Introduction

Advances in mechanical ventilation, the use of pulmonary surfactants, improved pharmacological management of expectant mothers and preterm infants and greater confidence in our overall intensive care techniques have resulted in a marked increase in the number of very immature infants who survive. The same ethical controversies of 20 years ago surrounding whether or not to resuscitate premature of 26–28 weeks gestation are now focused on 22–24 weeks. Those involved with the care of these survivors are faced with a constellation of problems that include prevention of morbidity and fulfillment of genetic potential. Nutrition is becoming a key factor not only for the growth of these infants during their neonatal intensive care unit (NICU) stay, but also for prevention of morbidity and enhancement of their life-long well being.

The major goal of this review is to provide the reader with an overview of a few recent advances in nutrition that can be applied in the daily care of these patients. In addition, a few emerging concepts about conditionally essential amino acids, long-chain polyunsaturated fatty acids (LC-PUFAs) and probiotics are presented that are likely to become important modalities in the future care of these infants.

Morbidities Amenable to Improved Nutrition

Both short- and long-term morbidity that might be amenable to nutritional intervention are encountered in the NICU (table 1).
Some of the major short-term morbidity faced by very low birth weight (VLBW) infants in the NICU include: chronic lung disease; hospital-acquired sepsis; necrotizing enterocolitis (NEC), and a high cost of care. One major long-term morbidity is poor neurodevelopmental outcome. Furthermore, the concept that nutritional deprivation during critical periods of development can ‘program’ the individual toward a greater disposition to adult diseases has emerged [1].

Although the focus of neonatal nutrition has previously been on the period after critical illness has subsided, it has become increasingly evident that nutrition during the first few weeks of life while the infant is struggling for survival is crucial. Evaluations of growth reveal that many VLBW infants do not attain the same growth, had they remained in utero during the time they are in the NICU [2] (fig. 1). From this figure, it is evident that infants born prematurely are being discharged from the NICU ‘small for gestational age’ when compared to fetuses growing in utero.

Although not yet fully substantiated, postnatal growth retardation appears to be analogous to infants being intrauterine growth-retarded (IUGR), which has been associated with the development of ‘metabolic syndrome’ or ‘syndrome X’ during adult life. This syndrome includes obesity, type-II diabetes and hypertension, and is thought to be due at least partially to the development of a ‘thrifty’ phenotype [3] secondary to nutritional deprivation during early development. Part of this failure to reach intrauterine growth potential stems from the fear of causing NEC by too rapid advancement of enteral feedings in an individual with an immature intestine. There are also major concerns of causing metabolic imbalances with parenteral nutrition [4].

In this review, we will first discuss the macronutrient needs of the low birth weight infant and methods used to meet these needs. The emphasis will be on continuation of growth and nutrition similar to that the infant would receive and attain in utero. We will then discuss a few nutritional supplements that are emerging as potential agents in the prevention of both short- and

<table>
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<tr>
<td>Chronic lung disease</td>
<td>Poor neurodevelopment</td>
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<tr>
<td>Hospital-acquired sepsis</td>
<td>‘Programmed’ for metabolic syndrome in adulthood (syndrome X: obesity, hypertension, type-II diabetes, coronary artery disease)</td>
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<td>Intestinal problems</td>
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<td>(necrotizing enterocolitis and perforations)</td>
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<td>High cost of care</td>
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Nutritional Needs of the VLBW Preterm Infant

Energy Requirements
The fetus gains approximately 5 g/day at 16 weeks of gestation, 10 g/day at 21 weeks, and 20 g/day at 29 weeks [5]. Between 24 and 40 weeks gestation, water content declines from approximately 87 to 71%, protein rises from 8.8 to 12%, and fat from 1 to 13%. The American Academy of Pediatrics has recommended that the caloric and average intake of the growing preterm infant to be approximately 120–130 kcal/kg/day [6].

