Development of Motility

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Introduction

Advances in neonatology over the past 2 decades have resulted in the survival of very preterm infants. However, the major limiting factor to survival of such infants is the ability to initiate and maintain adequate nutrition.

Multiple maturational events are necessary for successful enteral nutrition of the infant: coordination of sucking and swallowing; effective gastric emptying; forward propagation of small intestinal contents, and finally, colonic elimination. Since normal gastrointestinal function relies on the integrated maturation of absorptive, secretory and motor function, a delay in any one of these processes will result in disturbed gastrointestinal function. Immature gastrointestinal motility manifested by vomiting, abdominal distention, delay in stooling and constipation commonly postpone the time of full enteral feeding in premature infants.

Recent advances in biomedical engineering have enabled the study of gastrointestinal motility even in very premature infants. Using miniaturized feeding catheters with an outer diameter of <2 mm, multiple recording sites and sleeve sensors and with rates of water infusion ranging between 0.005 and 0.04 ml/min, we have learned a great deal about the functional ontogeny of esophageal and antroduodenal motility in humans. In contrast, due to the difficulty in studying the human colon under physiologic conditions, very little is known about the development of colonic motility. Placement of manometric or barostat catheters in the colon requires endoscopy and cannot be justified in healthy infants, while noninvasive techniques such as scintigraphic transit studies or ultrasonographic evaluations have not yet been standardized for children.
**Development of Myogenic Control**

The fetal development of the structure and function of the gastrointestinal tract is a complex process. Throughout the intestine, three layers of muscle contract in a coordinated fashion: the muscularis mucosa, a thin layer that lies beneath the villi; the circular muscle, which lies outside of the muscularis mucosa and serves as the pacemaker for gut muscle contraction, and the longitudinal muscle, the outermost layer of the three muscles. These muscles have oscillatory membrane potentials and their contraction rate is reflective of the electrical slow waves. The slow wave has different frequencies at each level of the gut (i.e., 3–5 times/min in the stomach, 9–11 times/min in the duodenum, 8–10 times/min in the jejunum, and so forth). Thus, at each level of the gut, there is an intrinsic phasic contraction rate.

The muscular layers derive from the mesenchymal tissue in the gut by the 4th to 6th week of gestation in a rostrocaudal fashion [1]. The circular muscle layer appears first, followed after 2–3 weeks by the longitudinal muscle coat, while the muscularis mucosa is formed later by 22–23 weeks of gestation. Similarly, the contractile proteins of smooth muscle cells in animal models appear in a hierarchic manner; however, no such information is available in humans [2]. As the developmental changes in the contractile proteins occur, the frequency of the slow waves or electric control activity of the smooth muscle cells also changes. The frequency of electric control activity increases with the increase in post-conceptional age, reflecting developmental changes in the activity of membrane iron pumps or their modulation [3].

Until recently, some investigators suggested that groups of muscle cells located in the circular layer differentiated to form the interstitial cells of Cajal (ICCs), specialized cells provided with multiple processes that project in an ascending and descending manner throughout the length of the circular muscle and the longitudinal muscle. These cells act as pacemakers by driving the slow wave frequency and coordinate neural input to gut smooth muscle [4]. The ICCs are distinct from neurons and smooth muscle cells, and they play important roles in the regulation of gastrointestinal motility.

Anatomic studies characterizing the distribution of ICCs measure immunoreactivity to c-kit, a proto-oncogene coding for a receptor tyrosine kinase. Six distinct ICC populations were identified in the gut, including intramuscular ICCs, ICCs within the myenteric plexus, submucosal ICCs in the colon, and ICCs in the deep muscular plexus of the small intestine. A recent study reported the regional variability in colonic ICC density with the highest numbers observed in the transverse colon [5].

ICCs are present from an early stage of human gut development. Intrauterine maturation of ICCs correlates with the initiation of electrical rhythmicity, in fact in mutant mice lacking ICCs, no spontaneous pacemaker
activity is seen [6]. Such loss of pacemaker function leads to disruption of organized luminal propagation.

