Nutrient Requirements of Premature Infants

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Abstract

Exact knowledge of the nutrient requirements of premature infants is critically important for the prevention of postnatal growth failure and for improved neurodevelopmental outcome. Methods whereby nutrient requirements can be estimated fall into two categories, factorial methods and empirical methods. Each have their advantages and disadvantages. The factorial methods provide estimates of requirements for protein, energy and a number of other nutrients. The exact methods used can vary but still yield fairly similar results. Factorial methods also permit estimation of the extra nutrients needed for a given degree of catch-up growth, but cannot indicate the extent to which catch-up growth is actually possible. Empirical methods yield estimates of the requirements for protein and energy but not for other nutrients. They often give an indication of what degree of catch-up growth is possible, in addition to providing estimates of the requirements for protein and energy. The advantages of catch-up growth outweigh any possible disadvantages associated with it. The nutrients needed for catch-up growth should therefore always be provided.

Introduction

In recent years it has become apparent that many premature infants, in particular those born with very low birth weight, experience postnatal growth failure [1, 2]. The inadequate nutrient intakes that lead to this growth failure are suspected to be responsible for the impaired neurocognitive development that many premature infants show later in life. This has led to increased efforts to improve nutrient intakes in the hope that improved nutrient intakes will result in improved neurocognitive outcome.
Although it has been known for some time that the nutrient requirements of premature infants are considerably higher than those of infants born at term [3], there has not been much consensus about exactly what the nutrient requirements of premature infants are. The main source of discrepancy has been the different approaches utilized for defining requirements. Another source is the extent to which requirements take into account catch-up growth, of which most preterm infants are capable if given the requisite nutrients. Catch-up growth can occur after intrauterine as well as postnatal growth failure. Because requirements are strongly dependent on body size, they must be defined for specific body weight categories. Estimates of requirements by the factorial approach are weight-specific, but they do not include nutrients needed for catch-up growth. Estimates by the empirical approach typically include nutrients needed for catch-up, but estimates do not apply to infants that are smaller (or larger) than the infants studied.

There is principal agreement that postnatal growth of the premature infant should ideally emulate the growth of the fetus in utero. Such 'normal' growth would be proof of the absence of substantive nutrient deficiency and would provide assurance of unimpaired neurocognitive development. The American Academy of Pediatrics [4] recommends that 'postnatal growth that approximates the in utero growth of a normal fetus of the same postconception age' should be the basis for estimating nutrient requirements.

The fetal model is the basis for estimation of nutrient requirements by the factorial method [5]. Reservations about the fetal model, and about estimates of nutrient requirements based on it, have centered on demonstrated differences in extracellular fluid spaces between the fetus and the premature infant. However, there is no evidence that any other body constituents are affected by birth. There is thus no reason why acquisition of nonaqueous body constituents by the preterm infants could not proceed at the intrauterine rate. Because factorial estimates are based on the fetal model, they pertain to infants who grow at the fetal rate. Nutrient needs for catch-up growth can be estimated by the factorial method only if assumptions are made regarding the extent and speed of catch-up growth. Unlike the empirical approach, the factorial approach provides estimates of requirements for any nutrient for which the content in the fetus is known.

Empirical methods for estimating nutrient requirements depend on establishment of the relationship between intakes of key nutrients, such as protein and energy, and growth. They yield estimates of requirements for protein and energy needed to achieve a specified rate of growth. Empirical methods thus can provide estimates of nutrient needs for growth at the fetal rate as well as accelerated growth, i.e., catch-up growth. Unlike the factorial method, empirical methods do not provide estimated nutrient needs other than protein and energy needs.
**Requirements Determined by the Factorial Method**

The factorial approach derives nutrient requirements as the sum of two (in the case of parenteral requirements) or three components (in the case of enteral requirements). The largest component, and the component that changes most with body size, is the growth component, i.e., nutrient accretion. The other components are inevitable losses and, in the case of enteral nutrient requirements, efficiency of nutrient absorption.