Specific Nutrients
Glucose and Carbohydrates
Both hyper- and hypoglycemia are common problems in VLBW infants. Glucose utilization and production rates in VLBW average from 6 to 10 mg/kg/min [7]. The cause of hyperglycemia is not known, but may include...
stress, relative insulin resistance and a decreased utilization of glucose secondary to lipid infusion. What constitutes ‘hypoglycemia’ in the preterm infants is somewhat controversial. Fetal plasma glucose levels over the second half of gestation are usually greater than 2.8–3.1 mm/l [8]. These levels are barely greater than those below which repeated measurements of low glucose concentrations are associated with increased risk of mental and motor developmental delay [9]. Thus, the 2.8- to 3.1-mm/l glucose concentration range should be the lower limit for VLBW preterm infants. Because of its critical role in brain metabolism, glucose infusions should start immediately in critically ill prematures. The role of infusing insulin in order to increase energy intake for faster growth remains controversial.

Amino Acids and Protein

Growth cannot be attained without protein or amino acids. The growth rate of lean body mass of the normally growing human fetus is about 3.6–4.8 g/kg/day [10]. This is greater than the amount of amino acid or protein intake that these infants usually are fed. With current human milk or formula-feeding regimens, it is practically impossible to achieve intakes that are necessary to achieve and maintain the desired rates of protein intake [10]. This becomes especially critical in sick VLBW infants. If they receive glucose alone, they lose in excess of 1.2 g/kg/day of endogenous protein [11]. Provision of amino acids, even if total energy intake is low, spares endogenous protein stores by enhancing the rate of protein synthesis. Providing 30 kcal/kg/day with 1.1–1.5 g intravenous amino acid changes the balance of protein from substantially negative to zero or slightly positive [12]. Higher intakes of both protein and energy result in net protein anabolism [13]. Unfortunately, many VLBW infants do not receive even such modest intravenous amino acid intakes during their first several days of life, nor do they receive enough enteral feedings to meet these requirements, thus assuring the development of a catabolic state.

The above information suggests that ideally, we should not interrupt the flow of nutrition that the fetus has been obtaining from its mother and not hesitate to provide nutrition to the infant immediately after birth. Because of gastrointestinal immaturity, it is neither possible nor prudent to attempt full nutrition by the enteral route immediately after birth. However, there are very few, if any convincing reasons to withhold intravenous glucose, amino acids, lipids, vitamins and trace elements beyond the immediate stabilization period after birth (which should not be more than 6–12 h). There is a tendency to begin parenteral amino acid intake at only 0.5 g/kg/day or less, gradually achieving an intake of 2.5–3.0 g/kg/day over a period of 7–10 days to avoid protein ‘intolerance and toxicity’. This practice should become obsolete because of recent studies demonstrating that intakes up to 2.9 g/kg/day revealed little evidence of protein toxicity as measured by hyperammonemia, azotemia, or metabolic acidosis [14].
Lipids
Lipid requirements are limited to the essential fatty acids (linoleic and linolenic acid). Although lipid comprises about 50% of the nonprotein energy content of both human milk and formulas, both of which contain these fatty acids, the frequent practice of limiting enteral intake precludes the supply of these essential fatty acids, unless they are provided intravenously. Parenteral lipid emulsions provide these essential fatty acids but their use is often delayed or limited by concerns of adverse effects. These putative effects include impaired oxygenation, impaired lung function, impaired immune function, decreased platelets and increased free bilirubin levels. Despite in vitro studies which suggested effects of lipid emulsion on immune function, there is no conclusive evidence for in vivo effects. In vitro studies have shown that unesterified fatty acids can displace bound bilirubin from albumin, thus increasing free bilirubin. However, clinical studies have shown that infusion of lipid at rates up to 3 g/kg/day do not increase plasma concentrations of free fatty acids or free bilirubin [15]. Provision of lipid infusions at rates of less than 0.2 g/kg/h does not result in deterioration of oxygenation or lung function [16]. Despite thrombocytopenia being frequently listed as a side effect of intravenous lipids, provision of up to 3.3 g/kg/day has been shown to have no effect on platelet concentrations even if given for up to 4 weeks [17]. Controversy remains about whether intravenous lipids are associated with an increased incidence of sepsis. At this time there is no convincing evidence that lipids should be withheld because of an increased risk of sepsis.

