Long-Term Outcome Trials of Early Nutrition on Later Health and Development

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In therapeutic research, the principal objectives are generally to establish robust data on efficacy (benefit) and safety (risk) for any proposed intervention. If we are to apply these principles to infant nutrition research, we must address several key questions: What do we mean by “efficacy” or “safety” in a nutritional context? And what sorts of benefits or risks of early nutrition are biologically plausible? Is it practical to apply to infant nutrition the “therapeutic intervention” experiment—notably the randomized clinical trial? If so, what are the best windows of opportunity to do so? What are the practical issues in conducting such trials, and are researchers using this tool effectively? And, most importantly, are such clinical trials proving their worth by changing our biological perspectives and our practice of infant nutrition?

In this chapter, I touch on these issues in a general way and then use some of our own research findings on the long-term consequences of infant nutrition to illustrate key points.

"EFFICACY" IN NUTRITIONAL STUDIES:
A HISTORICAL PERSPECTIVE

Over the past two centuries, there has probably been more research on infant nutrition than on any other area of pediatrics. By 1953, Macy et al. (1) were able to collate over 1500 publications on the composition of breast milk, just one small area of infant nutrition research. Yet, despite the massive scientific effort, fundamental issues in infant nutrition practice remain unresolved, resulting in confusion among both health professionals and parents and in inconsistent, inadequately supported recommendations and standards of practice. When such uncertainty exists in the presence of such a large body of research and knowledge, it is reasonable to challenge whether the right questions have been addressed.

To throw more light on this, it is instructive to examine how other fields of therapeutic intervention have generally evolved. Usually, this has been a three-stage
process (2). In stage I, anecdotal observations raise the question, "Is there anything in this?" In stage II, epidemiological and physiological research provides descriptive and mechanistic data that raise testable hypotheses concerning the potential impact of a therapeutic intervention. Finally, in stage III, formal intervention experiments test the efficacy and safety of the treatment and practice. Thus, if we take the analogy of research into high blood pressure, stage III research tells us if intervention with antihypertensive drugs improves long-term health (reduced risk of stroke, improved survival, and so on) at an acceptable cost to the patient (for example, acceptably low incidence of side effects such as depression or impotence). The ability of antihypertensives simply to lower blood pressure (stage II research) has meaning for us only if in doing so they improve outcome (stage III research).

When I entered the field of infant and childhood nutrition some 20 years ago, it seemed that the field had mainly become stuck in stage II. Research largely focused on collection of physiological and epidemiologic data on growth, nutritional status, metabolic response to feeding, energetics, nutrient absorption and retention, composition of foods, prevalence of nutritional disorders, and so on. It is true that considerable earlier efforts had been made to define intakes that would prevent overt nutritional deficiency, and that was, of course, of obvious clinical importance. However, formal experimental stage III research on whether early nutrition mattered in terms of critical outcomes such as long-term health and development was seldom undertaken and usually poorly conceived. Whereas the outcome effects of blood pressure lowering are what now govern practice in that field, the corresponding data on the outcome of our practices in infant nutrition have usually not been available. Official bodies have had to make theoretical recommendations largely on the basis of short-term, stage II, studies. Clearly, however, parents and health professionals should be more concerned about whether our nutritional policies are formally proven to affect health and development (stage III research) than whether they affect, say, if the infant grows on the 25th rather than 75th centile, has a higher energy expenditure, retains more calcium in bone, or incorporates more $^{13}$C-glycine into protein (stage II research)—though if outcome effects of early nutrition are established, such stage II findings become important in providing insight into mechanism.

SAFETY

Safety in nutritional studies has received even less attention than efficacy. In many nutritional trials, safety is a real issue. In preterm infants, nutritional management policies could result in necrotizing enterocolitis (see below), infection, and death. Trial size for detecting adverse effects may need to be greater than for testing efficacy because a relatively large sample may be needed to detect differential incidence between groups of a relatively rare event.

