Feeding and Neonatal Necrotizing Enterocolitis

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Necrotizing enterocolitis (NEC) is an acquired syndrome affecting the gastrointestinal tract defined as "ischemic-inflammatory necrosis of neonatal bowel." This syndrome is one of the most serious problems affecting newborns, and its frequency is greatest among premature and low-birthweight (LBW) infants (increased between fourfold and 10-fold compared with full-term infants) (1). A multifactorial pathogenesis has been proposed, but the pathogenesis remains obscure. Nevertheless, the theory that NEC could be the final result of several etiological and pathophysiological events has been suggested. We know that there are at least three factors other than prematurity essential for developing NEC:

1. intestinal ischemia,
2. the presence of bacteria in the intestinal lumen, and
3. the availability of substrates (formula or human milk) to support bacterial growth.

These three factors can coexist and influence one another in a vicious cycle.

The mechanism by which all these events interplay in initiating an inflammatory cascade leading to NEC is not clear. However, raised concentrations of various proinflammatory cytokines, including interleukin-6 (IL6), tumor necrosis factor-alpha (TNF-α), and platelet-activating factor (PAF) have been reported in infants with NEC (2,3). Recently, it has also been found that nitric oxide (NO) is produced in large quantities by enterocytes in the intestinal wall of infants with NEC; this probably leads to abnormal apoptosis of enterocytes in apical villi through peroxynitrite formation (3).

At present, prematurity and enteral feeding are believed to represent the only primary risk factors in NEC development, with bowel ischemia playing only a secondary role. For this reason, feeding is associated with NEC in approximately 90% of cases (4). Therefore better knowledge of the strategy of feeding can improve the overall health of premature infants and reduce the NEC rate.
WHEN AND WHY TO START ENTERAL FEEDING

In 1960, Bauman introduced the concept of early enteral feeding in preterm infants (5). Initially, the early enteral feeding of sick preterm infants was thought to increase the risk of aspiration syndrome and failure to thrive (because of inefficient energy absorption and functional bowel immaturity), to cause mechanical damage (from the orogastric feeding tubes) and to make the development of NEC more likely. Hence, parenteral nutrition techniques were introduced and adapted for newborns with the intention of delaying enteral nutrition.

Now we know that both parenteral and enteral nutrition may cause morbidity in preterm infants; nevertheless we can achieve the goal of good nutrition in even the smallest preterm by the well-balanced use of both modes of nutritional support.

To reduce major complications, the concept of “early” enteral feeding must be related to the concept of “minimal” feeding—that is, small volumes (varying from 0.1 to 20 ml/kg-d) of enteral nutrition are given as early as 1 day after birth, whereas in the following days parenteral nutrition is used simultaneously to supply most of the nutrients intake (6). The amount of feeding must be advanced gradually to minimize the risk of NEC, while tolerance is carefully monitored. A daily rate of no more than 1 ml/kg-h is considered safe (7).

Various recent studies have proved that small volumes of nutrients introduced early in the gastrointestinal tract can have several benefits in premature infants. This initial enteral experience seems to support gut morphological and functional maturation, leading to an increase in mucosal thickness and villi height, increased plasma concentrations of gastrointestinal peptides, and better coordination of gastrointestinal motility (6). Moreover, the early presence of intraluminal nutrients allows the development of normal bacterial colonization, representing a further trophic stimulus for the immature neonatal bowel. Early-fed infants showed greater weight gain, fewer episodes of feeding intolerance, and more rapid achievement of full enteral feeding than late-fed infants. There have been no reports of an increase in the incidence of NEC after early minimal enteral intake (8).

A recent retrospective report from the National Institute of Child Health and Human Development Neonatal Research Network recommends the early introduction of enteral feeding and the early achievement of full enteral nutrition to reduce late-onset sepsis in very low-birthweight (VLBW) newborn infants (9).

WHAT KIND OF FEEDING? HUMAN MILK VERSUS FORMULA

As commented earlier, even if enteral alimentation is thought to be an important risk factor in the pathogenesis of NEC, some aspects related to feeding can be considered equally important in reducing the NEC rate.