Failure to provide essential fatty acids in the extremely low birth weight infant results in biochemical signs of deficiency within 72 h [18]. This can be prevented by the administration of as little as 0.5 g/kg/day of lipid emulsions. Although these emulsions contain high concentrations of linoleic and linolenic acid, they do not contain the LC-PUFAs, arachidonic (AA) or docosahexanenoic acid (DHA). These are thought to be critical nutrients for the developing central nervous system. The qualitative composition of lipids in these intravenous emulsions is quite different when compared to normal tissue and plasma lipids and human milk. The high content of linoleic and linolenic acid, but low content of saturated and monounsaturated fatty acids along with the absence of LC-PUFAs raises questions about the propriety of the present solutions for the VLBW infant. Furthermore, the concentration of n-3 fatty acid in these lipid formulations is relatively low. Whether an increased intake of these would provide an anti-inflammatory effect in these infants is not currently known.

Considerations for Enteral Feeding of the Sick Premature Infant

Gastrointestinal Development
One of the major reasons why neonatologists do not use the gastrointestinal tract of the premature infant for long periods of time after
Nutrition of Premature and Critically Ill Neonates

Table 2. Summary of nutritional approach to VLBW infants

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<th>Enteral intake</th>
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<tr>
<td>Begin as soon as possible (day 1 of life, e.g.) – minimal enteral nutrition during TPN</td>
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<tr>
<td>Breast milk – preferably from infant’s own mother, or premature formula</td>
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<td>Advance enteral intake as TPN is being decreased</td>
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<th>Parenteral intake</th>
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<tr>
<td>Begin glucose infusion immediately after birth at 4–8 mg/kg/min</td>
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<tr>
<td>Begin amino acid infusion at 2.5–3.0 g/kg/day on day 1 of life</td>
</tr>
<tr>
<td>Begin intravenous lipids at &lt;0.2 g/kg/h infusion but &gt;0.5 g/kg/day within the first 1–2 days of life</td>
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birth is that the gastrointestinal tract of these infants is poorly developed. What are these immaturities? These consist of suck-swallow incoordination, poor gastric emptying and intestinal motility, and immaturity of luminal digestion and mucosal absorption. How quickly should enteral feedings be advanced? Because of the individual characteristics of each patient, one feeding protocol or guideline cannot be used for all infants. Clinical judgement based on available scientific data and experience presently appear to be the best criteria upon which we should base our feeding practices. However, there are data showing that advancement of enteral feedings faster than 20 ml/kg/day is associated with an increased incidence of NEC [19]. From the available studies, minimal enteral feedings should be instituted within the first days of life. What constitutes ‘minimal enteral nutrition’ is not clearly defined. Review of the literature supports a definition of minimal enteral nutrition as being less than 20 ml/kg/day, an amount insufficient for the demands of the rapidly growing infant, but enough to promote intestinal trophic hormone release, improve motility and prevent atrophy induced by total parenteral nutrition (TPN) and lack of enteral nutrients. There is no clear evidence that the concomitant use of umbilical catheters, continuous positive airway pressure, mechanical ventilation, indomethacin or the presence of apneic and bradycardic episodes preclude the use of minimal enteral nutrition because of an increased risk of NEC.

Feeding milk from the infant’s own mother is the preferred enteral intake. This has been associated with less NEC, sepsis and better tolerance to advancement of enteral feedings [20].

Table 2 summarizes these recommendations for nutritional support.

**Nutritional Supplements**

The intestine is a primary origin of the systemic inflammatory response syndrome. It is therefore reasonable that nutritional agents might stabilize the
intestinal mucosal barrier, alter the balance of pro- and anti-inflammatory cytokines, and prevent excessive activation of nuclear factor κB (NFκB), a transcription factor that is thought to play a major role in the production of proinflammatory mediators.

