Abstract

Growth and nutrition during infancy are being viewed with renewed interest because of the possibility that they may be linked to cardiovascular and metabolic health in later life. Of particular interest are differences between breast- and formula-fed infants with regard to nutrient intake and growth because breastfeeding has been shown to be associated with a reduced risk of obesity in later life. During the first 6–8 weeks of life there is little difference in growth (gain in weight and length) between breast- and formula-fed infants. However, from about 2 months of age to the end of the first year of life formula-fed infants gain weight and length more rapidly than breast-fed infants. There are no consistent differences in adiposity during the first 4–5 months of life, but during the later part of the first year of life the preponderance of the evidence suggests that breast-fed infants are leaner than formula-fed infants. Formula-fed infants at 4–5 months of age show higher plasma levels of insulin-like growth factor-1 (IGF-1), insulin and certain amino acids than breast-fed infants. Whereas the protein intake of breast-fed infants decreases with age and closely matches the requirements for protein during the early months of life, the protein intake of formula-fed infants exceeds requirements after the first 1–2 months of life. The data are consistent with the hypothesis that differences in protein intake are mainly responsible for differences in growth between breast- and formula-fed infants. Differences in energy intake probably are responsible for differences in adiposity observed in older infants.

Introduction

In recent years growth and nutrition during infancy have been the focus of renewed and broad interest because of their association with health outcomes later in life. The seminal study by von Kries et al. [1] exemplifies
recent studies that show breastfeeding during infancy to be associated with a reduced risk of obesity in childhood. It has been appreciated for some time that breast-fed infants grow less rapidly than formula-fed infants. Also, it has been known or suspected for a long time that breastfeeding, besides its well-known health benefits in the short-term, confers protection against certain diseases in adult life. For example, subjects who were breast-fed as infants have lower plasma lipid concentrations and are therefore at a lower risk of cardiovascular disease than subjects who were fed formula during infancy [2–4]. A number of subsequent reports [5] have confirmed the initial observation by von Kries et al. [1] that breastfeeding is associated with less risk of obesity in childhood. These observations have generated considerable interest in view of the worldwide increase in overweight and obesity.

It is likely that breastfeeding in infancy and improved later health are manifestations of one and the same genetic or other causative factor. But it is also possible that breastfeeding per se is causally related to improved health in later life. If that is the case, it is pertinent to ask what it is that may confer to the breast-fed infant protection against disease in later life. Although it would seem implausible to expect a single factor, such as a single component of breast milk, to be responsible for protection against a range of conditions later in life, such a possibility is actually not entirely implausible. In premature infants it has been shown that a single factor (i.e., low protein intake during a relatively short period in infancy) is associated with lower blood pressure during adolescence [6] as well as reduced insulin resistance [7]. It is important to note that in the studies by Singhal et al. [6, 7] those subjects who enjoyed relative protection as young adults showed slower growth as infants than those with less protection. In other words, slow growth during infancy is a marker of health advantages later in life. It appears possible that the rate of growth in infancy is what determines individuals’ later cardiovascular health. Indeed, Singhal and Lucas [8] have proposed in their ‘growth acceleration hypothesis’ that it is a high rate of growth during infancy that causes increased later cardiovascular risk. A high rate of growth has, incidentally, also been shown by the same group to be associated with better neurocognitive outcome [9].

It is also possible that cardiovascular health in later life, rather than being associated with the rate of growth during infancy, is determined by the level of protein intake that produces the differences in growth in the first place. We shall show that high protein intakes during infancy elicit metabolic and hormonal responses that could explain not only the observed differences in the rate of growth but could also program individuals with regard to lifelong cardiovascular health. It is against this backdrop that the difference in growth between breast- and formula-fed term infants has become of renewed interest. A close examination of the growth differences, together with other relevant information, may not only shed light on the cause(s) of differential growth but also provide hypotheses regarding the association between infant feeding and later health.
Growth from Birth to 4 Months

From the perspective of comparing the growth of breast- and formula-fed infants, the early months of life are of particular interest. This is so because during that period breast- and formula-feeding exist for the most part in ‘pure’ form, i.e. without the confounding presence of complementary foods and, in the case of breast-fed infants, of supplemental formula. Also, because growth is most rapid during the early months of life, the effect of factor(s) causing differences in growth is likely to be most marked during that period.