Recent studies have reported that a delayed maturation of ICCs could be involved in the pathophysiology of gastrointestinal dismotility seen in some neonates and children [7, 8], and abnormalities in the density and distribution of ICCs have been described in human Hirschsprung’s disease and infantile hypertrophic pyloric stenosis [9, 10]. However, since ICC development continues well into postnatal life, interpretation of apparent abnormalities in their distribution as being of pathological significance should be tempered.

The finding that c-kit-positive ICCs are present from 9.5 weeks, when neural crest colonization of the gut approaches completion, is consistent with a modulating effect of the fetal enteric nervous system (ENS) on ICC development.

**Development of Neurogenic Control**

Initiation and coordination of muscle contraction is regulated by neural and hormonal input. Extrinsic neural regulation refers to all nerves that have a cell body located outside the intestinal tract. Extrinsic neural input to the gastrointestinal tract comes from the central nervous system (CNS); the sympathetic and the parasympathetic systems. Intrinsic neural regulation refers to all nerves whose cell bodies reside in the intestine. The ENS, or gut brain, provides most of this regulation. It is capable of functioning independent of the extrinsic nervous system in animals when connections to the extrinsic nerves have been severed [1].

Components of the ENS are formed in a temporal sequence that parallels the maturation of the muscle layers. Neural crest cells migrate to the intestine via the vagal and sacral portion of the spinal cord. The undifferentiated cells are first detected in the stomach and duodenum at 7 weeks and then in the rectum at 12 weeks. They quickly differentiate along a rostral caudal axis and establish the myenteric and submucosal plexuses by weeks 12–14. Contacts between the enteric nerves and the circular and longitudinal muscle cells develop between 10 and 26 weeks [11]. It appears that there is intimate cross-talk between the developing muscles and nerves, and if either of the two fail to develop properly, maturation of the other is arrested.

Several observations suggest that development of the ENS continues after birth and through at least the first 12–18 months of life. Study of the argyrophilia of neurons in the sigmoid colon of human neonates shows that, prior to term, the nerves are unable to take up silver and that, during the first 6 months of life, neurons in the myenteric plexus gradually assume argyrophilia [12]. Thus evidence suggests that just as the majority of CNS development takes place throughout fetal life and continues through the first 18 months of life, a similar pattern occurs in ENS.
Neurotransmitters are elaborated by the end of first trimester as are almost all of the hormones and peptides. N-Methyl-D-aspartate (excitatory) and nitric oxide (inhibitory) have been shown to be neurotransmitters in animal studies and may be the most potent agents in modulating bowel motility [13].

Recent studies have indicated that nitric oxide is involved in the nonadrenergic-noncholinergic (NANC) innervation of the gut, mediating its relaxation. Brandt et al. [14] reported that the onset and place of development of nitrergic innervation are similar to adrenergic and cholinergic innervation and occur before peptidergic innervation. Bowel segments from the esophagus, pylorus, ileocecal and rectosigmoid regions of 14 fetuses (gestational age range from 12 to 23 weeks) were studied with NADPH diaphorase histochemistry. By 12 weeks of gestation, nitrergic neurons had appeared in the myenteric ganglia, at all levels of the gut, and had begun plexus formation. Nitrergic innervation of the submucous plexus became evident after 14 weeks. By 23 weeks of gestation, the complete nitrergic pattern had matured, as observed in the postnatal gut.

These NANC nerves mediate the reflex opening of sphincters in the alimentary tract and the descending inhibition during intestinal peristalsis. Defects of nitrergic innervation have recently been found in congenital gut anomalies such as pyloric stenosis and Hirschsprung's disease, which suggests that a lack of nitric oxide-mediated NANC inhibitory control may be responsible for the failure of relaxation of the pylorus and hindgut, respectively [15].