Safety monitoring in clinical trials of infant nutrition is frequently relegated to trivial consequences of feeding, under the general umbrella of "acceptability," including observations on minor spitting up, stool color, stool frequency, and so on.
Not infrequently, however, significant risks are not factored into the trial design. The long-chain polyunsaturated fatty acid (LC-PUFA) supplementation trials provide a good example. There are around ten published efficacy trials, with neurodevelopment or visual endpoints, on preterm and term infants, though several more trials are in progress. The average sample size in these trials is 25 per group. Although Uauy et al. (3) do measure some “safety” aspects (for example, bleeding time, red cell membrane stability), none of the published studies was large enough to have addressed safety in any realistic way. Yet here is a group of lipids, linked to the ubiquitous prostaglandins, that may have wide ranging effects, for instance on gene expression (4,5), hemostasis (3), blood pressure (6), insulin resistance (7), calcium metabolism (8), and immune function (9). The latter is of particular concern. In Carlson’s second study (10) of LC-PUFA supplementation in preterm infants, 94 babies were randomized into two equal groups, and of these 95 babies, 35 were withdrawn before 2 months; five of the control babies were withdrawn because of infection \( n = 2 \) or necrotizing enterocolitis (NEC; \( n = 3 \)) versus 14 withdrawals because of infection \( n = 5 \) or NEC \( n = 9 \) in the LC-PUFA-supplemented group. These are worrying findings that require confirmation (Carlson herself recognized that a larger sample was needed to test the hypothesis that infection or NEC was individually influenced by the use of marine oil). Were these risks to be confirmed, most neonatologists would be more concerned about NEC (with its 20% to 40% mortality) or (potentially life-threatening) sepsis than they would be about transient promotion of visual acuity (10). We are currently exploring this question in three large preterm trials. Also, numerous small human milk fortification trials in preterm infants have focused principally on stage II–type outcomes (calcium retention, weight gain, and so on). In our own neurodevelopmental outcome study on 275 infants (11), we identified in the short term an increased overall risk of systemic infection (diagnosed on clinical plus hematologic grounds with or without bacteriologic confirmation) in the fortifier group. Bacteriologically confirmed systemic infection and NEC (together, but not separately) were also significantly more common in the fortifier group. The possibility that adding fortifier powder to human milk could reduce its antiinfective properties (previously shown in vitro) is just as relevant (if not more so) to the clinical decision-making process as the knowledge that fortifiers may confer a small short-term benefit for weight gain (11).

EARLY NUTRITION AND LATER HEALTH
AND NEURODEVELOPMENT

If, after all, our infant nutrition policies ensure freedom from immediate nutritional deficiency and ill health at the time, devising policies that optimize health and development would seem an important target. But is it plausible that such effects could occur? This question is part of a more general one as to whether there are sensitive or critical periods in early life when events may have lasting significance.
To describe this general phenomenon, some years ago, I proposed the term "programming" (12,13), the concept that a stimulus or insult, when applied at a critical or sensitive period of development, could result in a permanent or lasting effect on the structure or function of the organism. We now know of numerous examples of endogenous and exogenous triggers of a physiological or unphysiological nature (including hormones, drugs, physical stimuli, and so on) that may operate during windows to produce lifetime effects (12,13). Such early programming appears to be a normal part of development and, in some circumstances, might allow the organism to fine-tune its later biology in response to early environment.

A key question here is whether infant nutrition could operate in this programming way. Since the 1960s, the evidence on this from experimental studies in animals, including primates, has been extensive (14–20). What an animal is fed during a brief period in infancy may, in adult life, influence numerous outcomes that would be of major clinical and public health significance in humans. These include lifelong "programming" effects on intermediary metabolism, blood lipids, tendency to diabetes, body size, body fatness, blood pressure, and atherosclerosis. Smart (16) reviewed 165 animal studies on the impact of early nutrition on later learning and behavior, with a predominance of studies showing long-term or lifelong effects; and numerous parallel studies show that early nutrition may have lasting effects on the physical development of the brain.

As often occurs, application of knowledge from animal studies to humans has taken time, and only recently has the priority for equivalent nutritional intervention studies in humans been recognized. This need has been further heightened by nonexperimental, epidemiologic data (21–23) suggesting that early nutritional factors might be important in man. For instance, potential markers of early nutrition, notably size at birth and in infancy, are more highly predictive of death from ischemic heart disease and its risk factors (diabetes, high blood pressure, hyperlipidemia, central obesity) than most risk factors for vascular disease identified in adult life.