Determination of the growth component requires knowledge of nutrient accretion with ‘normal’ growth. Because it is generally agreed that postnatal growth should ‘approximate the in utero growth of a normal fetus’ [4], the fetus serves as the model from which nutrient accretion is derived. Beginning in the 19th century, the body composition of stillborn infants and infants deceased soon after birth, including premature infants, has been analyzed by a number of investigators. Sparks [6] and Forbes [7, 8] have provided comprehensive summaries of the chemical analysis of some 160 fetuses. Gestational age was not always available, but because most body constituents change as a function of body size (the notable exception being body fat [7]), the data can be used to derive accretion rates even when gestational age is not explicitly known [6, 7]. Ziegler et al. [9] used only data from fetuses with known gestational age for the construction of a ‘reference fetus’ and derivation of fetal accretion rates. In spite of the differences in approaches (i.e., size vs. age) to the establishment of fetal body composition, nutrient accretion rates derived by the different approaches [6, 7, 9] are actually quite similar [10]. The fetal accretion data presented in table 1 represent a synthesis of the different approaches [6, 7, 9] in combination with contemporary fetal growth data [11]. The data represent our current best estimates of nutrient accretion. In the case of protein, accretion rates shown in table 1 are corrected for presumed inefficiency (90%) of the conversion of dietary protein to body protein. In the case of energy, the accretion value includes the energy cost of growth, estimated by Micheli et al. [12] at 10 kcal/kg/day.

Inevitable losses of protein (nitrogen) occur through desquamation of skin and as urinary nitrogen excretion mostly in the form of urea (desquamation of intestinal cells is accounted for in the correction for efficiency of intestinal absorption). Based on dermal nitrogen losses determined by Snyderman et al. [13], we have assumed average dermal losses of 27 mg/kg/day. Based on published data [14, 15] we have assumed urinary nitrogen losses to be 133 mg/kg/day. Energy losses comprise resting energy expenditure plus an allowance for miscellaneous expenditures, e.g., occasional cold exposure and physical activity. Based on recent studies [16–18] we have assumed resting expenditure to be 45 kcal/kg/day in infants weighing <900 g and 50 kcal/kg/day in larger infants. Miscellaneous energy expenditures have been assumed to be 15 kcal/kg/day in infants under 1,200 g and 20 kcal/kg/day in larger infants.
Parenteral requirements for protein and energy (table 1) are calculated as the sum of accretion plus inevitable losses. Enteral requirements are calculated as accretion plus inevitable losses corrected for efficiency of absorption, assumed to be 88% for protein and 85% for energy. Requirements (per kg of

<table>
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<th>Body weight, g</th>
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<th>700–900</th>
<th>900–1,200</th>
<th>1,200–1,500</th>
<th>1,500–1,800</th>
<th>1,800–2,200</th>
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<td>g/day</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>3.5</td>
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<td>101</td>
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<td></td>
<td></td>
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<tr>
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<td>4.1</td>
<td>3.5</td>
<td>3.1</td>
<td>2.9</td>
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</tr>
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<td>Enteral</td>
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<td>3.7</td>
<td>3.4</td>
<td>3.1</td>
<td>2.8</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Because nutrient needs are closely related to body weight and weight gain, the nutrient needs apply to all postnatal ages. All values are per kg per day except where noted [modified from 18].

<sup>a</sup>Based on data of Kramer et al. [11].
<sup>b</sup>Urine nitrogen loss of 133 mg/kg/day [14, 15] and dermal loss of 27 mg/kg/day [13].
<sup>c</sup>Includes correction for 90% efficiency of conversion from dietary to body protein.
<sup>d</sup>Sum of loss and accretion.
<sup>e</sup>Same as parenteral but assuming 88% absorption of dietary protein.
<sup>f</sup>Energy accretion plus 10 kcal/kg/day cost of growth.
<sup>g</sup>Assuming 85% absorption of dietary energy.

Parenteral requirements for protein and energy (table 1) are calculated as the sum of accretion plus inevitable losses. Enteral requirements are calculated as accretion plus inevitable losses corrected for efficiency of absorption, assumed to be 88% for protein and 85% for energy. Requirements (per kg of
Although absolute fetal weight gain (g/day) increases with increasing body size, the fractional fetal weight gain (g/kg/day), as shown in table 1, decreases markedly as a function of weight. In spite of this decrease in the fractional growth rate, the rate of protein accretion remains constant up to a weight of 1,200 g. This is so because the protein content of fat-free body mass increases with increasing body size/age, and this increase offsets the effect of the decrease in fractional growth rate on protein accretion. Energy accretion, on the other hand, increases with increasing body weight. This is due to a marked increase in body fat content, which more than counteracts the decrease in fractional weight gain.