Prospective randomized controlled trials have examined milk feeding and NEC. In a large, prospective, multicenter study, Lucas and Cole (10) enrolled 926 premature infants with birthweight below 1,850 g (mean weight 1,300 g; mean gestation 31 weeks): 253 were fed only human milk, either raw milk or pasteurized donor milk; 437 on breast milk plus an infant formula; and 236 on formula only. Clinical NEC
developed in 5.5% of all infants studied (51 of 926). In the exclusively formula-fed group, the risk of NEC was three to five times higher than in infants fed breast milk and formula combined, and 10 times higher than in the group fed only breast milk. Hence human milk seems to be protective even when associated with formula. Only in formula-fed infants delaying the start of enteral feeding seem to reduce the incidence of NEC substantially.

Apart from clinical studies emphasizing the protective role of human milk against NEC, it is well known that this disease is very rare in those countries where almost all premature infants are fed human milk. Because in Italy more than 85% of all newborn infants are fed on breast milk, the incidence of NEC is very low (about 2.4% among VLBW infants). This was shown by a prospective multicenter study in which the occurrence of complications associated with acute respiratory disorders was examined (unpublished data). The NEC rate data are shown in Table 1.

How breast milk could exert such a protective role is not fully understood. Nevertheless, we know that human milk is rich in various specific and nonspecific immunoprotective factors. These factors confer passive protection against pathogenic microorganisms in the respiratory and alimentary tracts and modulate the mucosal immune system of neonatal bowel, counteracting the physiological systemic and local immune impairment. The immune system of human milk is composed of soluble factors and living cells, changing in quantity according to the time of delivery; in fact, the quantity of host defense factors in preterm milk is greater than that in term milk (11). Moreover, the daily production of many defense agents changes as lactation proceeds, in a way that is inversely proportional to the infant’s ability to produce them endogenously in the gastrointestinal tract (12). The complex of soluble factors can be subdivided into three groups of compounds with synergistic activity:

1. antimicrobial factors (such as lactoferrin, oligosaccharides, and specific antibody),

| Table 1. The relations between the necrotizing enterocolitis (NEC) rate and gestational age and birthweighta |
|-----------------|-----------------|-----------------|
| Weeks | NEC | Birthweight | NEC |
| 25   | 3/57 (5.3) | <1000 | 9/364 (2.5) |
| 26   | 1/77 (1.3) | 1000–1499 | 7/672 (1.0) |
| 27   | 4/98 (4.1) | 1500–2499 | 6/3864 (0.15) |
| 28   | 3/127 (2.4) | 2500–4000 | 2/55159 (0.03) |
| 29   | 2/148 (1.4) | >4000 | 0/3487 |
| 30   | 3/217 (1.4) | <1000 | 9/364 (2.5) |
| 31   | 2/257 (0.8) | 1000–1499 | 7/672 (1.0) |
| 32   | 2/344 (0.6) | 1500–2499 | 6/3864 (0.15) |
| 33   | 1/435 (0.2) | 2500–4000 | 2/55159 (0.03) |
| 34   | 1/636 (0.15) | >4000 | 0/3487 |
| 35   | 0 | 1000–1499 | 7/672 (1.0) |
| 36   | 0 | 1500–2499 | 6/3864 (0.15) |
| >36  | 2/57688 (0.03) | 2500–4000 | 2/55159 (0.03) |

Values in parentheses are percentages.
a A one year prospective study of the Italian Group of Neonatal Pneumology.
2. anti-inflammatory factors (such as protease antagonists, PAF acetylhydrolase, epithelial growth factors, antioxidant agents, soluble receptors for inflammatory cytokines, anti-inflammatory cytokines), and
3. other immunomodulating factors (such as some cytokines, nucleotides) (12).

The dominant immunoglobulin in human colostrum and milk is secretory IgA (sIgA), which has been linked epidemiologically with protection against several respiratory and enteric pathogens. Secretory IgA has high antigenic specificity, generated by the migration of immunologically-triggered B cells from Peyer’s patches and lymphoid centers in the small intestinal tract and bronchial tree, respectively, to the mammary gland. Hence, sIgA of human milk coats the intestinal villi of recipient infants, providing a specific passive immunity against antigens of the infant/mother dyad environment. The function of the entero-mammary immune system in the premature infant/mother dyad is even more relevant if the mother is able to produce specific antibody against the nosocomial pathogens of her infant’s nursery (13). Most sIgA remains intact after milk pasteurization (14), assuring efficient protection even in banked breast milk–fed infants.