Some nutrients, such as glutamine, arginine, n-3 fatty acids, and probiotics, have been shown to influence intestinal barrier function and the immune system.

**Amino Acids (Arginine and Glutamine)**

Even when high quantities of amino acid or protein are provided, an inadequate intake of certain ‘conditionally essential’ amino acids may exist. Examples of these include glutamine, arginine, glycine, histidine, taurine and tyrosine. If these are not provided, essential amino acids are diverted away from protein synthesis. One such amino acid that has recently received increasing attention is glutamine. Supplementation in adults has resulted in improved survival; decreased hospital-acquired sepsis in bone marrow transplant and trauma patients, along with improved nitrogen balance and decreased costs of hospitalization [21]. One study of parenteral glutamine supplementation has shown decreased requirement for mechanical ventilation in neonates with a birth weight of less than 800 g [22]. Another study of enteral glutamine supplementation has suggested decreased hospital-acquired sepsis, decreased catabolism and/or improved amino acid utilization, improved tolerance to enteral feedings, decreased cost of hospitalization and appeared safe at the doses used [23].

The rationale for supplementing glutamine is based on its ubiquitous metabolic role in energy metabolism (especially in the intestine and lymphocytes), nucleotide synthesis, glucosamine synthesis, and as an antioxidant precursor. Studies in animals have demonstrated both intravenous and enteral glutamine to be protective against various forms of experimentally induced enterocolitis and it has been found to be a ‘conditionally essential’ amino acid during times of stress. VLBW infants are catabolic and highly stressed during their first weeks of hospitalization. Despite this, glutamine is not added to their TPN and they do not receive glutamine unless they are enterally fed (they frequently are not, as previously mentioned). This constitutes a major interruption in the flow of glutamine these infants would be receiving had they remained in utero [24]. In the study of infants, analysis of T cells found a blunting of HLA-DR+ and CD16+ T lymphocytes, which was consistent with decreased stimulation of the immune response secondary to decreased translocation of bacteria or their antigens across mucosal surfaces.

In a study of a rat model of endotoxemia, Wischmeyer et al. [25] found glutamine reduced proinflammatory cytokine release, organ damage, and mortality. In another study, 9 fasted volunteers received either glutamine or saline orally over 6 h. Duodenal biopsies were taken and cultured for 24 h with or without glutamine. This study demonstrated that glutamine pretreatment
in vivo and in vitro significantly decreased production of proinflammatory cytokines (IL-6 and IL-8) by the human intestinal mucosa [26]. In a mouse model glutamine-enriched TPN preserved the expression of IL-4 and IL-10 mRNA (anti-inflammatory cytokines) in lipopolysaccharide-stimulated intestinal lamina propria [27]. Preliminary studies in Caco-2 cells by our group demonstrated that glutamine decreases IL-8 production after lipopolysaccharide stimulation (unpublished results). Investigations underway in our laboratory are designed to determine whether this downregulation is mediated via NFκB. These studies support the hypothesis that some of glutamine’s beneficial effects may be a result of improved gut integrity or immune function and that glutamine could be used to regulate the intestine-mediated inflammatory response.

Arginine

Another amino acid that some consider as either essential or conditionally essential in the neonate is arginine. This amino acid plays a critical role in immune function, as a stimulant to the production of growth hormone and as a precursor to energy carriers such as creatine. As a precursor for the synthesis of nitric oxide (NO), creatine, polyamines, urea, ornithine, proline, glutamate, and other molecules with enormous biologic importance, and as a stimulant to the production of growth hormone, L-arginine plays versatile key roles in nutrition and metabolism [28].

The plasma and intracellular concentration of arginine may be critical not only for tissue growth but also for normal physiological function. It has been shown that premature infants who subsequently developed NEC have a significant lower plasma concentration of arginine [29]. This may be due to an increased metabolic demand for arginine or limited endogenous synthesis. NO plays an important role in the gastrointestinal system. In the face of inflammation or injury, NO is a mediator critical to regulation of blood flow in the intestine. Study in a neonatal piglet model of NEC suggested a potential therapeutic use of arginine, which is the substrate of NO synthase [30]. The effect may be synergistic to protein and polyamine synthesis, which also would help maintain intestinal mucosal integrity. One study in VLBW infants demonstrated a lower incidence of NEC in arginine-supplemented infants [31]. Current TPN solutions remain suboptimal for arginine for preterm infants.