Differences in growth between breast- and formula-fed infants are evident already during the first week of life. Breast-fed infants typically have not quite regained birth weight by 8 days of age [10], whereas formula-fed infants by 8 days of age exceed birth weight on average by 50–100 g [11]. This difference is largely explained by the fact that breast-fed infants receive only small amounts of colostrum during the first 2 days of life, a time during which formula-fed infants already have free access to formula. The difference in early weight change is potentially significant in view of the findings by Stettler et al. [12] who reported that, among formula-fed infants, the risk of overweight and obesity in early adulthood was increased in proportion to weight changes during the first week of life.

Dewey [13] presented a comprehensive review of data concerning the growth of breast- and formula-fed infants published since 1980. The review was appropriately limited to studies in which data on breast- and formula-fed infants were collected simultaneously using identical methods. Of 19 studies, 5 reported data separately for the first 3–4 months of life. Of these, 2 showed significantly greater weight gain among formula-fed infants, with 1 study [14] showing also greater length gain. Two studies showed no difference in weight gain between breast- and formula-fed infants and 1 study showed actually higher weight gain in breast-fed than in formula-fed infants.

The report by Nelson et al. [14] concerned by far the largest cohort (419 breast-fed infants and 720 formula-fed infants). Infants were studied using identical methods between 1965 and 1987. Formula-fed infants received a variety of milk- and soy-based formulas. Until 1978 infants were permitted to receive limited amounts of solid foods and, in the case of breast-fed infants, of supplemental formula, and the majority of infants did actually consume these foods, although generally only in modest amounts. After 1978 infants received no foods other than breast milk or formula through 112 days of age.

The data of Nelson et al. [14] show very convincingly that during the first 6 weeks of life, although the small difference in weight that is established during the first week of life persists, gain in weight and length are almost identical in breast- and formula-fed infants. Data on gain in weight and length between 8 and 112 days of age reported by Nelson et al. [14] are summarized in table 1 on a sex-specific basis. It is evident that between 8 and 42 days of
age, differences in gain between breast- and formula-fed infants are very small and not statistically significant. In contrast, for the age interval 42–112 days, and also for the entire period from 8 to 112 days of age, differences in gain in weight and length are larger and statistically significant.

To answer the question of whether consumption of solid foods and, in the case of breast-fed infants, supplemental formula, may have had effects on growth during the early months of life, Nelson et al. [14] compared data for infants observed before 1978 when infants were permitted to receive limited amounts of other foods and formula, with data for infants observed after 1978 when no other foods were permitted until 4 months of age. There were no significant differences in any of the growth parameters before vs. after 1978, and growth differed between breast- and formula-fed infants before as well as after 1978. This shows that consumption of modest amounts of other foods does not affect the growth of infants and does not blunt the growth difference between breast- and formula-fed infants.

It is important that the differences in growth reported by Nelson et al. [14] concern not only weight gain but also length gain. It is well established that the energy intakes of breast-fed infants are substantially less than those of formula-fed infants [15, 16]. A difference in energy intake alone in the presence of an ample protein intake would be expected to lead to a modest difference in weight gain, reflecting a difference in gain of fat mass, but it would not be expected to lead to a difference in length gain since it would not have an effect on gain in fat-free body mass. The fact that there is a difference in length gain between breast- and formula-fed infants strongly suggests that the intake of protein is limiting gain in fat-free mass in breast-fed infants.