Whereas estimates of requirements for protein are quite firm, estimates of energy requirements are more uncertain. This is in part so because there is a paucity of data regarding resting energy expenditure of small premature infants and, especially, nonresting energy expenditure. Uncertainty also derives from the fact that body fat accumulation of the preterm infant may deviate from that of the fetus without apparent ill consequences for the premature infant. Available energy seems to be prioritized to meeting ongoing needs and is deposited as fat only after all other needs have been met.

Requirements for major minerals and electrolytes derived by the factorial method are summarized in table 2. Although the dermal and urinary losses (not shown in table 2) used in deriving these requirements are based on data from the literature [5], there is considerable uncertainty regarding the minimal urinary losses of electrolytes and of P by premature infants. Also, there is uncertainty concerning the efficiency of intestinal absorption of calcium, which is influenced by multiple dietary and other factors, and there is uncertainty with regard to the amount of bone mineral (Ca, P) that must be
deposited in order to maintain bone health. It has become evident that accretion of bone mineral at somewhat less than the fetal rate can be compatible with good bone health, but it is impossible to translate such observations into quantitative estimates of the amounts of dietary calcium and phosphorus needed to maintain bone health.

Requirements Determined by Empirical Approaches

Empirical approaches generally utilize feedings (formulas or human milk) that provide precisely known intakes of energy and protein. Growth and sometimes metabolic balance are used as outcomes. Because requirements are strongly dependent on body size, estimates obtained by the empirical approach apply only to infants that are similar in body size to the infants studied.

Based on analysis of published data, Ziegler [10] demonstrated that in infants weighing more than 1,200 g at birth, weight gain (g/day) increased with increasing protein intake until the latter reached about 3.6 g/kg/day. (There were insufficient data to determine the effect of higher protein intakes.) Intake of energy did not seem to be related to weight gain. A protein intake of 3.6 g/kg/day produced a weight gain of about 30 g/day. Such a weight gain exceeds that of the fetus of comparable weight and thus represents catch-up growth. A protein intake of 3.6 g/kg/day therefore supports a certain amount of catch-up growth.

Kashyap et al. [19–21] performed a series of growth and metabolic balance studies with feedings (human milk, formulas) that varied in protein and energy content. They used the data to derive equations predicting protein and energy intakes necessary to duplicate fetal weight gain. The data were obtained in infants weighing between 1,200 and 2,000 g and thus pertain to infants in this weight range. The authors estimated that protein intake necessary for duplication of fetal weight gain is about 3.0 g/kg/day.

The Life Sciences Research Office (LSRO) [22], based on a comprehensive review of reported nutrition studies of premature infants, concluded that the minimum protein intake of premature infants (weight not specified) is 3.4 g/kg/day with a protein/energy ratio of 2.5 g/100 kcal at the maximum energy intake of 135 kcal/kg/day. The LSRO panel also concluded that a protein intake of 4.3 g/kg/day (with protein/energy ratio of 3.6 g/100 kcal) is without adverse consequences, whereas intakes of 5.0 g/kg/day or higher are likely to be associated with undesirable consequences. It is not clear whether the estimates by the LSRO [22] include allowances for catch-up growth.

Using a variety of endpoints, including growth, body composition and nitrogen balance, Rigo [23] estimated the protein requirements (‘advisable recommendation’) of infants born at 26–30 weeks’ gestation (corresponding
to weight of about 800–1,500 g) at 3.8–4.2 g/kg/day (3.3 g/100 kcal) and those of infants born at 30–36 weeks’ gestation (corresponding to weight of 1,500–2,700 g) at 3.4–3.6 g/kg/day (2.8 g/100 kcal).

The various estimates of protein requirements are summarized in table 3 for infants with nominal weights of 800 and 1,600 g. It is apparent that there is rather close agreement in spite of the different methods used in arriving at estimates of protein requirements.