Probiotics

Probiotics are defined as live microbial food supplements that beneficially affect the host animal by improving its intestinal microbial balance. Their attachment to the intestinal epithelium can strengthen the host’s mucosal defenses through enhancement of secretory antibody responses, through a tightening of the mucosal physical barrier to microorganism translocation, and by a balance in T-helper cell response [32].
A better understanding of probiotic-epithelial crosstalk can be used to devise new strategies to prevent and treat bacterial infections of the gut. From the fact that largely bifidobacterial flora have been observed in breast-fed infants who show a greater resistance to various infectious diseases than do bottle-fed infants, the desire arose to generate a predominantly bifidobacterial flora in bottle-fed infants. Administration of *Bifidobacterium bifidum* to bottle-fed infants results in an increase in fecal counts of bifidobacteria and a decrease in fecal pH, which plays a role in protecting premature infants and other newborns from intestinal disease. One study documented a reduction in NEC in premature newborns given a daily enteral supplement of *Lactobacillus acidophilus* and *Bifidobacterium infantis* compared with a historical control group [33]. Additional prospective studies are needed.

**Long-Chain and n-3 Polyunsaturated Fatty Acids**

Dietary fatty acids such as linoleic acid (LA; 18:2 n-6) and α-linolenic acid (ALA; 18:3 n-3) of the n-6 and n-3 series of PUFAs, respectively, are considered ‘essential’ because they must be derived from the diet. Once ingested, the essential fatty acids are converted to longer-chain, more highly unsaturated fatty acids, including AA from LA and eicosapentaenoic acid (EPA) and DHA from ALA. Modulation of immune and inflammatory responses has been reported with increased intakes of PUFAs of the n-3 series [34]. The outcome is dependent on the type of PUFA, the target tissue, as well as the immune status of the host before exposure. Specific cellular mechanisms for these events may include modulation of transcription factor expression, e.g. NFκB; alteration of signal transduction protein (protein kinase C) activity; inhibition of cellular transport proteins (Mg2+-ATPase); inhibition of apoptosis; stimulation of the antioxidant system, and modulation of cytokine and prostaglandin metabolite receptor activation. Recently, Caplan et al. [35] indicated that dietary PUFA supplementation (AA/DHA ratio of 1.5:1) significantly reduced the incidence of NEC in the neonatal rat model by downregulating platelet-activating factor (PAF) production, PAF receptor synthesis, and endotoxin translocation into the systemic circulation.

Intake of LC-PUFAs may be related to structural and functional development of sensory, perceptual, cognitive and motor neural systems. DHA is selectively incorporated, retained, and highly concentrated in the phospholipid bilayer of biologically active brain and retinal neural membranes. LC-PUFA supplementation of neonatal formula has been studied extensively for the outcomes of central nervous system development and visual acuity. Additional research is warranted to delineate the specific cellular effects of PUFA on intestinal integrity, to clarify the specific components of PUFA responsible for improved intestinal health in animals and to confirm the beneficial role of these dietary supplements for premature infants.
Conclusion

In this brief overview, the main message is that during critical illness in newborn infants, emphasis should be placed on the provision of optimal nutrition. This is necessary for alleviation of not only short-term morbidity, but for optimization of health throughout the individual’s lifetime.

References


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**Discussion**

*Dr. Kudsk:* What is the normal amino acid composition of mother's milk?

*Dr. Neu:* The protein matrix is actually a little bit less than what you find in most of the commercial formulas, and so mother's milk actually provides less total protein than do some of the commercial formulas. Now one of the things that the commercial companies have done is they have actually made fortifiers for mother's milk so that once these babies are on full enteral nutrition they actually have more protein added.