Table 1. Gain in weight and length according to gender and type of feeding

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th></th>
<th>Females</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>breast-fed</td>
<td>formula-fed</td>
<td>breast-fed</td>
<td>formula-fed</td>
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<tr>
<td></td>
<td>(n = 230)</td>
<td>(n = 380)</td>
<td>(n = 216)</td>
<td>(n = 340)</td>
</tr>
<tr>
<td>Weight, g/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8–42 days</td>
<td>38.9 ± 9.7</td>
<td>39.8 ± 7.7</td>
<td>33.8 ± 7.7</td>
<td>33.3 ± 7.4</td>
</tr>
<tr>
<td>42–112 days</td>
<td>25.4 ± 6.2*</td>
<td>28.5 ± 6.4</td>
<td>22.6 ± 6.3*</td>
<td>24.7 ± 5.2</td>
</tr>
<tr>
<td>8–112 days</td>
<td>29.8 ± 5.8*</td>
<td>32.2 ± 5.6</td>
<td>26.2 ± 5.6*</td>
<td>27.5 ± 4.9</td>
</tr>
<tr>
<td>Length, mm/day</td>
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<td></td>
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<tr>
<td>8–42 days</td>
<td>1.29 ± 0.22</td>
<td>1.33 ± 0.22</td>
<td>1.24 ± 0.22</td>
<td>1.25 ± 0.19</td>
</tr>
<tr>
<td>42–112 days</td>
<td>0.96 ± 0.17*</td>
<td>1.03 ± 0.12</td>
<td>0.89 ± 0.13*</td>
<td>0.94 ± 0.11</td>
</tr>
<tr>
<td>8–112 days</td>
<td>1.07 ± 0.12*</td>
<td>1.13 ± 0.11</td>
<td>1.01 ± 0.11*</td>
<td>1.04 ± 0.09</td>
</tr>
</tbody>
</table>

Modified from Nelson et al. [14] with permission.
*Significantly (p < 0.001) lower than corresponding value for formula-fed infants.
Plasma Levels of Insulin-like Growth Factor-1, Insulin and Amino Acids

It is well established that insulin-like growth factor-1 (IGF-1) plasma concentrations reflect the intake of dietary protein [17, 18]. In a study comparing growth of infants fed formulas with different protein concentrations [19], determinations of plasma concentrations of IGF-1 were obtained [20]. One formula contained protein at a concentration of 2.39 g/100 kcal and the other at 1.90 g/100 kcal. Similar determinations were made in a group of exclusively breast-fed infants participating in another study (unpublished). The results summarized in table 2 show that plasma IGF-1 concentrations were similar in the 2 groups of formula-fed infants and in the breast-fed infants at 1 month of age. However, by 4 months of age, the IGF-1 concentrations of breast-fed infants and infants fed the lower protein formula had declined significantly, whereas they remained unchanged in infants fed the higher protein formula. At 4 months of age, the IGF-1 levels of breast-fed infants were significantly lower than the levels in either formula-fed group, and the IGF-1 levels in the lower protein group were significantly lower than those in the higher protein group.

The level of dietary protein also influences plasma insulin levels, probably mediated through the effect of the protein level on plasma concentrations of certain amino acids. Dewey et al. [21] reported that at 5 months of age breast-fed infants had lower plasma concentrations of insulin and of insulin-releasing amino acids than formula-fed infants (table 2).

Table 2. Concentrations of IGF-1, insulin and insulin-releasing amino acids (IRAA) in breast-fed and formula-fed infants

<table>
<thead>
<tr>
<th>Age</th>
<th>1 month IGF-1, µg/l</th>
<th>4 months IGF-1, µg/l</th>
<th>5 months IGF-1, µg/l</th>
<th>insulin, pmol/l</th>
<th>IRAA, mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast-fed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>74.9 ± 33.3</td>
<td>32.0 ± 18.7*</td>
<td>42.6 ± 25.8</td>
<td>0.967 ± 0.178</td>
<td></td>
</tr>
<tr>
<td>(n = 56)</td>
<td>(n = 35)</td>
<td>(n = 52)</td>
<td>(n = 52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formula-fed protein 1.90 g/100 kcal</td>
<td>79.3 ± 34.0</td>
<td>58.9 ± 37.8*</td>
<td>65.4 ± 31.7</td>
<td>1.133 ± 0.298</td>
<td></td>
</tr>
<tr>
<td>(n = 35)</td>
<td>(n = 41)</td>
<td>(n = 62)</td>
<td>(n = 62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formula-fed protein 2.39 g/100 kcal</td>
<td>77.5 ± 31.0</td>
<td>80.7 ± 37.8</td>
<td>65.4 ± 31.7</td>
<td>1.133 ± 0.298</td>
<td></td>
</tr>
<tr>
<td>(n = 21)</td>
<td>(n = 27)</td>
<td>(n = 62)</td>
<td>(n = 62)</td>
<td></td>
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</tr>
</tbody>
</table>