### Catch-Up Growth

Catch-up growth occurs when an individual, after a period of growth restriction, is returning towards his/her original growth channel. If the growth restriction occurs during a vulnerable period and is severe and/or prolonged, catch-up growth may not be possible or may be incomplete. With lesser degrees of growth restriction, catch-up is likely to occur, provided the requisite amounts of nutrients are provided. To the caregiver, the actual potential for catch-up growth is not known. The caregiver therefore must assume that the potential exists and must provide nutritional support of such a nature as to enable catch-up growth should the potential exist.

#### Catch-Up Growth after Postnatal Growth Failure

Although all infants experience some weight loss after birth due to adjustment of extracellular fluid spaces, in small premature infants there commonly is actual loss of body substance or at least growth arrest. This severe growth failure is temporary and is typically followed by a period during which growth proceeds, albeit at a slower pace than it would have occurred in utero. There is ample documentation that premature infants usually are capable of at least partial catch-up growth. However, it is not possible to predict with any certainty the degree and the speed with which infants will be catching up. It is quite likely that the extent and speed of catch-up depends on the duration

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**Table 3.** Protein requirements (enteral) of premature infants without catch-up

<table>
<thead>
<tr>
<th>Weight 800 g</th>
<th>Weight 1,600 g</th>
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<tbody>
<tr>
<td></td>
<td>g/kg/day</td>
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<tr>
<td>Ziegler (table 1)</td>
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<tr>
<td>Kashyap et al. [19–21]</td>
<td>–</td>
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<tr>
<td>Klein [22]</td>
<td>3.4–4.3</td>
</tr>
<tr>
<td>Rigo [23]</td>
<td>3.8–4.2</td>
</tr>
</tbody>
</table>

\(^a\)At energy intake of 120 kcal/kg/day.
and severity of the preceding growth failure. Catch-up growth requires extra
nutrients and will not occur unless the required extra nutrients are provided.

Because of the uncertainties surrounding catch-up growth and the pre-
sumed high degree of individual variation, the extra nutrients required for
catch-up can be estimated only in general terms. An example will serve to
illustrate this. A hypothetical infant weighing 900 g with a modest degree of
postnatal growth failure might be able to catch-up and show accelerated
weight gain of 23 g/day, which is about 15% higher than the intrauterine rate
of 20 g/day. With this, the infant would reach a weight of 1,200 g in 13 days
rather than in 15 days, as would occur in utero. This accelerated growth
would increase the daily accretion of protein from the intrauterine rate of
2.5 g/kg/day (table 1) to 2.88 g/kg/day and, with inevitable losses unaffected,
would increase the parenteral protein requirement from 3.5 to 3.88 g/kg/day.
Energy required for growth would increase from 36 to 41.4 kcal/kg/day and
the total parenteral energy requirement would increase from 101 to
106.4 kcal/kg/day. The protein/energy ratio would have to increase from 3.5 to
3.65 g/100 kcal. This example illustrates the principle that catch-up growth
requires disproportionately more protein than energy and thus increases the
required protein/energy ratio of the feeding.

Kashyap et al. [24] used their prediction equations to determine protein
and energy requirements for catch-up growth. They estimated that for an
infant with a birth weight of 1,400 g to reach a discharge weight of 2,200 g 1
week earlier than would occur at the intrauterine growth rate, protein intake
would have to be 3.36 g/kg/day and energy intake 99.6 kcal/kg/day
(protein/energy ratio 3.37 g/100 kcal). For the same infant to reach the dis-
charge weight of 2,200 g 2 weeks earlier would require a protein intake of
4.5 g/kg/day and energy intake of 116.8 kcal/kg/day (protein/energy ratio
3.85 g/100 kcal). When subjected to testing in a feeding trial, these predic-
tions were generally found to hold.

Rigo [23] has provided specific advisable protein recommendations for infants
with catch-up growth. They are 4.4 g/kg/day (3.4 g/100 kcal) for infants of 26–30
weeks gestational age and are higher than recommendations for infants of the
same age without catch-up growth (3.8–4.2 g/kg/day and protein/energy ratio
3.3 g/100 kcal). Similarly, for infants of 30–36 weeks’ gestation, the recom-
mended protein intake for those with catch-up (3.8–4.2 g/kg/day, protein/energy
ratio 3.3 g/100 kcal) is higher than for those without catch-up growth.