Oligosaccharides account for the third main component of human milk, after lactose and lipids; they are increased in colostrum and decrease progressively in mature milk (15). The quantity of oligosaccharides is higher in preterm milk than in term milk (16). By contrast, mature bovine milk, which is currently used to produce infant formulas, has a low level of oligosaccharides (17). Some oligosaccharide fractions stimulate the bifidus flora, resulting in control of the growth of pathogenic strains (15). Other milk oligosaccharides, having structures that mimic specific bacterial antigen receptors, inhibit the binding of several viral and bacterial agents by blocking their adherence to epithelial surfaces, preventing enteric infections (18,19).

Among immunomodulating factors, nucleotides are widely present in human milk. Nucleotides are thought to enhance immune function by stimulating natural killer and antibody activity while maintaining intestinal mucosal integrity. This reduces the incidence of diarrhea (20). On such premises, supplementation of starter infant formulas with sialyl-oligosaccharides and nucleotides is recommended to provide broad-based protection against gastrointestinal infections when breastfeeding is impossible.

Some investigators have suggested that circulating platelet-activating factor (PAF) may play a part in NEC pathogenesis by inducing profound vasoconstriction or changes in microvascular compartment (2,21). PAF acetylhydrolase (PAF-AH), a degradation enzyme, has been found in human milk (22). This enzyme may serve to metabolize PAF produced by inflammatory cells and intestinal flora, and thus may exert a protective role against the development of NEC. Recently, it has been reported that levels of PAF-AH activity are higher in preterm human milk than in term milk. Such activity remains unchanged in preterm milk with advancing lactational age, opposite to what happens in term milk (23).

A peculiarity of human colostrum and milk is that they are rich in living neutrophils, lymphocytes, macrophages, and monocytes, which exert several complex and protective functions (24). These cells survive in the gastrointestinal tract and can
pass through the epithelial surface, providing not only local immunity but also sys-

temic immunity.

Pitt and colleagues (25) were able to prevent klebsiella-induced NEC by feeding
rats with colostral macrophages but not by feeding them with the soluble colostral
factors. Such findings do not confirm previously reported data about poor activity of
milk leukocytes and macrophages (26).

**FEEDING AND GUT COLONIZATION**

NEC has never been observed *in utero* (4). This shows that gut colonization plays an
important, if not definitive, role in NEC pathogenesis (8). It is well known that there
is a close correlation between the type of infant feeding and the type of intestinal flora
derived from it. In fact, the fetus is germ-free until shortly before birth, if the amni-
otic membrane remains intact. After birth, the gastrointestinal tract is soon colonized
by commensal bacteria.

In the ecosystem of breastfed babies, there is a predominance of Gram-positive or-
ganisms such as enterococci, bifidobacteria, and particularly lactobacilli. Among
Gram-negative bacilli, *Escherichia coli* is the most frequent but is present in rela-
tively small numbers. Other Gram-negative bacilli rarely colonize breastfed infants.
In bottle-fed neonates, there are fewer bifidobacteria and relatively larger numbers of
*E. coli*; moreover, bacteroides and other anaerobes are detected in higher numbers,
as in adult intestinal flora (27).

As previously reported, colostrum and human milk contain a bifidus factor that
might allow selective growth of nonpathogenic bacteria. In addition, the presence of
other antimicrobial factors—such as lactoferrin and lysozyme—is essential in regu-
ling the growth of intestinal pathogens. In the breastfed infant bowel, lactose-fer-
menting bifidobacteria lower intraluminal pH. As a result, the growth of potentially
pathogenic bacteria, such as *E. coli*, is considerably reduced (27).

In a prospective, double-blind study, Carrion and Egan showed that gastrointesti-
nal acidification decreased bacterial colonization and reduced the incidence of NEC
in preterm infants (28).