The combined maturation of the ENS and CNS, together with their interconnections, is likely to be responsible for many of the major ontogenetic changes observed in intestinal motor activity before and after birth.

Characterization of Motor Activity

Gastric Motility

Many aspects of gastrointestinal motility appear to be less mature in the preterm infant than in the term infant, and those of the term infant less mature than those seen in the child and adult.

Although fetuses in utero are able to swallow amniotic fluid from as early as 20 weeks of gestation, the sucking mechanism does not appear until 32–34 weeks of gestation [16]. Gastric emptying of swallowed amniotic fluid into the intestine may be demonstrated in the human fetus at 30 weeks of gestation [17]. Between 28 and 38 weeks of gestational age, the gastric antral contraction amplitude increases from 10 to 40 mm Hg. Emptying half-time doubles when newborns of 28–34 weeks are compared with full-term neonates independent of feeding.
Contractions may occur singly, but occasionally phasic contractions may be sustained for 3–5 min. However, preterm infants had fewer antral clusters coordinated with duodenal clusters than term infants [18].

**Small Intestinal Motility**

Although complete interdigestive cycles can be observed occasionally in term infants, they are very rarely seen in preterm infants. Approximately 75% of the recordings obtained from neonates are occupied by a motor pattern that is not typically seen in adults: the nonpropagating cluster of contraction. This pattern consists of contraction bursts of 11–13/min lasting 1–3 min that do not migrate from the proximal gut to the distal gut [1]. With increasing gestational age, motor contractions become more organized, the duration of a single cluster becomes longer as does the duration of the motor quiescence separating the clusters. As a result this dominant pattern still occupies 75% of the recordings of term infants but clusters are longer (3–4 min) and their occurrence is lower (6–8 times/min). The migrating motor complexes (MMCs) appear between 32 and 35 weeks post-conception, as the overall occurrence of clusters decreases [19]. Some of these MMCs are poorly organized with slower propagation velocities.

In spite of an apparent immaturity of fasting activity, the intestinal motor activity pattern in preterm and term infants changes in response to feeding. However the appearance of a fed pattern is different at different gestational ages. Term neonates shown a fed pattern similar to that seen in adults. In contrast to term infants, only 25% of preterm infants display a mature type of fed pattern while about 75% display a prompt cessation of motor contraction after feeding. This pattern, associated with a delay in gastric emptying, is probably due to the immaturity of vagal regulation.

**Feeding and Development of Motility**

There is convincing evidence that an acute response of motor activity and peptide release are present with the first enteral feeding and that the provision of early enteral feedings facilitates functional maturation of the human intestine. Babies can respond to enteral nutrition as early as 25 weeks of gestational age [20]. This evidence suggests that the small intestinal fed response is a more primitive form of motor activity than is the fasting motor activity. For this reason the practice of delaying the use of enteral nutrition in the very low birth weight infant may not coincide with the preterm intestinal physiology of motor function.

Several studies have shown that gut function and subsequent milk tolerance is improved by trophic feeding. Trophic feeding (minimal enteral feeding, gut priming, early hypocaloric feeding) is a practice that involves feeding small volumes of milk, nutritionally insignificant but beneficial to the developing gut. Recent studies have reported that this practice accelerates the whole gut transit probably by enhancing the MMCs. The mechanism by
which trophic feeding exerts its influence is unknown. It is responsible for surges in the plasma concentration of several enteric hormones and peptides which alter gut motility (motilin, gastrin, neurotensin and peptide YY) and may cause stimulation of the ENS [21].

The manner in which babies are fed may also trigger differences in motor responses. Maturation of motor function requires that nutrients be fed to the neonates because feeding sterile water does not produce this effect [22]. Preterm infants fed by a 2-hour infusion display a brisk increase in motor contraction that is associated with faster gastric emptying compared to infants fed by a 15-min bolus. Feeding volumes that provide as little as 10% of the daily fluid intake significantly induce the premature appearance of MMCs in comparison to those that provide 30 or 100% [23].