*Dr. Endres:* If you investigate breast milk longitudinally, you can show that the composition of amino acids is changing in the first week. For example in the colostrum there are very high amounts of taurine which decrease thereafter. This could be interpreted teleologically that the young infant is not able to produce taurine from cystine or methionine. Many amino acid solutions in pediatrics as well as infant formulae are designed on the standard of breast milk. But there are of course a lot of other issues as mentioned by Dr. Neu, e.g. if premature babies receive pumped breast milk, it should be supplemented by a fortifier so that it has a caloric density of about 85% instead of only <70 kcal/100 ml, and this should be continued after hospital discharge.

*Dr. Neu:* This is something that people could take hours to try to answer. I think that probably to try to answer this as concisely as possible, it is not only a nutritional...
fluid, it also has a lot of very bioactive components, lactoferrin, cellular components, IgA, very long chain fatty acids (e.g. docosapentaenoic acid, DHA) that we haven’t been able to fully duplicate commercially yet.

Dr. Cynober: You mentioned that glutamine is the first amino acid taken up by the fetus and you mentioned that glutamate is the first amino acid released by the fetus. If I try to make a balance, the net balance is one ammonia molecule production without any energy production, without any substrate of interest production. What is the rationale about this rather surprising thing?

Dr. Neu: This is called the glutamine/glutamate shuttle, and this was a sort of schema that was developed by the people at the University of Colorado starting at the mid 1970s [1]. They found that glutamine is the major amino acid going into the placenta, it is actually enriched somewhat by the placenta. Then it goes to the mother, it goes to the fetal liver, and then more than 50% of it is converted to glutamate. The glutamine is used for various purposes in the fetus. The glutamate goes back to the placenta and enters the tricarboxylic acid cycle, and it is thought that it is actually important in the pyruvate malate conversion reaction to help maintain progesterone production. There are some studies [2] that suggest that this is a very important component of that glutamate coming back to the placenta. The fetus also is not able to make glucose through gluconeogenesis and it is thought that glutamate is the most important gluconeogenic substrate for the fetus. So there is a very interesting interrelationship with that particular glutamine/glutamate shuttle in the fetus and the mother and the placenta.

Dr. Moore: We had an interesting discussion yesterday of comparing necrotizing enterocolitis (NEC) with this nonocclusive bowel necrosis. What you are describing in these children is exactly the fear that we have in these sick adults. How do you assess bowel function or tolerance while you are advancing enteral feeding?

Dr. Neu: That is still very crude and yesterday we discussed that there are methods that we have right now to look primarily at how much gastric residual remains in the stomach 2 or 3 h after feeding, and there are certain loose criteria that we use to see if we should continue to advance feedings. One criterion is looking at abdominal distension. If there is abdominal distension, sometimes it may be too late. Our colleague Dr. Berseth [3] has done some studies looking at motility and migrating motor complexes, and she has found that this can be correlated to gut motility and capability for advancement of feedings. The only problem is that this is a technique which is, at least at this point, not very useful practically for routine use.

Dr. Martindale: My understanding is that the fetus swallows a significant amount of amniotic fluid in the last trimester and the highest amino acid in the amniotic fluid, I understand, is also glutamine. What is the reluctance of neonatologists to drip in small amounts of glutamine? I mean if the child normally would have been swallowing very large amounts of glutamine in utero, I am still not clear. It doesn’t make sense to me why they want to prevent that.

Dr. Neu: This is also a question that has to do with a sort of neonatological culture and I think that we are at a point right now where we are very afraid of trying new things. Sometimes when I mention glutamine to my neonatology colleagues they ask why are you giving this drug? This is not a pharmacologic agent, this is not a drug, this is primarily a food replacement that the infant is not getting in the ICU which he/she would be getting had the infant remained in utero or was able to ingest a normal diet. This is where our discussions have been in the last couple of days, if this is something that we are trying to replace which really should be there but is not there. The Pediatrix enteral glutamine supplementation trials actually involve putting glutamine into water so that we are able to provide about 0.3 g/kg/day of glutamine to these babies enterally. That is really the approach that I would like to take if we are going to use glutamine in the future: to use it by the enteral route as a primary route. You are
Nutrition of Premature and Critically Ill Neonates