**FEEDING AND PREVENTION STRATEGIES**

Human milk feeding, especially from mothers delivering preterm neonates, is the pri-
mary step in reducing NEC risk in preterm infants. As this is not always possible, for-
mula milk should be supplemented with agents that play a role in the anti-infective
properties of human milk, particularly nucleotides and oligosaccharides. At the same
time, other strategies may be used to prevent NEC, such as those based on the path-
ogenic hypothesis developed since the 1960s.

In a randomized clinical trial, Eibl and coworkers have evaluated the efficacy of
an oral immunoglobulin preparation containing IgA and IgG in reducing the inci-
dence of NEC (29). They enrolled 179 low-birthweight (LBW) infants fed formula
alone or formula plus pasteurized human milk. These were randomly assigned to
receive an oral IgA/IgG preparation daily as a supplement to their feeds. NEC developed in six of 91 control infants during the 4-week study period, while no cases occurred in the IgA/IgG-treated infants. We obtained similar results in Padova (30), in a randomized clinical trial involving 132 formula-fed LBW infants. During the first 15 days of life, the infants in the treatment group were fed 500 mg/d of monomeric IgG (Sandoglobulin®), subdivided into five doses, as a supplement to their feeds. Four infants in the control group developed NEC, but none of the 65 treated infants developed it (Table 2).

Abnormal intestinal gas production, probably caused by carbohydrate fermentation by gut microflora, has been observed in most NEC patients studied radiologically. This suggests that it might be possible to prevent NEC by employing probiotic agents that stabilize the gut ecosystem. Such probiotics have been shown to play a positive role in the prevention and treatment of gastrointestinal disorders (31). Lactobacillus casei GG, a strain of human origin, is normally found in the bowel of healthy term and preterm infants, though it disappears when antibiotics are given. On the other hand, the intestinal flora of sick preterm infants treated in neonatal intensive-care units is predominantly represented by enterobacteriaceae and coagulase negative staphylococci. In a study of the administration of Lactobacillus casei GG to such infants, a dose of $5 \times 10^8$ colony-forming units (cfu) a day did not affect the degree of intestinal colonization by potential pathogens (32). However, in a preliminary study of our own, we found that a larger dose ($10^9$ cfu/d) was capable of inhibiting the pathogenic strains. Those findings led us to initiate a wider collaborative study to identify which, if any, infants might benefit from the treatment. The study was a placebo-controlled multicenter trial of Lactobacillus casei GG (Dicofarm, Italy), given to premature infants admitted to neonatal intensive-care units. The protocol

<table>
<thead>
<tr>
<th>Causes of morbidity</th>
<th>Placebo group</th>
<th>Monomeric-IgG group</th>
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</thead>
<tbody>
<tr>
<td>NEC</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Sepsis</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Meningitis</td>
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<td>0</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Pneumonia</td>
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</tr>
<tr>
<td>Enteritis</td>
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<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>9/67 (13%)</td>
<td>6/65 (8.9%)</td>
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<tr>
<th>Causes of mortality</th>
<th>Placebo group</th>
<th>Monomeric-IgG group</th>
</tr>
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<tbody>
<tr>
<td>Infection</td>
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<td>0</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Pneumothorax</td>
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<td>0</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
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<td>5</td>
</tr>
<tr>
<td>NEC</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>12/67 (18%)</td>
<td>7/65 (10.4%)</td>
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NEC = necrotizing enterocolitis.
Modified from Rubaltelli et al. (30).
was double blind, using sealed envelopes to ensure randomization. Between March and November 1997, 202 premature infants, consecutively admitted to neonatal intensive-care units in the participating hospitals with birthweight of less than 1,500 g and/or gestational age of less than 33 weeks, were enrolled in the study. From the first day of enteral feeding until discharge, $10^9$ cfu/d of *Lactobacillus casei* GG (a freezedried preparation dissolved in raw or pasteurized human milk) were given to the infants. We recorded two cases of NEC in the control group and none in the study group (unpublished data). These findings suggest the need for a larger-scale multicenter study.

**REFERENCES**

DISCUSSION

Dr. Schanler: I was intrigued by your IgG feeding study. What do you know about the integrity of the IgG? Is it digested and absorbed by the infant, or does it line the gastrointestinal tract?