In conclusion, minimal feeding volumes can be used to trigger maturation of motor function, at the same time avoiding the risk of enterocolitis that larger feeding volumes include. However, since cluster represents 60–75% of the motor activity in term infants who have completed the interdigestive cycle, the motor activity in these neonates is still very dissimilar from that seen in adults, suggesting that further changes occur throughout infancy.

**Colonic Motility**

The role of trigger that enteral nutrition occupies in the development of gastrointestinal function also represents a major factor in the ontogeny of colonic motility. It seems that colonic motility matures late in gestation and has different characteristics in infants compared to older children and adults.

Meconium can be found in the fetal rectum after 21 weeks of gestation, and as much as 10–20% of total amniotic fluid proteins are derived from the fetal gut. These data suggest that defecation in utero occurs physiologically during the late stages of pregnancy, and it is now believed that the detection of meconium in the amniotic fluid might reflect impaired clearance of meconium rather than excessive or inappropriate elimination in the amniotic fluid.

The correlation among early enteral feeding, passage of the first stool, stool frequency and consistency has largely been discussed in the pediatric literature.

Coordinated sucking and swallowing, required for the independent utilization of milk feeds, is not achieved until 32–34 weeks of gestation, after which time most preterm infants are capable of taking feeds by mouth. This gestational age coincides with a significant increase in the defecation rate and a surge in circulating concentrations of intestinal regulatory polypeptides (gastrin, motilin and neurotensin) in response to milk feeds.

In newborn infants, who do not have voluntary control, evacuation probably occurs in response to an increasing volume of stool in the rectum. In a large study observing bowel habits in 844 preterm infants, a direct relation between the volume of milk ingested and stool frequency throughout the first 8 weeks after birth was reported [24]. Infants who received no milk had a modal
frequency of 1 stool/day whereas those receiving $\geq 150\text{ml/kg/day}$ passed between 3 and 4 stools/day. Infants receiving human milk had a consistently higher defecation rate and passed softer stools than those receiving formula milk, regardless of the gestational age and feed volume. The finding of a modal frequency of 1 stool/day in the unfed neonate suggests that there is an intrinsic pattern of large bowel motor activity present as early as 25 weeks of gestation. This daily passage of stool may perform the 'housekeeping' function of clearing the colon of intestinal secretions and other unwanted material. Probably, milk feeds override the intrinsic fasting motor activity of the colon and induce regular defecation at a frequency determined directly by the volume of the products of digestion that reach the rectum: the more feeds, the more stools.

In full-term and preterm infants, the peak stool frequency occurs during the first week after birth, after which there is a decrease in spite of the increasing milk intake, indicating a maturation of the water-conserving ability of the gut. It is not known, however, whether this is due to the increasing efficiency of small intestinal absorption or colonic water retention.

Term newborn infants average 4 bowel movements/day for the first week of life. The frequency of defecation decreases with age, so that 85% of children 1–4 years old defecate once or twice daily. High-amplitude ($\geq 60\text{mm Hg}$) propagating contractions (HAPCs) are the manometric correlate of the radiologic 'mass movements' and are responsible for the rapid movement of feces. The presence of HAPCs together with an increase in colonic motility after a meal are markers of the neuromuscular integrity of the colon in toddlers and children [17]. HAPCs decrease in frequency from several per hour after a meal in awake toddlers to just a few per day in adults [25]. The gastrocolonic response also seems more prominent in younger compared to older children. Nevertheless the colon in toddlers seems to have fewer tonic and phasic non-HAPCs compared to the colon of older subjects. Information about age-related changes in colonic tone is absent.