absolutely right about the amniotic fluid. In the last trimester of pregnancy the fetus
swallows approximately 450 ml/day of amniotic fluid. You have a flux of amniotic fluid,
a tremendous flux going through their gastrointestinal tract, and that would translate
to about 10 liters going through the adult gastrointestinal tract a day. Nobody has even
tried infusion of just amniotic fluid in those kinds of volumes because we are just
scared to death of hypomotility problems in the neonate.

Dr. Zazzo: What about trace elements in neonates, the pool may be very small, and
the question is, did any study you presented contain trace elements and vitamins in a
large enough amount, and is this an explanation for a lack of results in the infection
rate for instance?

Dr. Neu: They did supply trace elements in the total parenteral nutrition solution
that they gave to these babies. It is routine practice now to give vitamins and trace
elements, but we still don’t know the exact requirement. But remember, both groups
received the same amount of trace elements, the control and the glutamine-
supplemented group received the same amount of trace elements. I see one potential
flaw in that study. This is something that I am very concerned about, and we had a
controversy about this the other day, about making isonitrogenous controls. The flaw
is that they tried to make isonitrogenous control studies and the way they did this was
that they added 20% glutamine in the glutamine-supplemented group but they took
out 20% of the other amino acids including essentials. So the glutamine-supplemented
group had more glutamine, but had less total amino acids including essential amino
acids. So this may be a very important point in that particular study.

Dr. Herndon: There is a basic assumption, and this seems to be a neonatologist
culture, that NEC comes from feeding or overfeeding, whereas the reverse may be
true, that it comes from underfeeding. Can it only be studied in humans? Are there no
models? Is there any experimental evidence that early feeding in neonates contributes
to NEC?

Dr. Neu: There is feeding with the big F and there is feeding with the little F. The
feeding with the big F is the one where we try to get to full enteral nutrition in the 1st
week of life, 120 cal/kg/day in the 1st week of life. That was tried by many
neonatologists back in the 1970s, and it almost invariably lead to major detrimental
consequences.

Dr. Herndon: Was NEC one of those?

Dr. Neu: That is the major detrimental consequence that I am talking about. There
have been several studies looking at the advancement of feeding [4, 5] and usually
an advancement of >20 cm³/kg/day of formula has been associated with a higher
incidence of NEC. But studies [5] that have been done with the minimal enteral
nutrition, the little F, where you provide them with a very slow onset of enteral feeding
over the 1st week of life, those studies actually suggested a lower incidence of NEC,
not statistically significant but the analysis that was done suggested that there was
actually less NEC. It certainly appears to be safe and has all those other positive
consequences that I showed on that slide.

Dr. Calder: You mentioned the very high rate of protein accretion during the third
trimester but also during that period there is a very high rate of accretion of specific
fatty acids, arachidonic acid and DHA. I wonder if people have considered those
specific fatty acids, and then thinking about that I remembered the study Carlson
et al. [6] did of egg yolk phospholipids which showed a decreased incidence of NEC,
particularly I think in preterm boys rather than girls. So there might be some
functional effect in addition to the traditional structural role of those fatty acids.

Dr. Neu: Yes, I fully agree with you and that is certainly an area that we have to
look at more closely, the lipid area in neonatology. I think we neonatologists have been
so focused on the survival aspects that some of these things have just kind of gone by
the wayside. Now we need to start looking at things like that, and the Carlson study I think was very provocative but certainly more work needs to be done in that area.

Dr. Allison: The NEC story is an interesting one. On other side of the equation is the circulation in the microvillus which is a very counter-current system, and of course feeding makes demand upon this. Is there anything you can do to improve the other part to increase the tolerance? My daughter did an observational study where she showed that all 9 cases of 180 babies admitted to her unit over a year or 18 months all followed immediately from red cell transfusion. So obviously this changes the viscosity very abruptly and this can make a critical change in the microcirculation. So is there any way to increase the tolerance by paying attention to that microcirculation to improve that?