To Catch-Up or Not to Catch-Up?

It has been shown that preterm infants with slow growth due to receiving a
nutrient-poor formula have less insulin resistance during adolescence than
preterm infants with more rapid growth due to receiving a nutrient-enriched
formula [25]. On the basis of this finding it has been suggested that in pre-
mature infants rapid growth should be avoided in order to reduce the risk of
diabetes later in life. This conclusion may not be warranted because insulin
resistance of the more rapidly growing preterm infants was similar to that of
term infants [25]. Moreover, the same group [26] had shown previously that
the slow-growing premature infants (those receiving the nutrient-poor for-
mula) had substantially lower cognitive achievements in childhood than the
faster-growing infants who received the nutrient-enriched formula. These
data [25, 26] provide strong evidence for late effects of early nutritional expe-
riences (programming). But they also clearly demonstrate that more rapid
growth of premature infants caused by improved nutrient intakes is associ-
ated with improved neurocognitive outcome. Morley [27] showed that the
rate of weight gain of male premature infants was positively associated with
verbal IQ at 7.5–8 years of age and that weight at 9 months of age was posi-
tively associated with overall verbal and performance IQ. Thus, there can be
no questions that the advantages associated with catch-up growth outweigh
any possible disadvantages. Premature infants should always be assumed to
be capable of catch-up growth and the extra nutrients required for catch-up
growth should be provided.

Catch-Up after Intrauterine Growth Failure

The majority of infants born small for gestational age (SGA) are infants
who have experienced intrauterine growth restriction and have the potential
for catch-up growth. But the extent, speed and time of onset of catch-up
growth are highly variable and unpredictable. In this regard, as in most other
regards, catch-up after intrauterine growth restriction is not different from
catch-up after postnatal growth failure. Catch-up growth requires nutrient
intakes above and beyond those required for normal growth and can occur
only if the additional nutrients are provided.

For the purpose of illustrating how the factorial approach can be used to
estimate the extra nutrients needed for catch-up growth, requirements for sev-
eral hypothetical scenarios are shown in table 4. The hypothetical infant is born
SGA at 30 weeks gestation weighing 900 g. Shown for comparison are a nor-
mally grown (appropriate for gestational age, AGA) infant born at 26 weeks
weighing 900 g, and a normally grown infant born at 30 weeks weighing 1,500 g.
The assumption is made that the 30-week SGA infant has the body fat (1.5%) of
a 26-week infant but has the fat-free body mass composition of a 30-week
infant. If the SGA infant grows at the intrauterine rate for a 900-gram AGA
infant (20 g/day), the protein and energy requirements are shown in table 4.
The main difference between a 26-week AGA and a 30-week SGA infant is a
somewhat higher energy expenditure (and hence lower protein/energy ratio)
of the SGA infant. This is explained by the more mature composition (i.e., lower
water content) of the fat-free body mass of the SGA infant.

We then asked what the protein and energy requirements would be if the
SGA infant had partial or complete catch-up by the time of hospital discharge
with a weight of 2,200 g. Complete catch-up is not very likely to occur and
may not even be possible, but it is used here mainly to illustrate the effect of
catch-up growth on nutrient requirements. Partial catch-up, on the other hand, whereby the infant makes up about one half of the growth deficit before discharge from the hospital, may occur. Estimates of energy requirements for catch-up growth are based on the assumption that it involves restoration of body fat content to a level commensurate with that of the fetus of similar weight. The data in table 4 show that catch-up growth, whether complete or partial, increases requirements for protein more than requirements for energy. Hence required protein/energy ratios are increased for partial and especially for complete catch-up compared to the 900 g SGA as well as the 900-gram AGA infant. Since otherwise satisfactory catch-up growth could theoretically occur with less than full restoration of body fat, it is possible that energy needs could be less than those shown in table 4 and that protein/energy ratios could be higher.