IGF-1 data for formula-fed infants are from Steenhout et al. [20] and those for breast-fed infants are unpublished data. The insulin and IRAA data are from Dewey et al. [21]. Values in same column with different superscripts differ significantly: p < 0.01. *Value significantly lower than corresponding value at 1 month: p < 0.01.
The protein requirements of infants decline relatively rapidly during the first few months of life [22] (fig. 1). Although the protein intakes of breast-fed infants match the requirements relatively closely, figure 1 suggests that, contrary to the first 2 months, beginning at about 2 months of age protein intakes may be marginally low relative to the requirements. The age at which protein intake begins to be marginal coincides with the age at which growth of breast-fed infants begins to be less than that of formula-fed infants. This is consistent with the hypothesis that protein intake begins to limit the growth of breast-fed infants beginning at 2 months of age.

Contrary to the variable protein content of breast milk, the protein content of formulas is constant. Their protein content is such that it meets the protein needs of infants at all times, including the first 2 months of life when protein needs are highest. Therefore, the protein intakes of formula-fed infants exceed the protein needs by an increasing margin beginning at 2 months of age. This relative excess over requirements is reflected in the plasma levels of IGF-1, insulin and amino acids of formula-fed infants at 4–5 months of age (table 2). These hormonal responses to protein intakes are consistent with the hypothesis that differences in protein intake explain differences in growth between breast- and formula-fed infants.

**Growth from 4 to 12 Months**

After 4 months of age the majority of breast-fed infants begin to receive complementary foods and many receive supplemental formula. Among the
studies reviewed by Dewey [12], 12 reported measurements beyond 6 months of age. Ten of these studies reported that breast-fed infants gained significantly less weight at least during some portions of the first year of life. In 4 of the 8 studies reporting length data, breast-fed infants also showed significantly slower gain in length than formula-fed infants. Thus, a clear predominance of studies shows that breast- and formula-fed infants differ in growth during the later parts of the first year of life.

As part of 2 unpublished studies concerning the iron nutritional status of breast-fed infants, weight and length were measured during the first year of life. Although many of the breast-fed infants also received supplemental formula after 4 months of age, a sizable number of infants did not receive supplemental formula in accordance with parental choice. The data therefore offer the opportunity to examine the effect of supplemental formula on growth. Infants in the iron study were exclusively breast-fed for the first 4 months of life. They were permitted to receive cereal and other complementary foods from 4 months of age and most infants did receive complementary foods. Regardless of whether they received complementary foods, infants were classified as ‘breast-fed’ if they did not receive formula at 9 months of age, as ‘breast + formula-fed’ if they received formula at 9 months of age, and as ‘formula-fed’ if they were no longer being breast-fed at 9 months of age. The data are summarized in table 3 which, for reference purposes, includes data for predominantly formula-fed infants [23] and for infants observed in the Euro-Growth study who were breast-fed according to WHO recommendations [24].

At 4 months of age there were no differences in weight. At 9 months of age, female infants who were breast-fed with no supplemental formula were

<table>
<thead>
<tr>
<th>Age months</th>
<th>Iowa</th>
<th>Euro-Growth</th>
<th>Fels [23]</th>
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<tbody>
<tr>
<td></td>
<td>breast-fed</td>
<td>breast + formula-fed</td>
<td>formula-fed</td>
</tr>
<tr>
<td>Females</td>
<td>n = 33</td>
<td>n = 16</td>
<td>n = 15</td>
</tr>
<tr>
<td>4</td>
<td>8,168 ± 787a</td>
<td>8,527 ± 872</td>
<td>8,758 ± 637b</td>
</tr>
<tr>
<td>9</td>
<td>8,968 ± 873</td>
<td>9,238 ± 893</td>
<td>9,471 ± 714</td>
</tr>
<tr>
<td>12</td>
<td>9,704 ± 686</td>
<td>9,707 ± 957</td>
<td>9,925 ± 964</td>
</tr>
<tr>
<td>Males</td>
<td>n = 26</td>
<td>n = 19</td>
<td>n = 22</td>
</tr>
<tr>
<td>4</td>
<td>8,937 ± 628</td>
<td>8,883 ± 869</td>
<td>9,165 ± 837</td>
</tr>
<tr>
<td>9</td>
<td>9,704 ± 686</td>
<td>9,707 ± 957</td>
<td>9,925 ± 964</td>
</tr>
<tr>
<td>12</td>
<td>9,704 ± 686</td>
<td>9,707 ± 957</td>
<td>9,925 ± 964</td>
</tr>
</tbody>
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Values in same row with different letters differ significantly (p < 0.05); analysis of combined genders by ANOVA shows differences between breast- and formula-fed infants to be significant at 9 (p = 0.014) and 12 months (p < 0.05).