**RANDOMIZED TRIALS IN INFANT NUTRITION: GENERAL CONSIDERATIONS**

Clearly, public health and clinical policy would be most soundly based on experimental rather than epidemiologic studies. In the light of this, 15 years ago, I elected to devote the major attention of my research group to developing the use of the infant nutritional intervention experiment in a formal way to explore the concept of nutritional programming in humans and to underpin nutritional practice. The elements of this program, which, collectively, were novel at that time, included the following in each clinical trial:

1. Formal randomized nutritional intervention in infancy, with planned long-term follow-up;
2. Carefully calculated size to detect differences between groups for a key targeted health or developmental outcome ("efficacy") with adequate power; and
LONG-TERM OUTCOME TRIALS

trials large enough to detect differences in adverse outcomes ("safety") between groups;
3. Trials conducted in a similar manner to a pharmaceutical intervention trial employing what are now termed "good clinical practice" guidelines;
4. Cohort details documented to facilitate long-term (or lifetime) follow-up.

There are several windows of opportunity for infant nutritional intervention experiments that are feasible and ethical. (a) Preterm infants can be randomized to diet to test the importance of the perinatal period for nutrition. Some years ago, milk banking was commonly practiced in neonatal care, so that for babies whose mothers did not provide their own milk, it was possible, among other interventions, to randomly assign infants to human milk (from unrelated donors) or formula, a key "experiment" that would be difficult to achieve in full-term infants. (b) Formulafed full-term infants could be randomly assigned to formulas of different nutrient contents to test ways in which early infancy might be critical for nutrition. These interventions can also be targeted to full-term infants growth-retarded at birth, who have been shown epidemiologically to be at long-term risk for growth and neurodevelopmental deficits and for ischemic heart disease and its antecedents. A key question is whether early nutritional intervention could "reprogram" these infants following poor intrauterine growth and ameliorate risk. (c) Infants can be randomly assigned to different weaning foods to test whether nutritional sensitivity extends into infancy.

Specific interventions depend on the hypothesis but may involve the use of "whole diets" (for example, multinutrient-enriched formulas) or supplementation of specific factors of hypothesized benefit for outcome, such as iron or LC-PUFAs. In 15 major outcome studies now, we have around 5000 infants and children in all of these categories, in various stages from the intervention period to long-term follow-up, the oldest subjects followed prospectively now to 14 years.

One important objective in these outcome studies has been to use them to identify medium-term outcomes that have predictive value for long-term health and development, so that valuable data in future studies can be collected within a practical period. For cognitive development, for instance, we find scores at 18 months have some correlation (around $r = 0.5$) with scores later in childhood. However, by age 7 to 8, formal cognitive tests, for example, WISC-R IQ, are highly correlated with adult performance (24). Thus, in a study designed to test the hypothesis that an infant nutrition intervention has a permanent impact on cognitive function, follow-up to 18 months would provide suggestive evidence only, but follow-up to 7.5 to 8 years, compelling evidence. We are also attempting to identify childhood health measures that have predictive value for adult health. For instance, at what point does bone mineral content determined, say noninvasively, by dual x-ray absorptiometry, begin to predict peak bone mass and hence adult osteoporosis—a disease that could, theoretically, be influenced by infant nutrition (25). When does endothelial dysfunction, assessed noninvasively by vascular ultrasound, predict risk for adult atherosclerosis? When does children’s blood pressure or blood lipid pattern have
good predictive value for adult measurements? New information here will help to
define the duration of follow-up needed to demonstrate lasting benefits or adverse
effects from early nutritional interventions convincingly. To achieve this, the first
studies, like our own, may need to be conducted into adult life.

Another important principle in such studies is to use them as a vehicle for concomi-
tant explanatory physiological research, so that mechanistic physiology can be re-
lated to outcome and not studied in isolation in circumstances where the significance
of the findings may remain unknown.

After a study has been designed with adequate size, a major problem in published
follow-up studies is attrition in sample size. In our experience, this is largely avoid-
able with good tracing techniques and the use of noninvasive measurement end-
points. The consequences of failing to achieve near-complete follow-up of the sample
in some studies is serious. For instance, in one of our neurodevelopmental outcome
studies involving 424 preterm infants randomly assigned to the diet given in the
neonatal period (26), we achieved a follow-up rate of 89% at 18 months postterm.
The 11% loss to follow-up was to a large extent linked to a temporary staffing
problem in one center. We reported major differences between groups in neurodevel-
opment (see below for a presentation of the findings). However, we found no differ-
ence between groups in neuromotor impairment ("cerebral palsy"). At our 7.5- to
8-year follow-up on the same cohort, we resolved to achieve near-complete follow-
up. We traced and saw 98% of survivors still resident in Britain (though now widely
dispersed). At this follow-up, we noted a significant and potentially important difference
in neuromotor impairment (to be published). This should have been detected
at the 18-month follow-up but was not because the relatively small loss of subjects
turned out to be a selective one. Many reported follow-up studies have losses well
in excess of 30%, and one can only speculate on the possible loss of data and
distortion of findings.