Prof. Rubaltelli: No, it is not absorbed. We showed that serum IgG was the same in treated and control groups. We have not performed studies in the feces, but Blum showed that IgG is excreted intact [1]. IgG has a role in treating infants with rotavirus infection, as reported in The Lancet some years before our study [2].

Dr. Koletzko: What do we know about the role of feed osmolality? Are there any data to show that osmolality above a certain threshold level would increase the risk of necrotizing enterocolitis?

Prof. Rubaltelli: There have been cases reported where NEC appears to have occurred in association with the use of hyperosmolar formulas. In Italy we are very aware of this problem and are very cautious about using milk fortifiers or anything that can increase the osmolality of the feed. There are data on experimental animals to show that hyperosmolar nutrients can induce NEC. An osmolality of more 400 mOsm/kg is dangerous [3].

Prof. Ziegler: I'd like to make a comment on the osmolality question, because it is always mentioned. The only human data in existence are the results of a study carried out in Salt Lake City by Book and coworkers [4]. They compared a then new formula, in which the sole carbohydrate was glucose and which had an osmolality of 650 mOsm/kg, with a control group. Significantly more babies fed the new formula developed necrotizing enterocolitis. That is the grand total of human clinical data on osmolality and NEC. No current formula has an osmolality anywhere near 650 mOsm/kg, and we don't even know whether it was the osmolality or something else in that formula that caused the NEC—for example, the high glucose concentration. So I think it is unjustified to worry about whether an osmolality of, say, 350 or 380 mOsm/kg water could cause NEC.

Prof. Rubaltelli: Yes, but if drugs such as antibiotics are given in the feeds they can cause a large increase in the osmolality, which may then certainly exceed 400, or even 500, mOsm/kg [5].

Dr. Schanler: Fortified human milk in the United States has an osmolality of between 400 and 450 mOsm/kg water, and we see less NEC with that than with formula. I don't advocate that the osmolality of all milk be that high, but I think we know that this is within the safe range.

Prof. Rubaltelli: The approach is quite different in Italy from that in the United States. We
only use banked human milk, without fortifier, during the first 2 to 3 weeks of life, until the infant is getting 60% of the total energy intake enterally. Then, if the mother is not producing milk, we gradually shift to a preterm formula. Growth may not be as good as we would like on this regimen, but the risk of NEC is very low.

Prof. Lucas: Your data compared fortified human milk with formula, but when we did an internal randomized comparison of fortified versus unfortified human milk, we found a higher incidence of NEC six cases in fortified group versus two cases in the unfortified group. Our interpretation was that this was an effect of adding cow's milk proteins to human milk and influencing the protective factors, but the other interpretation is that it was the increased osmolality. There are very few randomized trials that allow one to look at the effects of osmolality. Very few experimental studies have addressed the question. So we simply don't know.

Dr. Walker: There have been some studies on the degree of osmolality liable to damage cells [6–8]. It requires levels of more than 600 mOsm/kg water to cause direct cell damage. This is thought to be the basis for gut damage from elemental formulas. Lower levels of osmolality only cause changes in fluid shifts across the epithelium.

Prof. Berger: I seem to recall from my physiology textbooks that osmolality was an important factor in gastric emptying and that the gastric contents were first made iso-osmolar before being released. Is this correct? Maybe this doesn’t happen in the normal way in the preterm baby. Shouldn’t we expect more problems in the stomach rather than further down the intestine if osmolality was playing a role?

Prof. Rubaltelli: I have no idea whether gastric emptying depends on osmolality, but I do know that emptying is much more rapid with modern whey-protein-predominant formulas than with the older casein-predominant types. I don’t know whether that depends on osmolality or not. However, we sometimes find that very preterm infants can’t accept even a small amount of saline, so gastric emptying must depend on other factors as well, such as the clinical situation of the infant.