Dr. Neu: One of the interesting aspects of the arginine supplementation trial is that in the discussion section of that article [7] in the *Journal of Pediatrics* just 3–4 months ago, they were talking about the effect of nitric oxide on the arginine supplementation. I think that is certainly one area that is very interesting. Arginine supplementation might be a way to go about that.

Dr. Moldawer: You commented on large prospective clinical trials, one with intravenous glutamine and one with enteral glutamine, and you talked briefly about some of the reasons why the enteral study was not positive. I was just curious where your thoughts were going in terms of future large clinical trials with enteral/parenteral studies. Are we going to see additional studies now? The fact that you can get beneficial effects on secondary outcomes is always optimistic, but the primary objectives tend to be looked upon a little less favorably. I was wondering if there is an effort now to redirect those studies or are we going to see more large scale?

Dr. Neu: I think it is too early to tell. What I am afraid of is that the negative result in this very large National Institutes of Health multicenter trial may have killed the enthusiasm for studying glutamine further, at least at the National Institutes of Health level.

Dr. Moldawer: That is where I was going. It is very difficult these days to get enthusiasm based on one poorly designed negative study with inappropriate entry criteria and inappropriate outcome variables, to then go ahead and design the appropriate study based on those results.

Dr. Neu: If the secondary outcome results with the enteral trial hold up, there is tremendous concern amongst neonatologists about intraventricular hemorrhage and periventricular leukomalacia. If we can demonstrate a therapy that decreases this, and if this really holds, along with further information on mechanisms for this, then I think that the enthusiasm for looking at glutamine will be reinvigorated.

Dr. Allison: You spoke about the lipids, but what about the lipid profile because of the demand of the growing brain for phospholipid and so on? Have you developed the lipid profile of your preparations far enough, or which direction are you going with that?

Dr. Neu: The answer to your first question is no, in my opinion the work on lipid profiles has not yet been fully elucidated. There are studies on the central nervous systems of human milk-fed babies and formula-fed babies looking at the brain and red cell composition [8]. I think that we have some handle on that but I don't think that those are necessary ideal studies. The gold standard we use in terms of lipid composition for feeding is human milk, but that may necessarily not be the gold standard for a baby that is born very prematurely. So there are still a lot of questions in that area and, as I mentioned, some of formula companies have put millions of dollars into the studies of long chain fatty acids, adding the long chain of fatty acid DHA to formulas, and also some arachidonic acid. Studies were done looking at the various combinations of these, and at least in Europe I think most of the formula
companies include these long chain fatty acids and in the US the Food and Drug Administration has just given approval to a couple of the companies to add DHA. But we have not yet looked at the anti-inflammatory effects and more studies are needed in that particular area, and the question is should more eicosapentaenoic acid (EPA) be added and can we be getting anti-inflammation by adding EPA to the formulas?

Dr. McClain: You showed that glutamine was downregulating proinflammatory cytokines. Is there any thought that its important role in utero might be to keep a tolerance state there, which is vital for normal in utero growth?

Dr. Neu: That could be one mechanism. I think we can certainly speculate on that. There are very interesting results in both the neonatal and obstetrics literature. There is now a growing body of information that inflammation of the placenta in the mother associated with elevated amniotic fluid proinflammatory cytokine concentrations, and plasma cytokine concentrations in the fetus are associated with the development of intracranial hemorrhage and periventricular leukomalacia. This is why I think that if glutamine is downregulating the inflammatory response, it could potentially be the reason why we are seeing less intracranial hemorrhages and periventricular leukomalacia in these babies. If the glutamine administration is started shortly after these babies are born, and you downregulate that response, could this be where some of that benefit comes in?

Dr. McClain: Actually the Centers for Disease Control and Prevention in the United States is very interested in the proinflammatory cytokines, and so not only those complications but also premature delivery and overall poor outcome are associated. They are looking at this in an inner city minority population as a risk factor for all those complications.

References