LONG-TERM FINDINGS FROM INTERVENTION STUDIES

A review of long-term outcome data from our own and other studies is beyond
the scope of this chapter, and I shall be selective. From our own most long-standing
trials on preterm infants, for instance, we have published evidence that a randomized
nutritional intervention for on average 1 month, with blind evaluation at follow-up,
had a major impact on health and developmental outcomes. Bone mineral content
5 years after random assignment to human milk rather than formula was higher in
the former, despite the low mineral content of human milk for preterm infants in
the newborn period (25). These data could imply that early nutrition programs later
bone metabolism, and we are currently completing a study on around 400 of these
children aged 9 to 12 years to explore whether these findings persist and could have
relevance for the development of adult peak bone mass and hence osteoporosis risk.
We also conducted in preterm infants what we believe to be the only prospective
and strictly randomized study (in term or preterm infants) comparing the effects of
human milk (from unrelated donors) and cow's-milk-based formula on the later incidence of allergic and atopic disease (27). Brief early exposure to cow's milk "programmed" a range of allergic and atopic phenomena (notably eczema) in those infants with a positive family history of allergy but appeared marginally beneficial in those without a family history, indicating an important interaction between genes and environment in the development of atopy.

The most important findings from our trials, however, are those relating to the impact of early diet and later neurodevelopment. These unique findings, discussed in more detail in the following section, have influenced clinical practice, provide major justification for the long-term ("stage III") nutritional intervention trial approach, and illustrate a number of the general points I made earlier.

EARLY DIET AND LATER NEURODEVELOPMENT

Numerous studies have addressed whether suboptimal nutrition in early life, at a critical or vulnerable phase of early brain development (15,28–32), could affect later cognitive function. Most studies have been on malnourished children in developing countries, where malnutrition is so closely associated with poverty, poor social circumstances, and lack of stimulation that it has been difficult to extricate influences of these factors from any potential long-term effect of nutrition itself (32,33). Although evidence supporting the view that early nutrition influences later cognitive development in humans is accumulating (34), firm conclusions are still hampered by lack of randomization in the great majority of studies. Yet unequivocal data on the later effects of early nutrition on brain development would be of critical public health and clinical importance.

In humans, the so-called critical brain growth spurt is between the third trimester and 2 years postterm (31). We have designed a series of strictly randomized prospective studies that test the vulnerability of the human brain to nutrition during specific periods of the brain growth spurt. Our most long-standing series of studies, started in 1982, were on preterm infants (26,35) and were therefore designed to test the effects of diet in the earliest part of the brain growth spurt—the period before full term; it is these studies that I report here. In the early 1980s, diets available for preterm infants varied grossly in nutrient content (26), and it was ethical and feasible to randomly assign these diets because there was considerable uncertainty at that time on the best nutritional strategies. In our prospective randomized five-center trials on the effects of diet on long-term growth and development in infants weighing less than 1850 g at birth, 926 infants were randomly allocated to their diet in the neonatal unit, as shown in Fig. 1.

Study 1 was conducted in three centers that had donor breast milk banks; infants were randomly allocated to (A) banked donor breast milk or (B) preterm formula, with 159 infants in the sole diet group and 343 in the supplement group. In study 2, the random allocation was to (A) standard term formula or (B) preterm formula,
Informed consent from parents

Does the mother wish to provide her own expressed breast milk for her baby?