The ongoing developmental maturation of bowel function results in intestinal hypomotility with consequent postponement of meconium passage. The first studies to measure intestinal transit in humans used amniography; aboral transport of contrast did not occur in the intestinal tract of fetuses younger than 30 weeks of gestation. Using amniography, McLain [16] observed that gastrointestinal motility increased with advancing gestational age; progression of contrast material from the oral cavity to the colon took as long as 9h at 32 weeks of gestation, but only half of that time by the time of labor. Intestinal transit is approximately three times slower in preterm infants compared with that seen in adults.

It has been noted previously that more than 90% of full-term infants and 100% of post-term infants passed meconium within 24h. There has been agreement on the general principle that defecation should be avoided in utero and that lack of defecation after birth is a sign of disease. In fact it is generally believed that the passage of meconium into the amniotic fluid is an indicator.
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of fetal distress. Nevertheless meconium-stained amniotic fluid is found in up to 30% of all deliveries, and no cause of fetal distress is found in up to 25% of all occurrences of meconium-stained amniotic fluid [26].

In premature infants with a birth weight of 1,000 g or less the first stool is passed at a median age of 3 days and 90% have their first stool by 12 days after birth [27]. Meetze et al. [28] found a median age of 43 h for passage of the first stool in 47 patients with birth weights 1,259 g or less. One forth of these infants had not passed stool by 10 days of age. Weaver and Lucas [24] reported a 32% delay in passing meconium at >48 h, with an inverse relation between gestational age and the time of first bowel action. Extreme prematurity and delayed enteral feeding were significantly associated with delayed passage of the first stool in more than one study [29, 30].

Therefore delayed passage of meconium and constipation could be induced by a delayed intestinal transit which is evident at the level of the colonic segments in particular. Naturally, normal development of the upper gastrointestinal tract (stomach; small intestine) is essential to warrant correct maturation of the colonic motility, too.

In conclusion, we have stressed that the ontogenesis of gastrointestinal motor activity is influenced by several factors such as smooth muscle activity, the CNS, the ENS and the neurohumoral system.

We have also seen that early enteral feeding plays a main role in the promotion of the development of small intestinal functions and colonic motility.

Further understanding about the timing of specific motor patterns in humans and their control mechanisms may enable neonatologists to reach optimal feeding strategies to induce better gastrointestinal function and to obtain optimal feeding tolerance.

References

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Discussion

Dr. Taminiau: You were talking about prematures with stomach emptying, but how does that relate to the retention? If you feed premature infants they usually have retention in the stomach and passage problems, delaying this emptying of the stomach. How is this related to the things you said about development? You said osmotic things are not important, but perhaps different foods are important.

Dr. Staiano: Dr. Benninga's studies show that in prematures, as young as 30 weeks of gestation, gastric emptying is normal as well as the antropyloric motility [1]. Perhaps
the delayed emptying is strictly related to the volume of the feed. In these last studies it was shown that with a larger volume there is inhibition of the propagated antral contractions and the appearance of isolated pyloric pressure waves that slow gastric emptying. So, the function of gastric emptying is strictly related to gestational age. It is mainly due to volume, to the caloric density and to the composition of the meal.

*Dr. Taminiau:* You said that continuous infusion is an advantage. Is that in the stomach also or just duodenal?

*Dr. Staiano:* Also in the stomach. Berseth et al. [2] in their study explained that perhaps the continuum infusion is better in the stomach because nutrients will stimulate the G cells in the antrum and therefore there is a larger secretion of gastrin which is an important motility hormone. The way in which nutrients are instilled determines faster gastric emptying or more mature duodenal motility. It always has to be instilled in 2 h, not by a bolus in 15 min, but the result is the same even if instilled just in the stomach [3].

*Dr. Taminiau:* So when these measures don’t work and you still have retention, do you then recommend a change of formula, going into more medium-chain triglycerides or polymers? What do you do in your unit?

*Dr. Staiano:* It depends if there is normal or abnormal gastric emptying. I don’t advise the use of this kind of feed in all prematures just to improve gastric emptying that is perhaps normal already. It is different if we talk about a premature infant with delayed gastric emptying.