aFeeding at 9 months of age.

bInfants breast-fed according to WHO recommendations [23].
significantly \((p = 0.018)\) lighter than infants fed formula. Breast-fed infants who received supplemental formula (‘breast + formula’) weighed substantially more than breast-fed infants receiving no formula, but the difference was not statistically significant. Breast-fed infants receiving supplemental formula were similar in weight to the Euro-Growth reference [24] and to formula-fed infants [23]. By 12 months of age, the difference between breast- and formula-fed infants no longer was statistically significant \((p = 0.0612)\), although substantial differences persisted. Similar differences were observed among male infants, but the differences were smaller than in female infants and were not statistically significant. However, for the combined (females and males) data, the differences between breast- and formula-fed infants were significant at 9 months \((p = 0.014)\) and remained significant \((p < 0.05)\) at 12 months.

**Body Composition**

Dewey [12] found that of 9 studies that reported measures of adiposity, 5 found that adiposity was less in breast-fed infants, 3 reported no difference and 1 found that breast-fed infants had higher adiposity than formula-fed infants. The latter study [25] concerned exclusively breast-fed infants who had restricted length gain in addition to increased adiposity. In 2 of the studies that found differences in adiposity, the differences persisted to 18–24 months of age. The 3 studies that found no difference in adiposity were limited to the first 4–6 months. This agrees with our own findings [26] in a group of 18 infants who had total body water determinations at 42 days and again at 84 days of age. Gain of fat-free mass between 42 and 84 days was significantly greater in formula-fed than in breast-fed infants but gain in fat mass was not, regardless of whether fat mass was expressed as grams per day or as percentage body mass. Thus it appears that during the first 4–6 months of life breast-fed infants do not differ in adiposity from formula-fed infants. In contrast, after 6 months of age there is considerable evidence that breast-fed infants are leaner than formula-fed infants.

**References**


Discussion

Dr. Lönnerdal: I wonder how you can call the low blood urea nitrogen (BUN) levels in the formula-fed infants unsafe when they were similar to those of breastfed infants?
Dr. Ziegler: The term ‘safe’ in the title of our paper did not apply to the BUN. It applied to the fact that these babies seemed to consume an excessive amount of calories on the low protein formula.

Dr. Lönnerdal: I just question the validity of using BUN as an indicator for adequacy of protein intake.

Dr. Ziegler: The BUN is an indicator of current protein intake and that is true in all infants. The BUN can be influenced by other factors such as the hydration state, but given other things being equal, the BUN is a reflection of protein intake.

Dr. Dewey: I am a bit puzzled by your conclusion. From what I understand you did not find a significant difference in growth in the first study, in which you had the lower protein, and in the second one you also did not find a significant difference in length gain. We did a study in Honduras of babies who were exclusively breastfed to either 6 or 4 months of age and then given complementary foods that were high in protein and had high quality (egg) protein as well. These foods were fortified with iron and they were nutritionally adequate so the infants' growth wasn't being limited by any other nutrients. Those complementary foods had no significant effect on growth. So if the growth of exclusively breastfed babies was being limited by protein I would have expected to see a difference, and you didn't see one in your experimental studies either. My conclusion is that giving them more protein does not affect their growth at that age. We also did a double-blind randomized controlled trial with formulas that had either standard levels or lower levels of protein. We reported it in the abstract that you cited for the insulin levels. We used a two-stage lower protein formula, as close as we could get to breast milk. We did not find significant differences in growth between the two groups, even though we did find differences in plasma amino acids and in BUN. So I differ in my conclusion, which is that protein is not a limiting nutrient for breastfed infants at that age.