Conclusions

Exact knowledge of the nutrient requirements of premature infants is critically important for the prevention of postnatal growth failure and ensuring optimal neurodevelopmental outcome. Methods whereby nutrient requirements can

<table>
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<th>Gestational age at birth</th>
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<td>4.0</td>
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Requirements estimated for the first 2 weeks of growth, which is assumed to begin with regained birth weight.

aAssuming body fat content to be that of a 26-week fetus (1.5%) and composition of fat-free mass to be that of a 30-week fetus (86.8% water, 10.6% protein).
bPartial catch-up assumed to reach 1,850 g in 4 weeks, complete catch-up assumed to reach 2,200 g in 4 weeks.
be estimated fall into two categories, factorial methods and empirical methods. Either methods have advantages and disadvantages. The factorial methods provide estimates of requirements for protein, energy and a number of other nutrients. Factorial methods permit estimation of the extra nutrients needed for a given degree of catch-up growth, but cannot indicate the extent to which catch-up growth is actually possible. Empirical methods yield estimates of the requirements for protein and energy but not for other nutrients. They often provide estimates of the protein and energy needs for catch-up growth. The advantages of catch-up growth outweigh any possible disadvantages associated with it. The nutrients needed for catch-up growth should therefore always be provided.

References


Discussion

Dr. B. Koletzko: Your data are extremely valuable and give a great basis for orientation of feeding practice. Obviously one would love to have studies with a longer follow-up to test whether your hypothesis regarding the relationship between different levels of intake and outcome can be substantiated. You observe a growth deficit relative to intrauterine growth up to 37 weeks of gestational age. Do you still find the same relative deficit in these infants at 2 or 3 months after expected term birth. Obviously, all infants born at term lose weight after birth and need time to regain weight. Thus I assume that the growth deficit you describe at 37 weeks would be much smaller at 2 weeks after term birth. We do not know whether or not it is important to catch up this growth deficit by 37 weeks, 42 weeks or later. My second question relates to catch-up growth in SGA infants: do we really have any basis to conclude in the length of time a SGA needs to catch up, or even if it should catch up at all? My third question relates to the fascinating studies of Dr. Singhal and Dr. Lucas who reported that long-term outcomes in preterm infants were related to weight change during the first 2 weeks after birth. Do these data allow us to draw conclusions on the feeding of preterm infants? In the first 2 weeks of life the weight change really was mostly weight loss, and I wonder how much of this is related to feeding and how much is related to other factors?

Dr. Ziegler: Catch-up growth certainly continues after discharge. There are follow-up studies that show that even at age 8 years catch-up continues. But as a group, former premature infants are short and have small heads. This reflects practices 15 and 20 years ago; of course I cannot tell you how the babies that we observed in 2005 are going to be. Hopefully they will be better. As a group, premature infants do catch up given appropriate nutrition.

The next question was about SGA infants. I did not address the question whether we should try and make SGA babies catch up. I personally think we should because these infants have undergone a period of undernutrition and the sooner we correct this situation the higher the likelihood that they make up for what they have missed in terms of growth and development. But I know this is controversial and there are arguments against my position.
Your last question was about Dr. Lucas's findings. When he says that split proinsulin levels during adolescence are related to the speed of growth during infancy, he refers to weight change in the first 2 weeks. Both groups at 2 weeks are below birth weight, but those who received the good formula lost less weight since birth than those receiving the bad formula. But what is really important is that the ones with more weight loss also have a low IQ on follow-up. For a while it was thought that accelerated growth should be avoided because of the increased risk of diabetes. I don't think this is justified because slow growth carries the risk of decreased IQ.

**Dr. Koletzko:** But the IQ outcome was really related to weight gain during a different time period of about 30 days after preterm birth, whereas the data on flow-mediated dilatation and split proinsulin were related to weight change during only 14 days.

**Dr. Ziegler:** I should remind you that Dr. Lucas also had a control group of term breastfed infants who had split proinsulin levels like the fast-growing premature babies.

**Dr. Rivera:** The data are in some way idealistic. In practice it is sometimes very difficult to achieve this amount of protein intake because premature babies tend to have a lot of complications. You have shown a correlation with protein intake and IQ in those infants.

**Dr. Ziegler:** Dr. Lucas's data show a correlation between IQ and the degree of undergrowth. The babies who were the most undergrown at discharge had the lowest IQ on follow-up. Now, with regard to your earlier comment, it is really not that difficult to improve protein intake. For instance if you don't have a commercial breast milk fortifier available you can make your own; you can use skim milk powder. We used to do that before commercial fortifiers became available. So, it can be done, perhaps not perfectly but something can be done.