Prof. Moro: I think we are overestimating the problem of osmolality. We routinely use human milk fortifiers, and the final osmolality is between 300 and 315 mOsm/kg water. When we use bovine fortifiers, the level is around 400 to 450 mOsm/kg water. We have not had a single case of NEC for more than 5 years in our unit. So if human milk is used with caution, starting with minimal enteral feeding, and if fortification is begun when the baby is able to tolerate a volume of around 100 ml/kg/d, then I think we are safe.

Dr. Rashwan: We know that some ELBW babies are born with a degree of asphyxia, and this may affect the gut. Do you still advise early feeding under these conditions? And if pre-NEC signs develop, do you advise stopping oral feeds?

Prof. Rubaltelli: Our protocol in asphyxiated newborns, who are mostly full term, is not to feed these babies orally for the first few days of life. In preterm newborns, the Apgar score is of course always lower than in full-term infants, but if we feel there is good evidence of severe asphyxia, we defer enteral feeds. If infants develop abdominal distention, we stop enteral feeding, and we restart it after 12 or 24 hours, using very small quantities of human milk. With this very cautious approach, I have not seen a genuine case of NEC in our unit in the last 3 years. We believe we can probably prevent NEC by stopping feeding at the first clinical signs.

Prof. Wu: About 10% of our patients develop NEC without having been fed, though abdominal distention is less severe in these cases. During the passage through the birth canal, the baby swallows maternal blood. I believe this can be a substrate for bacteria in the gut and lead to NEC.

Prof. Lucas: Several studies have shown that NEC occurs in about 10% of babies who’ve received no enteral feeding at all. This must mean that other factors are involved.

Prof. Polberger: This is a puzzling issue. In Sweden, NEC is very rare and has almost no
mortality. We routinely start enteral feeding with human milk during the first hours of life, even in very sick infants on ventilators. However, in the recent past we have seen a few cases of focal spontaneous perforation, though still with no mortality. I wonder whether this is in fact NEC or some other entity.

Prof. Rubaltelli: We have also seen a few cases of spontaneous perforation. One happened after indomethacin treatment, and we thought that this had caused damage to the intestinal mucosa. In another case, the perforation was thought to have resulted from a congenital malformation. I don’t think either case was true necrotizing enterocolitis. Our approach to feeding babies is the same as the Swedish approach.

Prof. Ziegler: I’d like to make a comment about the diagnosis of NEC, because I think what we call NEC is almost certainly more than one disease. We appear to have only one diagnosis in premature neonates for any acquired gastrointestinal disease, and that includes isolated punched-out lesions, and even indomethacin-induced perforations. When our colleague from China describes NEC as occurring in 10% of term infants, he is probably referring to a condition with intestinal distention, but it’s almost certainly not the same disease that kills premature babies. Therefore all the statistics we are currently using are suspect and confounded by this nonuniformity of diagnosis.

Dr. Berseth: We see babies in our nursery who do not have pneumatosis intestinalis, yet when they go to surgery the surgeon finds flagrant NEC. On the other hand, we have cases where we will clinically make a diagnosis of NEC but when the baby dies the pathologist tells us that we were really dealing with a baby who had ileus secondary to sepsis, and that there is no evidence of NEC at all. All these permutations suggest that we need refinement in diagnosis. It is obvious that we are dealing with a variety of clinical diseases and situations.

Prof. Rubaltelli: May I ask you what is your indication for surgery in an infant without any clinical or radiological signs of NEC?

Dr. Berseth: These are babies who have continued to deteriorate and who have symptoms related to the gastrointestinal tract, such as abdominal distention. If there is rapid clinical deterioration, the surgeons will sometimes agree to evaluate the problem.

Dr. Walker: Presumably, one begins enteral feeding early to stimulate the intestine. Has anyone looked at hormone release from epithelial cells in the intestine under conditions of enteral feeding in the very premature infant? Do we know what actually happens?

Prof. Rubaltelli: I don’t know. Maybe Dr. Lucas can comment?

Prof. Lucas: We coined the term minimal enteral feeding after looking at gut hormone release in preterm infants. We discovered that if you did not feed preterm babies at all after birth, they had the same hormone levels as in cord blood. But if you fed them, then they got a massive release of gut hormones. We then discovered that even trivial amounts of enteral feeds, 0.5 ml for a couple a days, was all that was required to produce maximal gut hormone release [9,10].