No

↓

Randomise
(Sole diet study)

Trial A

Study 1

banked donor breast milk

Trial B

preterm formula

Study 2

term formula

↓

Randomise
(Supplement study)

Trial A

Study 1

banked donor breast milk

Trial B

preterm formula

Study 2

term formula

preterm formula

FIG. 1. Study design.

with 160 in the sole diet group and 264 in the supplement group. The major nutritional constituents of these diets are shown in Table 1. The values for human milk are mean values for 6000 pooled samples. The donor breast milk was donated by breast-feeding mothers in the community who collected milk that dripped from the contralateral breast as they fed their own infants. The preterm formula was designed (by us) to meet the calculated nutritional requirements of preterm babies. Study details are described elsewhere (26). Many of the infants required initial parenteral nutrition, and the median time to attain full enteral feeds was 7 days in study 1 and 9 days in study 2. Intake of trial diet in the supplement trials depended on the mother's success in providing her own milk; median intake in study 1 was 47% of the infant's feed volume and 53% in study 2. The assigned diet was given (for a median of 4 weeks) until the baby attained a weight of 2000 g or was discharged

<table>
<thead>
<tr>
<th>Component (per 100 ml)</th>
<th>Preterm formula</th>
<th>Term formula</th>
<th>Mother's expressed breast milk</th>
<th>Banked donor breast milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein (g)</td>
<td>2.0</td>
<td>1.5</td>
<td>1.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>4.9</td>
<td>3.8</td>
<td>3.0</td>
<td>1.7</td>
</tr>
<tr>
<td>Carbohydrate (g)</td>
<td>7.0</td>
<td>7.0</td>
<td>7.0</td>
<td>7.1</td>
</tr>
<tr>
<td>Energy (kcal)</td>
<td>80</td>
<td>68</td>
<td>62</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Na (mg)</td>
<td>45</td>
<td>19</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>Ca (mg)</td>
<td>70</td>
<td>35</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>P (mg)</td>
<td>35</td>
<td>29</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>
TABLE 2. Growth data from a five-center feeding trial on 926 infants: growth measurements are between regaining birth weight and hospital discharge

<table>
<thead>
<tr>
<th></th>
<th>Mean weight gain (S.E.) (g/kg per day)</th>
<th>Mean head circumference gain (S.E.) (mm/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial A (sole diets)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BBM(^a) ((n = 83))</td>
<td>12.6 (0.4)</td>
<td>1.28 (0.05)</td>
</tr>
<tr>
<td>PTF ((n = 76))</td>
<td>17.2 (0.6)***</td>
<td>1.49 (0.05)*</td>
</tr>
<tr>
<td>Trial A plus trial B (supplement to EBM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BBM ((n = 253))</td>
<td>13.4 (0.3)</td>
<td>1.30 (0.03)</td>
</tr>
<tr>
<td>PTF ((n = 249))</td>
<td>16.0 (0.3)***</td>
<td>1.46 (0.04)**</td>
</tr>
<tr>
<td><strong>Study 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial A (sole diets)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TF ((n = 79))</td>
<td>13.0 (0.6)</td>
<td>1.21 (0.10)</td>
</tr>
<tr>
<td>PTF ((n = 81))</td>
<td>16.6 (0.5)***</td>
<td>1.53 (0.08)**</td>
</tr>
<tr>
<td>Trial A plus trial B (supplement to EBM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TF ((n = 211))</td>
<td>13.3 (0.3)</td>
<td>1.33 (0.05)</td>
</tr>
<tr>
<td>PTF ((n = 213))</td>
<td>15.8 (0.3)***</td>
<td>1.45 (0.04)</td>
</tr>
</tbody>
</table>

\(^a\)BBM, banked breast milk; TF, standard term formula; PTF, preterm formula; EBM, mother’s own expressed breast milk.

\(^b\)Significance, * \(p < 0.05\); ** \(p < 0.01\); *** \(p < 0.001\).

from the neonatal unit, whichever was sooner. After discharge from the neonatal unit, mothers fed their babies as they and their advisers chose. Follow-up staff were blind to the original dietary assignment.

Data on the characteristics and clinical status of this cohort have been published elsewhere (26). Two aspects are reported here for reasons discussed below. These are growth and necrotizing enterocolitis. Growth data in Table 2 show that in both study 1 and study 2, the babies both in trials A and A–B (a combination of trials that preserves randomization) fed preterm formula had faster weight gain and faster head circumference gains and therefore faster brain growth (36).