*Dr. Benninga:* In the last slide you showed the mechanisms of constipation and you mentioned that difficulties in defecation might be one of them, but I think this counts more for toddlers. Can you speculate on why in 60% of all constipated children, constipation already starts in the first 6 months of life? Do you have any explanation for this?

*Dr. Staiano:* I don’t know if you are talking about infant dyschezia, due only to the lack of coordination between the increasing abdominal pressure and the relaxation of the pelvic floor during defecation. For sure in the first 6 months of life we don’t just have infant dyschezia, we can also have constipated infants, and the change from human milk to a formula may worsen the bowel habit. The latter group represents the only set of children in which dietary manipulation can improve the bowel habit. It has been reported in many studies that the hardness of the stools, which is one of the most important events in establishing chronic constipation, may be improved by infant formulas containing a prevalence of palmitic acid in the S2 position of the triglycerides, with a better absorption of the fat as monopalmitin instead of free fatty acid [4].

*Dr. Benninga:* With regard to the diet, do you believe in the new concepts of adding oligosaccharides to the feed in an early phase to prevent constipation?

*Dr. Staiano:* I was expecting this question from you. I don’t have any experience and I believe that in the literature there is still little information about that. But probably if the concept is that oligosaccharides have better fermentation in the colon, they can probably work similar to the disaccharides that we use to treat constipation.

*Dr. Bueno:* The migrating motor complex has been described as a housekeeper and a lot of work has been done on this pattern because it has two major functions, the first is to propel digesta within the small intestine and the second to prevent bacterial overgrowth. In preterm children there is a cluster-type motility pattern called the ‘fetal pattern’. Do you have any clinical data suggesting that we have more or less bacterial overgrowth with this pattern compared to the migrating motor complex, or do we see a change in the frequency of intestinal infection at the time of changing from the fetal pattern to the migrating motor complex?
Dr. Staiano: To my knowledge there are no studies on the frequency of bacterial overgrowth in premature infants. One of the main reasons for speeding up the maturation of motor activity in the small bowel is just to have a migrating motor complex earlier to avoid a superimposed bacterial overgrowth.

Dr. Schmitz: Would it be possible that water fluxes or variation in the capacity of water and sodium reabsorption in the colon play a role in the very early occurrence of constipation in some children?

Dr. Staiano: There is a study, I don’t know at which age but probably in the first year of life, where they tried to improve the bowel habits by increasing the fluid given to the child, and the only effect of increasing the amount of the fluid given to the infant was to have a larger volume of urine but it didn’t change the stool factor [5, 6].

Dr. Caroli: You said that only 5% of children have organic constipation due to motility alterations. Can you tell us which are the most common alterations and if there is some special symptom or sign besides constipation that can be used for early detection of the special problems.

Dr. Staiano: The most frequent cause of organic constipation in children is Hirschsprung’s disease with a frequency of 1 in 5,000 births, and then there are anorectal malformations and other organic causes such as endocrinial disorders or disorders of the central nervous system. Anyway, you are right that in these patients with organic constipation there are perhaps other associated symptoms different from functional constipation. The history and clinical examination will definitely help to differentiate between functional and organic constipation. For example, in patients with Hirschsprung’s disease we have a delayed passage of meconium, or there are much more common obstructive symptoms that are not frequent in children with functional constipation. On the other hand encopresis or soiling, which are very common in children with functional constipation, are almost never seen in children with Hirschsprung’s disease.

Dr. Benninga: I would like to make a comment on that because we have just finished a study evaluating the best diagnostic test in 130 babies suspected of having Hirschsprung’s disease [7]. In 25% of the patients we found Hirschsprung’s disease and it was striking that more than 50% of the healthy babies with functional constipation also had a delay in meconium production. We don’t have a good explanation for the latter finding.

Dr. Staiano: Were they premature?

Dr. Benninga: No, but you are right in saying that if we have a combination of delayed meconium production with signs of obstruction then Hirschsprung’s disease must be considered.