Dr. Ziegler: We ask the same question and, looking at different data, we come to different conclusions. To come back to the study with the very low BUN, I think that is a question of statistical power. If we had more than 16 subjects, the difference in growth would almost surely have reached statistical significance. It was just a small group of babies that we studied. The data that I showed you concerning breastfed babies from 4 to 9 months were with formula supplements vs. without. I interpret that to be the effect of protein so I think that is consistent with my hypothesis. In Guatemala and Honduras you fed foods other than formula, maybe therein is the difference.

Dr. Dewey: There is fairly consistent evidence that milk products are in some way growth-enhancing or accelerating. This has been observed in populations in developing countries and in other studies where they have compared different sources of protein. Milk sources seem to have a growth-promoting effect, and we see this consistently in all the studies of infants. When they are supplemented with formula they do grow more rapidly. I certainly agree with you on that. I don't think it is protein, however; I think it is something else. I don't know what it is but definitely milk has a growth-promoting effect.

Dr. Koletzko: Following on from Dr. Dewey's thought I would just like to point your attention to a wonderful study that Michaelson et al. have done in Copenhagen. They compared the effect of milk protein and meat protein and found that milk protein had a significant effect on enhancing IGF-1 whereas meat protein did not, underlining the concept that Dr. Dewey has just proposed, that it is something other than protein in milk that might be relevant. I would just like to raise a question about the choice of words that you used, regardless of the underlying data you and Dr. Dewey just discussed on how to interpret the data. If you chose to use the wording 'protein intake limits the growth of breastfed infants', imagine that there is a reporter from the Saigon
Times in this room, tomorrow the headline of the Saigon Times might be ‘breastfed infants need protein supplement from birth because breastfeeding limits growth’. I have some concern whether the your data should not be interpreted a bit more cautiously in order to avoid such a conclusion. I think with the evidence we have we really cannot say that a higher growth rate would be of benefit in the long term.

Dr. Ziegler: I appreciate your comments, but I am speaking here not to the press I am speaking to colleagues who are scientifically trained and this is a scientific discussion. I would not speak to the press and say that breastfed babies are protein-deficient. And as I said earlier this is my interpretation of the same data that we all see and I interpret it to indicate that breastfed babies grow slightly slower because their protein intake is such that they can’t grow faster. And I am not attaching any value to it. It may be that a slower growth is beneficial in the long run, just as it is in many animal species; when you restrict food intake they live longer and have other benefits.

Dr. Hernell: Just alluding to what Dr. Koletzko mentioned about the growth-promoting effect of milk; are there any data similar to what you have shown that are based on soy formulas? Do you see the same difference with soy formula as with milk-based formula?

Dr. Ziegler: The growth data I showed about formula-fed babies, about one third of the infants were fed soy-based formulas and two thirds were fed milk-based formulas, and we have never seen a difference in growth between soy formula-fed and milk formula-fed babies. We have analyzed the data very extensively and especially because the study that was mentioned by Stettler et al. [1] was based on our cohort and we carefully looked at soy vs. milk because the objective of the follow-up study was to compare those who were fed soy formula with those who were fed milk formula as infants. As you know, we found some differences in the young adult women, but we found absolutely no difference in growth, and that is why I don’t think this so-called growth-promoting effect of milk is something specific to milk.

Dr. Roggero: You said that IGF-1 is low when the protein intake is low [2]. Do you think that IGF-1 could be a good prediction marker of adiposity or only of protein intakes?

Dr. Ziegler: As I said IGF-1 reflects protein intake. I don’t think it has anything to do with later adiposity or energy intake. There was no difference between boys and girls. Yes, I think IGF-1 is a marker of protein intake.

Dr. Lönnerdal: I just want to follow up the discussion about the potential growth-promoting effect of milk proteins. Perhaps what you just said is showing that, because soy formulas have an about 20–40% higher protein content. Therefore, if you had the same growth with 20–40% higher protein, there would most likely be a growth-enhancing effect of milk protein.