Among the major, and potentially diet-related, causes of morbidity, we monitored the incidence of NEC. Previous inconclusive evidence tentatively linked human-milk feeding to a lower incidence of NEC (37–39). The only trial in which we could test this in a randomized comparison was study 1, trial A, in which we found 1/83 confirmed cases of NEC on banked breast milk and 4/76 cases on preterm formula (odds ratio 4.7; 95% confidence interval, CI, 0.5 to 43) (40). The sample in this trial was too small for anything less than a tenfold difference in NEC to be detected. However, we then split the entire cohort of 926 infants into three groups: formula alone (preterm or term formula); formula plus mother’s milk; and human milk alone (banked milk or banked milk with mother’s own milk). In these three groups, the incidence of confirmed NEC was 17/236 (7.2%) in the formula-only group, which was significantly higher than in the formula plus mother’s milk group, 11/437 (2.5%);
TABLE 3. Bayley Mental Development Index (MDI) and Psychomotor Development Index (PDI) at 18 months corrected age

<table>
<thead>
<tr>
<th>Developmental test</th>
<th>Milk formula</th>
<th>Advantage or preterm formula (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BBM</td>
<td>PTF</td>
</tr>
<tr>
<td>Study 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDI</td>
<td>n = 62</td>
<td>n = 52</td>
</tr>
<tr>
<td>94.8 (2.1)</td>
<td>95.3 (2.7)</td>
<td>0.5 (−6.2 to 7.1)</td>
</tr>
<tr>
<td>PDI</td>
<td>93.0 (1.8)</td>
<td>94.2 (2.2)</td>
</tr>
<tr>
<td>Trial A plus B</td>
<td>n = 196</td>
<td>n = 191</td>
</tr>
<tr>
<td>MDI</td>
<td>99.9 (1.3)</td>
<td>101.5 (1.4)</td>
</tr>
<tr>
<td>PDI</td>
<td>94.7 (1.1)</td>
<td>94.4 (1.2)</td>
</tr>
<tr>
<td>Study 2</td>
<td>TF</td>
<td>PTF</td>
</tr>
<tr>
<td></td>
<td>n = 55</td>
<td>n = 59</td>
</tr>
<tr>
<td>MDI</td>
<td>92.6 (2.7)</td>
<td>98.6 (2.4)</td>
</tr>
<tr>
<td>PDI</td>
<td>84.2 (2.1)</td>
<td>98.9 (2.2)</td>
</tr>
<tr>
<td>Trial A plus B</td>
<td>n = 156</td>
<td>n = 154</td>
</tr>
<tr>
<td>MDI</td>
<td>99.6 (1.6)</td>
<td>102.2 (1.6)</td>
</tr>
<tr>
<td>PDI</td>
<td>89.6 (1.4)</td>
<td>95.8 (1.4)</td>
</tr>
</tbody>
</table>

*Tests exclude those with cerebral palsy. BBM, banked breast milk; TF, standard term formula; PTF, preterm formula; **p < 0.01; ***p < 0.001.

odds ratio 3.0; 95% CI 1.4 to 65; p < 0.005); and also higher than for human milk alone, 3/253 (1.2%; odds ratio 6.5; 95% CI 1.9 to 22; p < 0.001).

At long-term follow-up of this cohort, the principal targeted outcome was neurodevelopment. Within each study (26,41), calculated sample size was for one-third of a standard deviation (5 quotient points) for trials A–B combined and half a standard deviation (8 quotient points) for trial A alone. The subjects were seen at 18 months corrected age and at 7.5 years. Only data from the 18-month follow-up are published so far and are shown in Table 3. For study 1, despite the low nutrient content of banked breast milk, infants did not have lower scores than those fed preterm formula. However, in study 2, babies in trial A fed standard formula had a 6-point lower mental development index (close to 5% significance) and a 15-point lower psychomotor score (p < 0.001); and in trials A–B (n = 310; a balanced addition, preserving randomization) a 6-point lower psychomotor score (p < 0.01), despite the blunting effect of mothers’ milk usage (trial B) in both randomized groups.

Recently, we confirmed that the significant developmental disadvantage seen in preterm babies fed a standard term formula, which we now recognize does not meet the nutrient needs of this group, is also seen at 7.5 years, when verbal IQ was significantly depressed (unpublished).