Dr. Staiano: It is interesting because very often neonatologists ask us to perform anorectal manometry and sometimes also rectal suction biopsy in children with delayed passage of meconium, but very rarely do we find Hirschsprung’s disease in these infants. How do you explain this delayed passage of meconium in non-Hirschsprung’s disease? Do you have any explanation?

Dr. Taminiau: Is there any system that is delayed in development? You said that one system takes about 12–15 months.

Dr. Staiano: There is a strict relation between the passage of the first stools and the first feed. The first feed definitely improves motility in premature infants. The composition of meconium is also sometimes involved in delayed elimination. Premature infants have a hard meconium in comparison to full-term infants with an increased amount of mineral and calcium and less production of intestinal secretions which allow elimination of the first stools. But I don’t have an explanation in normal children.

Dr. Waterland: Why is gastric emptying quicker with breast milk versus formula feeding?
Dr. Staiano: There are different studies but no one has the answer. One study suggests that probably breast milk has a prokinetic substance that may accelerate gastric emptying. There is no reason, no explanation until now.

Dr. Taminiau: Why do you ask?

Dr. Waterland: I think it is of direct relevance to the question of how infant feeding practice affects motility and constipation and all these things. I thought there might be studies correlating duodenal motility with, for example, hormones in breast milk; anything like that might explain it.

Dr. Staiano: While I was preparing this talk I was looking for some explanation to answer this question and in that last study I found an interesting explanation which says that human milk probably contains something that will accelerate it, but it is not known yet.

Dr. Schmitz: I come back the discussion between you and Dr. Benninga about normal babies who have no Hirschsprung's disease. According to what you know about motility, what would be the physiological explanation for such a big range of stool elimination in breastfed babies? On one hand breastfed babies are said to normally have 5 stools/day, but on the other hand one can see normal breastfed babies who are producing a stool once a week or even once every 10 days without any symptoms. So what makes the difference here?

Dr. Staiano: The main reason is better fat digestion of human milk because human milk contains a specific lipolytic enzyme, the bile salt, which stimulates lipase, and because human milk has a higher prevalent proportion of palmitic acid in the S2 position. So these are the main reasons.

Dr. Schmitz: But this does not explain the range from 1 stool every 10 days to 5/day with the same breast milk.

Dr. Staiano: There are studies trying to see if improving the fat composition of milk could also improve the number of stools per day in infants fed infant formula, but the number is not improved. These special infant formulas that are much more similar to human milk improve the softness of the stools but they don't improve the amount. One conclusion is that perhaps this is better because the use of diapers is smaller and it costs less [4]. This is mostly related to the maturation of the water-conserving ability of the gut.

Dr. Schmitz: This is what I wanted you to say. At some point water reabsorption is something important in constipation.

Dr. Lafeber: What interests me is the concept of minimal enteral feeding which is very popular amongst us neonatologists and is applied now in most countries. But if you look at the Cochrane meta-analysis of this practice it is not yet evidence-based [8]. Trials, like the one performed in the US by Berseth et al. [9], were stopped because after the introduction of larger amounts of feeding there was more necrotizing enterocolitis. But what intrigues me is what is behind this concept, I mean the amounts you showed in your slide, 4 ml/kg; if a baby is 700 g it is only 3 ml so that is not so much, so what is really happening here? If you give this small amount of food, is it stimulating motility? I cannot really believe that it is doing much to the trophic function of the gut because it is such a small amount of food. If you look at animal experiments what happens if you give food: you get a trophic effect of food on the gut mucosa if you give more than 40 or 50% of the needed amount of nutrition, so I cannot imagine that minimal enteral feeding really has a substantial effect on gut function [10]. So do you think it is motility?