Dr. Ziegler: What you said is true, soy formulas all contain more protein than milk-based formulas. But my concept of infant growth is that the infant has a certain growth potential, and you either realize it or you don’t realize it. I don’t believe that you can accelerate growth beyond the genetic potential. So whether the formula has a little bit more or less protein, as long as it meets the requirements the baby grows at its predestined rate.

Dr. Rigo: I want to come back to the discussion that we had this morning regarding the long-term effect on obesity. Your data differ from what was shown this morning which was exclusively related to the formula-fed group. You showed that there is a decrease in body weight during the first 8 days of life in the human milk group and you have an increase in body weight in the formula-fed group. So the causality is could be related only to the fact that they were fed human milk and formula, and not only to the weight gain during the first week of life.
Dr. Ziegler: What you are saying is that whatever later health benefits we see could be strictly due to some property of breast milk and have nothing to do with growth; that is entirely possible.

Dr. Turck: Did you observe differences in head circumference between breastfed and formula-fed infants at any age?

Dr. Ziegler: We did not measure head circumference. We know that length and head circumference growth are very tightly correlated. Head circumference growth can be affected in severe malnutrition, which we did not study.

Dr. Zhuoqin Jiang: How do you control the preterm babies weight gain if the body weight is increasing by less than 15 g/day? Should we use a standard fortifier or concentrated fortifier?

Dr. Ziegler: You are asking about premature infants, if the weight gain is less than 15 g/day; that is a very low weight gain. Regarding the use of a fortifier, I think all premature infants who receive mother's milk should receive a fortifier regardless of what their initial weight gain is, and they should receive it from early on. So it is given from the beginning, not only when the baby is not growing.

Dr. Fan Yang: You mentioned that there is a difference in the plasma IGF-1 of formula-fed and breastfed babies, and we know breast milk contains IGF-1. Regarding the IGF-1 content of breast milk, does it also contribute to the difference in growth of breastfed and formula-fed babies?

Dr. Ziegler: I don't think that the IGF-1 that is present in breast milk is absorbed intact, it is almost surely digested. So I think the IGF-1 in breast milk may have some effect on the gastrointestinal tract but no systemic effect because it is digested down to its peptides and amino acids.

Dr. Do Van Dung: I appreciated your lecture very much and I understand that you want to imply that formula feeding is better than breastfeeding, although there were differences in the measurement of the height, weight and length. To return to height and length differences between the formula-fed and breastfed infants, I wonder whether you took into consideration the role of confounding factors such as nutrition programming, the difference in height and weight, and the different anthropometric measurements of the infant's parents? We suspect that confounders played a role because you showed that breastfed infants had a lower birth weight than the formula-fed infants.

Dr. Ziegler: I simply pointed that out because I have never noticed before that both male and female breastfed babies are a little bit lower in birth weight. I have no idea what this means. I did not say that I prefer formula feeding over breastfeeding because the babies grow faster. I simply said that formula-fed babies grow a little faster than breastfed babies, and I don't know whether it is good or bad. I am simply stating this as a fact.

Dr. Thu Nhan Nguyen: What about immunology? For instance we have compared the immunology in breastfeeding and formula feeding and the results show that the breastfed infants have fewer diseases but formula-fed infants often become respiratory insufficient, have gastroenteritis and diarrhea. In our cities people are using formula more than breastfeeding, and the babies vomiting more after the formula. What about the immunology of formula compared to breast milk?

Dr. Ziegler: We did not measure immunologic components, but it is of course very well documented that breastfed babies have much more advanced immunologic responses because breast milk really complements the newborn infant's immunity. My topic was to review growth. The reason why growth is currently of interest is because it seems that late health effects may be related to early growth, but there is absolutely no question that the immunology of the breastfed infants and many other things are much better and preferable. As you pointed out, there is absolutely no
question that babies should be breastfed and should only be fed formula when breast-
feeding is not possible for some reason.

*Dr. Dewey:* I just wanted to respond to the question about head circumference
that was asked before. In the studies that we have done we matched on birth weight.
The breastfed babies indeed grew less rapidly in weight by a substantial margin, a lit-
tle bit less rapidly in length by 12 months, but there was absolutely no difference at all
in head circumference. The same result has been found in a few other studies that
have also measured head circumference.

**References**

   in adulthood: a cohort study of European American subjects fed infant formula. Circulation