
<tr>
<td></td>
<td>with: Human milk—‘drip’ or ‘expressed’</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Milk formula</td>
<td></td>
</tr>
<tr>
<td>b) Parenteral—</td>
<td>Total or supplementary</td>
<td>amino acids, fat, glucose</td>
</tr>
<tr>
<td></td>
<td>Continuous</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyclical</td>
<td></td>
</tr>
</tbody>
</table>
METABOLIC AND ENDOCRINE INTERRELATIONS

Blood glucose, plasma insulin and GIP concentrations after feeding in preterm infants
(n = 8-12 infants for each time period; mean ± SEM)

FIG 10. Development of effect of a milk feed on blood glucose plasma insulin and GIP concentrations in preterm infants during the first 24 postnatal days.

measured (23). This implies that developmental changes occur during the last few weeks of gestation, which prepare the infant born at term to respond immediately.

We have now published a series of papers documenting the development of postnatal hormone concentrations in preterm infants (24), and I would like to illustrate the main conclusions from these studies in the following paragraphs.

The first point relates to postnatal changes in the profile of circulating hormone concentrations. There is, however, an immediate potential problem in trying to interpret any results from studies in premature infants, and this is due to the different methods of feeding which are currently employed in newborn nurseries. Table 2 outlines some of the different approaches to the nutrition of such infants and it can be seen from this that preterm infants are given routinely milks of widely differing composition, either into the stomach or through the pylorus into the jejunum. The milk may be given by regular boluses, with differing volumes and time intervals, or alternatively as a continuous infusion by means of a syringe pump. In some nurseries premature infants receive routinely intravenous alimentation for several days after birth, before being introduced to enteral milk. It might be concluded from a consideration of the different methods currently in vogue, that each of them could affect profoundly the development of postnatal hormone secretion.

Figure 9 shows the development of hormone profiles in healthy preterm infants who have received full volumes of human milk
from birth, the feeds given by regular boluses into the stomach. This Figure shows the development of hormone concentrations in preprandial blood samples—in other words, samples drawn immediately before feeds—at different ages ranging from 2.5 days after birth to 24 days after birth. These concentrations are related to the levels detected in cord blood. It can be seen that all six hormones demonstrate a marked increase in their circulating concentrations within 2.5 days after delivery, and that these concentrations are extremely high when compared to the adult fasting concentrations. In the same Figure can be seen data from a group of infants who had never been fed enterally, and who had received only intravenous fluids during the first six days after birth. With the exception of the change in pancreatic polypeptide, none of the other five hormones increases in concentration after birth. These data suggest that food introduced into the gut in the form of milk is a powerful stimulus to the secretion of gut hormones, and that these changes do not occur in infants who have never been fed (25).

The second point relates to the development of postprandial responses to milk. As
Postnatal concentrations of gut hormones in breast and formula fed preterm infants

FIG 13. Preprandial hormone concentrations in preterm infants receiving human milk or milk formula from birth.

stated above, no change in the circulating concentration of any metabolic or hormone measured occurred after the first bolus feed. However, Figure 10 shows changes in plasma GIP, insulin and blood glucose concentrations after feeds during the first 24 days after birth. The regular provision of milk into the stomach, in the form of boluses, rapidly induces a definite cyclical response to the feed which is evident by 2.5 days after birth in the concentrations of glucose and insulin. Thus the ability to develop feed-related cycles can be induced before term by the environmental trigger of regular bolus feeding. Moreover, a change in the pattern of responsiveness occurs during the first three weeks after birth with
a tendency to an earlier peak in glucose, perhaps related to greater efficiency of absorption of lactose; interestingly, there is also a greater insulin response. From the change in the pattern of plasma GIP levels it is tempting to suggest that it is this which induces changes in insulin responsiveness.

Cyclical feed responses are also evident for plasma gastrin, secretin, motilin, neurotensin and growth hormone (24, 26).

Figure 11 shows, for comparison, changes in hormones in two groups of similar healthy infants who had been given the same volumes of milk from birth either by regular boluses or by continuous infusion into the stomach (27). The hormone concentration shown in the Figure from the bolus-fed group are similar to the levels documented in preprandial blood samples in bolus-fed infants. Thus it can be seen that both methods of feeding induce hormone surges, implying 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 above, namely, the development of cyclical responses to feeding. Figure 12 shows for comparison the changes in plasma insulin concentrations after birth in preprandial samples from bolus-fed infants as well as from continuously fed infants; superimposed on the Figure are shown schematically the magnitude of the insulin responses to a bolus feed at different ages. It can be seen from this that the bolus-fed premature infant is experiencing major cyclical changes in hormones and metabolites that are not seen in the steady state circumstances of the continuously fed infant.