Dr. Staiano: I think it is not just motility, it is also hormonal secretion. In fact this minimal volume stimulates the secretion of gastrin and neurotensin and such a small volume has an effect on hormonal stimulation and inhibits the polypeptides that are against the maturation of motility. I believe that both effects may improve maturation.
Berseth et al. [11, 12] did a study comparing the 4- and 10-ml volumes against 50\% of the daily fluid required, and the effect they obtained with 4 ml was better than with larger volumes, which may precipitate necrotizing enterocolitis. So I believe even if the meta-analysis does not support this finding, there is definitely an effect.

Dr. Exl-Preysch: I just wanted to add something to the discussion about gastric emptying and hydrolyzed formulas. Just have a look at the studies done by Billeaud et al. [13] and Tolia et al. [14]. They were able to demonstrate that only pHF (Nestlé NAN HA) matched the gastric emptying time of mother's milk. Therefore, as discussed before, it just cannot be the fat that is determining the gastric emptying time because those formulas have the same fat content as the other formulas based on unaltered cow's milk protein, whey or casein. The casein-dominant formulas were always those with the slowest gastric emptying time. Therefore it seems much more to be the protein source and how it has been treated (hydrolyzed or not) that determines the gastric emptying time. In addition studies conducted by Mihatsch et al. [15] and also Sievers et al. [16] showed clearly that formulas with hydrolyzed proteins had a much quicker gastrointestinal passage than non-hydrolyzed formulas, a reason why, for instance, in Germany, in preterm nutrition, hydrolyzed formulas are highly preferred.

Dr. Staiano: I agree. There are still a lot of conflicting data on this issue and probably we need further studies to clarify this aspect better.

Dr. Keller: You briefly mentioned the physiological appearance of hyperplastic ganglia in the hindgut. We were talking about these young infants having no Hirschsprung's disease, but defecation difficulty. You know the German data that intestinal neuronal dysplasia had a sort of wrong definition or a change in definition over the time [17, 18]. Do you think intestinal neuronal dysplasia still exists? Is it a disease, or is it a wrong interpretation?

Dr. Staiano: I believe that intestinal neuronal dysplasia exists, depending on the definition. If we are talking about intestinal neuronal dysplasia of the myenteric plexus then the diagnosis exists and it is a serious disease which manifests clinically as severe intestinal pseudo-obstruction. If we refer to the German definition of intestinal neuronal dysplasia, which is based only on findings from rectal suction biopsy, I don't believe that the diagnosis exists anymore. There are two well-conducted studies, one from Cord-Udy et al. [19] and one from Koletzko et al. [17], in which they showed that there is a very high inter-observational variation in analyzing suction rectal biopsy samples. Cord-Udy et al. [19] showed that infants who in the first months of life received a diagnosis of intestinal neuronal dysplasia according to the German criteria, were all healthy children at the 4- to 5-year follow-up. Most probably there is a defect of maturation in the first year of life.

Dr. Keller: That means that we need a full-thickness biopsy to rule out intestinal neuronal dysplasia.

Dr. Staiano: Yes, but we need severe clinical manifestations to think about the presence of intestinal neuronal dysplasia, not just chronic constipation.

Dr. Sinaasappel: Regarding your comment on malabsorption of fat in babies drinking cow's milk or being bottle-fed, a product is now being developed to produce bile salt-stimulated lipase, so in the future bile salts can be added to cow's milk or to formula to stimulate lipase. Are you in favor of this? Do you think that is a possibility to increase fat absorption and also probably to prevent it.

Dr. Staiano: In association with a higher proportion of palmitic acid in the S2 position, it could perhaps work.

Dr. Taminiau: In addition to what was said about the development of constipation and neuronal dysplasia, the cells of Cajal are diminished in many obstructive diseases and this seems only to be a reaction to obstruction. They are diminished whatever artificial obstruction is produced in animals, or it seems to be a secondary thing. So if
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there is any obstruction the development might be delayed; this very sensitive system has not been studied as far as I know. Do you know?

Dr. Staiano: No.

Dr. Taminiau: So this may be another area that might be involved in early constipation, and it has not been studied yet.

References