**Dr. Fakhraee:** Did you check the ammonia level or pH in the babies who got this amount of protein? There are different forms of SGA infants; some are asymmetric and some are symmetric. The symmetric SGA might be due to chromosomal anomalies or other factors like intrauterine infections, and the asymmetric is usually due to malnutrition or placental insufficiency. Did you make any sort of differentiation between these two kinds of SGA infants?

**Dr. Ziegler:** High ammonia and acidosis are things that were observed in very early studies with extremely high intake of poor quality protein. But in recent studies with higher protein intake there has been no hyperammonemia and no acidosis. There sometimes is a slightly higher BUN which is a normal correlate of protein intake. We see no adverse effects today because the proteins we use are of a much better quality. With regard to the heterogeneity of the SGA population, I haven't differentiated them. I don't know of anyone who has tried to differentiate the nutrient needs or the growth of these different categories of SGA babies. So I agree with you that it is a heterogeneous group but I don't know what to do about it.

**Dr. Cooke:** We prospectively compared a protein intake of 3g/100 kcal with 3.6g/100 kcal in a group of preterm infants [1]. Infants retained more nitrogen and gained more weight when fed a protein intake of 3.6 g/100 kcal. At the same time, none of the infants developed uremia or metabolic acidosis. These data suggest an intake of 3.6g/100 kcal better meets protein requirements, as recommended by Dr. Ziegler. However, this study only lasted 2 weeks and longer-term studies are needed to more adequately examine this issue.

**Dr. Dhanireddy:** It is very hard to argue that babies should grow according to their intrauterine rates when they are not in the uterus; homeostasis is totally different. What data do we have to show that achieving these growth rates would lead to a better outcome? Is the efficiency of energy requirement dynamic in the first several
weeks because they are ill, have sepsis, and lung disease, and so even your best estimates may be different from what is needed?

Dr. Ziegler: How do we know that achieving fetal growth gives us better outcomes? We don't know until we have tried to do it. If we achieve fetal growth and still have bad outcomes we can say maybe there are other things causing poor growth. But nobody has achieved fetal growth and until we do, we don't know. My hypothesis is that poor growth and poor neurocognitive outcome are mostly due to inadequate nutrition. I don't know how complications affect caloric requirements, but they certainly do affect growth. Each bout of sepsis slows growth and also affects late outcomes, and each course of steroids causes a brief growth cessation. But there can be no doubt that the main cause of growth retardation is poor nutrition. Premature babies do not have the same amount of body water as fetuses have; they are a little dryer. Should we therefore expect them to grow a little slower than fetuses? I don't think that differences in body water can explain the massive growth failure that we regularly see in premature infants.

Dr. Milla: You have largely been considering short-term morbidity and you alluded to long-term morbidity in quoting Dr. Lucas's data about proinsulin. One of the things you have to think about is whether all preterm infants are the same, whether they all behave in the same way. If you look at the experimental data about perinatal nutrition it is clear that metabolic entrainment occurs and our latest data show that if you continue to be malnourished for a long time after birth, then this together with prenatal malnutrition results in the type of situation Dr. Lucas was describing. Some of his data are diluting your message. Do premature infants need to be handled differently in terms of their nutritional rehabilitation? For example, if they are small for dates born prematurely are they going to have different problems from those that are appropriate for weight?

Dr. Ziegler: What I have shown are data where all babies are lumped together, SGA and AGA. But if I showed you SGA and AGA separately, you would see that the growth curves are the same.

Dr. Milla: I think that is because one is just looking at growth in the short term and in the long term it probably matters whether you become hypertensive or you become diabetic.

Dr. Ziegler: I could not agree more with you but I have no long-term data. The only long-term data we have are from Dr. Lucas.

Dr. Fusch: We are sometimes comparing apples with peaches when we look at preterm babies because they have such different perinatal and postnatal pathology. If an infant is born due to placental disruption or due to chorioamnionitis they behave completely differently, and also their outcome is different. When comparing the SGA children with regard to the difference between symmetric and asymmetric retardation, we have more than two types of children, AGA and SGA; we have at least six sub-groups.