Dr. Costalos: We did a study a couple of years ago concerning premature babies and NEC. We found a disturbed pattern of peptide hormones in these babies. We know that the hormones can be affected by asphyxia, so I think it would be worth exploring whether there really is a close relation between the hormone pattern and NEC.

Prof. Rubaltelli: I think gut hormones play a role in promoting maturation of the intestines. I don’t believe they have anything to do with NEC per se.

Dr. Costalos: In our studies, we showed that babies with NEC had a different pattern of gut hormones from controls. We don’t know whether this is an effect of the NEC or whether these disturbances contribute to its cause. I think this should be looked into further.

Dr. Da Silva: When starting to feed extremely low-birthweight infants, with or without
asphyxia, is there any role for diluted formulas or semielemental formulas if you have no human milk available?

Prof. Rubaltelli: I can only give my advice, without scientific support. You can start giving distilled water and then move to diluted preterm formula, assessing tolerance by distention and gastric residual volume. Generally, we give parenteral nutrition to very sick preterm babies, with a very small amount of enteral nutrition. If human milk is unavailable, we start with diluted preterm formula. I have no experience of semielemental diets in very low-birthweight infants.

Dr. Al-Siyud: What is the effect of sedation on gut motility?

Prof. Rubaltelli: We don't sedate our infants, even if they are on ventilators, so I have no experience with the effects of sedation on the gut motility. However, in full-term infants who are severely asphyxiated and who are treated with phenobarbital, there is no decrease in intestinal motility.

Prof. Cooke: In your talk, you emphasized the importance of prematurity and feeding practices in the etiology of NEC, but you rather dismissed the importance of gut ischemia. But there is really quite a lot of evidence that abnormal gut blood flow in the fetus before birth that can be demonstrated on Doppler studies is associated with later enterocolitis, as are problems with persistence of the ductus arteriosus, umbilical vessel catheters, recurrent apnea, and so on. These all point to a primary ischemic problem rather than, as you were suggesting, to a secondary one. I wonder whether the modified feeding regimes—minimal enteral feeding or simply delaying feeding—and their effect on reducing clinically evident NEC is simply that we are providing an opportunity for the gut to recover from an earlier ischemic insult rather than overloading it too early, thus producing florid NEC.

Prof. Rubaltelli: My topic was feeding related to NEC, so I concentrated on the feeding aspects. But I agree with you that intestinal ischemia plays an important role in the pathogenesis. If we are very prudent with our feeding practices in these babies, probably giving only minimal enteral feeding during the first days of life, I accept that this allows time for the intestinal situation to improve so the infant doesn't develop clinical symptoms.

Prof. Cooke: I just wonder whether some of the cases of isolated perforation described earlier are simply the extreme end of the asphyxia spectrum, where recovery has not occurred even though you have not fed the child; lesser degrees with asphyxia recover without symptoms using the more modern feeding approach that you've been describing.

Prof. Rubaltelli: Theoretically, that is possible, but the cases I described were definitely connected with indomethacin administration and a congenital malformation. Ischemia may have played a role, but not on its own.

Prof. Lucas: I like the idea of human milk and minimal enteral feeding exerting a protective effect in a damaged gut. I think that is a very good synthesis of the available data.

Prof. Rubaltelli: It is possible that not feeding at all is worse than giving a small amount of human milk, because of the atrophic effect on the gut mucosa. A study by a colleague in Padova, Dr. Carnielli, which has not yet been published, showed that there was no difference in the rate NEC between parenterally fed infants and formula-fed infants, so it seems that withholding oral feeding and using only parenteral nutrition does not provide any additional protection.

Dr. Berseth: I'd like to comment on blood flow. There is a very intimate relation between enteral feeding and vascular responses. We need to be aware of hyperemia as much as of ischemia. One of the physiological responses that occurs with feeding is a decrease in splanchnic resistance and an increase in blood flow. There is some work from Sweden showing that this obligatory change does in fact occur in preterm infants, but it may occur at the expense of
redistribution of blood flow, specifically to the cerebral circuitry. We have to look at what we are doing in the gastrointestinal tract in terms of the whole organism.

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