The third point relates to the provision of different forms of milk in the premature infant. We recently performed a study in which we compared the development of preprandial hormone concentrations in two groups of healthy preterm infants who received from birth either regular boluses of human milk, or a proprietary milk formula specifically designed for the premature infant (28). The major difference between this study and those discussed above relates to the fact that the data from the former are derived longituudinally, in that blood samples were drawn from the same infant throughout the study period.

Figure 13 shows the development of these concentrations in preprandial blood samples drawn from the two groups of infants. These results confirm the postnatal development of surges in molitin, 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 around the second week after birth, whereas pancreatic polypeptide concentrations are higher in human milk-fed infants around 3 weeks after birth. The mechanism and significance of these differences are unclear, but it does suggest that not only the method of feeding but also the composition of the feed may influence the development of postnatal hormone concentrations for some of the peptides.

Turning now to the normal infant born at term, the same considerations as those listed above in the context of the preterm infants...
can be discussed. We have shown, as in the preterm infant, that demonstrable surges in preprandial hormone concentrations can be detected after birth for most hormones we have studied (24) as indicated in Figure 14. However, it is of interest that the magnitude of the increase is rather less in the term infant than in the preterm infant.

In connection with the postnatal development of responses to feeds, in term infants we have documented impressive differences between the breast-fed and formula-fed infant on the sixth postnatal day (29, 30), as exemplified in Figure 15 where it can be seen that there is a greater insulin response to the feed at this age in formula-fed infants than in the breast-fed infants, and this appears to be related to differences in GIP secretion (31). There are also differences in the responses of the motor hormones of the gut, motilin and neurotensin, (29) together with a tendency to greater growth hormone secretion (26).

Plasma cortisol concentrations after feeding in breast fed and formula fed infants on day 6

- Breast fed
- Formula fed

\* p < 0.01
\*\* p < 0.05

Plasma prolactin concentrations after feeding in breast fed and formula fed infants on day 6 (mean ± SEM)

FIG 17. Effect of a feed on plasma prolactin concentrations (±SEM) in 6 day old term infants who were breast fed (C) or fed on a cow milk formula (Δ). Cross sectional data from 105 infants, each contributing only one blood sample.

Plasma cortisol concentrations show a definite feed-related cycle on the sixth day in both breast-fed and formula-fed infants (Fig 16). This study showed for the first time that the human infant appears to have regular feed-related cycles of cortisol much earlier than had been expected on the basis of the development of diurnal patterns similar to the adult.

Plasma prolactin concentrations are massive in the infant compared with the adult (Fig 17); and, unlike adults who demonstrate postprandial surges of prolactin (32), there is a tendency to a postprandial fall in the infant.

It is also worth remembering that plasma thyroxine concentrations are very high in the infant at this age compared with the adult. But not unexpectedly, there is no difference either in the breast-fed or the formula-fed group, nor is there any postprandial increase in these babies (24).

Collectively, these studies confirm the postnatal development of hormonal and
metabolic responses to feeding in the infant at term. As in the preterm infant, the composition of the feed affects the response, and this in the case of the full term infant can be detected even as early as the first feed (33).

It is of interest to consider when the differences between the breast-fed and bottle-fed infants disappear. Preliminary results from a collaborative study with Dr Perheentupa in Helsinki, show that by the age of 9 months, infants exclusively breast fed from birth have a similar glucose and insulin response to those who have received formula during the same period (Fig 18).

What is the physiological significance of the data obtained from our studies? The factors regulating the ontogeny of the intestinal tract have been reviewed recently (8, 9). Many are known to be involved in this process, including the genetic endowment, the existence of a "biological clock" regulating developmental chronology, as well as other endogenous mechanisms and environmental influences. The expression of the genetic endowment at various stages of fetal gastrointestinal development is accomplished by way of regulatory mechanisms, and although most of these mechanisms have been studied in experimental animals, there is evidence that parallelism exists for the human fetus.

There is good evidence that the fetal hypothalamic-hypophysial-thyroid adrenal axis plays a major role (9). The more recent demonstration that regulatory peptides can be demonstrated from an early stage of gestation in the fetus, together with evidence of migrating cell population and changes in hormonal product, raise important questions as to the role of these substances in local and general gastrointestinal development. Our new data showing differences in profile of circulating and amniotic fluid concentrations of regulatory peptides in the mother and fetus at 18–21 weeks of gestation support the thesis that they may be of importance in the development of the fetal gut as well as, possibly, the lung. This represents an interesting area for further exploitation and research.