Dr. Jochum: How do you estimate the influence of the carbohydrate intake on the protein needs?

Dr. Ziegler: I have no way of estimating the effect of carbohydrate intake on protein needs. The group of Kashyap et al. [2] have shown that carbohydrate and fat differentially affect protein metabolism. But I don't know how to translate this into actual protein requirements.

Dr. Fusch: In the studies by Kashyap et al. there were constant protein intakes and constant calorie intakes at two different levels. They switched the amount of non-protein calories between more fat and more carbohydrate. With biochemical methods, with stable isotopes and with nitrogen retention, they showed clear differences: nitrogen use was different if more calories were given by carbohydrates than by fat. I don't
remember if they showed, as in your experimental set, whether at the end they had different weight gains.

**Dr. Fuchs:** The outcome you are looking at is growth and I wonder to what extent you have looked at functional outcomes? Even at this young age, have you been able to look at markers of immunity, rates of morbidity and mortality?

**Dr. Ziegler:** No, I have no such data and I don’t know of such data. We all hypothesize that better nutrition improves host defenses, but there are no data. None of the studies that I know of have looked at the outcomes that you ask about. At age 18 months behavioral data have been looked at, this is the earliest age at which it makes sense to look at behavior.

**Dr. Thureen:** I would like to respond to the question of Dr. Fakhraee regarding types of SGA infants. I believe that IUGR infants are a subset of SGA infants. Unfortunately, many studies have investigated these two groups of infants as a single group. As a result, studies in SGA infants have produced contradictory conclusions because very heterogeneous populations of infants were studied. The extremely growth-restricted infant in utero likely has a very different metabolism than most SGA infants, and thus these two groups need to be studied separately. I think the obstetrical work looking at categorizing the fetal ‘metabolic status’ using Doppler blood flow and other studies is probably a first start at trying to decide how infants at birth are metabolically very different.

**Dr. Beaumier:** We are looking at nutrition as though they were term infants, and as if carbohydrate calories from lipids and carbohydrate and protein were independent. What do you think about amino acid as energy used by the fetus ex utero at 32 or 35 weeks for growth? You show that increasing protein intake will improve growth. Is it really just lean mass accretion or amino acid used for calories or something else? Should we think of extremely low birth weight infants as being the same as 1- or 2-month-old babies that are born at term? I don’t think we should use the same tools and the same approach.

**Dr. Ziegler:** I could not agree more with you. I think we should treat the recently born premature infant like a fetus. We should give him parenterally a high carbohydrate and a very high amino acid intake. It has been estimated that the fetus is taking up amino acids at a rate of 5 or 6 g/kg whereas only 2 g/kg are deposited, and so the conclusion is that the remaining amino acids are utilized for energy. I do think we should mimic that in our parenteral nutrition regimen that we apply right after birth. But by the time the infant is fed enterally we have switched over to the typical postnatal regimen where a large part of the calories comes from fat and where the protein intake is barely at the requirement. When I talk about growth, I talk about an infant who has made this transition from the fetal to the postnatal diet.

**Dr. Beaumier:** But can we confirm that when we switch from parenteral to enteral nutrition that they actually have a different metabolism or a newly adapted metabolism.

**Dr. Ziegler:** We assume that the infants, when they tolerate enteral feedings, have made the transition or are capable of making the transition. High protein and carbohydrate may be beneficial in enteral feeding. As I pointed out, the phobia of protein is so prevalent and so strong that to propose a higher protein intake would fall on deaf ears. Remember that even protein intakes sufficiently high to meet requirements are not generally accepted.

**Dr. Putet:** You give some recommendation for an infant growing stably. What about the one who is not growing, what about the metabolic load and some organs like the kidney? The kidney is not mature at all; it is still maturing. What is the metabolic load in the 28-week-old babies and their kidney function? What are the consequences later on at 6–8 months?
*Dr. Ziegler*: The only consequence I know of is that the kidneys of premature babies with a higher protein intake tend to be larger. Even if there are more serious consequences my priority would still be the brain. In other words, I would be glad to sacrifice some kidney function if it meant that I can salvage the brain.

**References**