The interaction of environmental influences on the ontogeny of the gut seems to be well exemplified by the adaptation of the premature infant to postnatal feeding. We have speculated in a number of publications that postnatal surges could well be of importance in the adaptation of the normal infant born at term (24), but it is quite clear that changes in hormone concentrations of greater magnitude can be induced in the preterm infant up to three months "too soon" in biological terms. The data also show that the method of administering feeds to preterm infants determines the endocrine milieu. Marked differences occur in infants who are bolus fed when compared with continuously fed infants; the type of milk presented to the gut may also alter the development of hormone profiles.

The latter point also seems to be true in the infant born at term where substantial differences can be detected by the sixth postnatal day in infants entirely breast fed or bottle-fed from birth. More recent data suggest that this phenomenon eventually disappears, and that similar feed responses are
seen at subsequent ages. Nonetheless, it is intriguing to consider if feeding responses immediately after birth could "program" the pattern of satiety and feeding habit in later life.

One unexplained point relates to why preterm infants and to a lesser extent, the infant at term, have concentrations of peptides 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 term infants have a feeding regime imposed upon them, so that within days of birth very large quantities of milk are introduced into their guts. Whatever the mechanism 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 the functional effects in target tissues (9).

The stimulation of postnatal 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, perhaps having important roles in regulating the postnatal growth of the gut mucosa and the pancreas. GIP could be an important stimulus to insulin release and could mediate changes in the enteroinsular axis; pancreatic polypeptide may be involved in the development of gall

![Image of graph depicting jejunal pressure wave and transmural potential difference](image)

**FIG 19.** Jejunal pressure wave and transmural potential difference in a preterm infant with pseudoobstructive ileus a) before and b) during infusion of motilin. (Data by courtesy of Dr P Milla and Dr E Wozniak).
bladder contractility and pancreatic exocrine secretion.

It is also noteworthy that the "classical" hormones such as cortisol and thyroxine may well have essential roles in the adaptive process after birth, particularly since cortisol has been shown to influence the development of gut enzyme activity (9). More recently, Sperling and his colleagues have suggested that thyroxine has a key role in regulating the development of insulin receptors on liver cell membranes (34).

What is the practical significance of our results? The aspects of greatest clinical relevance are likely to be those relating to the nutritional management of the preterm infant. Current feeding practice is largely empirically based, and although a subject of much controversy, there is no consensus as to the optimum method of feeding such babies. It could be argued that a closer understanding of the factors regulating the postnatal development of the gut and pancreas, and of intermediary metabolism, could well lead to a more rational basis for nutritional policies.

Our data 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 data whether one method or composition is to be preferred or recommended, and further work is needed to investigate the potential consequences. However, whilst it could be argued that feed-induced surges of anabolic hormones in relation to bolus feeding might stimulate faster growth (and this is yet to be proved), it could be postulated equally well that postprandial hormone changes after bolus feeding could

**FIG 19. (Continued).**
be deleterious, by inducing changes in blood pressure and cerebral blood flow which might predispose to further problems, such as intraventricular hemorrhage (35, 36).

These data can also be used to question 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. Could this practice lead to delay in gut adaptation once enteral feeds are started? We have unpublished evidence that short periods (up to 10 days) without intraluminal food in the gut are followed by the development of gut hormone surges of normal amplitude when food is reintroduced, and the infants eventually thrive perfectly well on enteral feeding. What, however, of the newborn infant who has undergone gastrointestinal surgery or who is fed solely by the parental route for more prolonged periods? Dr Lucas has analyzed some of our data to show that very small volumes of milk are needed to induce some surges in hormones. Such results raise the fascinating possibility that milk could be given in small volumes as a therapeutic maneuver to induce gut development rather than for nutritional reasons.

It is possible that hormones and peptides could be given therapeutically to overcome disorders of the adaptation to postnatal feeding. Somatostatin has already been given to infants with profound hyperinsulinemic hypoglycemia due to nesidioblastosis of the pancreas (37). More recently we have investigated, through collaboration with Dr P Milla and Dr E Wozniak, a preterm infant who developed pseudo-obstructive ileus which led to a prolonged period of intravenous feeding interspersed with repeated failure to tolerate enteral feeding. Analysis of jejunal motility patterns demonstrated a grossly abnormal gut, with a failure to initiate migrating motor complexes, and a lack of coordinated motility (Fig 19). Normal induction of transmural potential differences and motor activity could be induced by means of an infusion of motilin (Figure 19), following which tolerance to enteral feeding was established. This case represents the first attempts to use specific gut hormones to treat gastrointestinal motility disorders in the neonate; it opens a whole new area of developmental therapeutics in infancy.

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 postnatal period. Answers to some of the questions posed in this review may be of practical importance both in defining more scientifically the nutritional management of different groups of newborn infants and in the investigation and treatment of disorders interfering with normal adaptation to postnatal nutrition.

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References

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