DISCUSSION

These data are considered in greater depth elsewhere. However, I have juxtaposed here short-term data on growth and NEC with longer-term data on neurodevelopment
to illustrate concepts developed earlier in the chapter. First, in study 2, we showed that a brief period of dietary manipulation in the neonatal period (4 weeks on average), using a nutrient-enriched rather than a standard formula, significantly influenced neurodevelopment at 18 months. Our further follow-up at 7.5 years (unpublished), when IQ is more predictive of that in adults, indicates that the disadvantage for the standard-formula-fed group had persisted and could now, therefore, represent a permanent effect. These data provide some of the only evidence from a large long-term randomized trial that early diet, during a "critical" or vulnerable period, could "program" neurodevelopment.

Surprisingly, in study 1, despite the poor nutrient content of donor breast milk, outcome of those individuals fed on it in the neonatal period was no worse than that seen with preterm formula (we have published data suggesting this may reflect a beneficial effect of factors in donor milk on development that ameliorate the potentially adverse effect of its low nutrient content).

Given these outcome findings, it is pertinent to reconsider the neonatal growth data. Short-term growth has been measured as a key outcome in nearly every neonatal nutrition trial. Yet here, neonatal growth did not have any predictive value for the main long-term outcome. Compared with babies fed preterm formula, those fed term formula grew poorly and had poor neurodevelopment at follow-up. However, infants fed donor milk grew particularly poorly compared with those fed preterm formula in the neonatal period, but at follow-up, developmental scores in these two groups were the same. Our unpublished data also show that early diet, with its major effect on short-term growth, had no effect on any aspect of body size at 18 months or 7.5 years. Although it is possible that at future follow-up we may identify some factor for which early growth is predictive, we have not done so yet, perhaps illustrating the weakness, discussed earlier, of relying on short-term (stage II) physiological findings.

Our findings indicate that the risk of NEC, a life-threatening complication, is greater in formula-fed than in breast-milk-fed infants. This conclusion was based on nonrandomized comparison of formula- and human-milk-fed groups, but the data are compelling. If this was confirmed, breast milk would emerge, at least from the present findings, as the diet of choice for babies not fed their mother’s milk. As it happens, the HIV scare has resulted in closure of most milk banks so that the use of donor milk is not usually an option, and there are other aspects of unsupplemented donor milk that are unsatisfactory. But as an exercise in using research data to support practice, we can summarize the situation for babies not fed their own mother’s milk as follows: if only stage II research had been done (growth), we would reject banked milk and term formula and choose preterm formula. If a randomized outcome trial with neurodevelopment as an endpoint was undertaken, we would reject term formula but could not distinguish between banked milk and preterm formula. If, however, we do an outcome study, as we have done, with safety monitoring (that is, we incorporate as suggested above, both efficacy and safety in our trial), we might then choose banked breast milk—the opposite conclusion to that derived from a stage II study.
OVERVIEW

Formal stage III intervention experiments in infant nutrition are only recently gaining acceptance to explore the impact of infant nutrition on clinically relevant short- and long-term outcomes. I have illustrated the value of such trials in approaching the critical issue of whether early nutrition affects later health and development. Ultimately our public health and clinical recommendations would be most secure if based on such an approach. Indeed, it is possible that recommendations based on more conventional physiological ("stage II") work could turn out to be inappropriate (as illustrated above), bearing in mind the lack of predictive value some short-term physiological findings may have for later outcome.

Unfortunately, clinical trials are still being used suboptimally in many circumstances, with targeted outcomes of unproved clinical relevance (for example, short-term growth), inadequate and uncalculated sample size, inappropriate blinding procedures, inadequate follow-up duration, and incomplete follow-up.

The current regulatory climate is likely to impose more rigorous standards on researchers and a need to prove efficacy and safety for new advances in infant nutrition. The clinical efficacy trial is not, of course, a new development—it is simply that in the past, infant nutrition researchers, funding bodies, and industry have been resistant to the use of this powerful tool.

EPILOGUE ON HUMAN MILK AND NEURODEVELOPMENT

Although randomized trials are an ideal in infant nutrition research, some are not possible or ethical. Our inability to do randomized outcome studies of breast-milk-fed versus formula-fed infants poses problems, particularly because the breast-fed infant is used as a model for performance.

The major problem of interpretation of studies of breast milk versus formulas, at least in more recent decades, is that mothers who choose to breast-feed have higher education, higher socioeconomic status, and show a greater degree of positive health behavior (42). Because these factors may independently influence many of the outcomes of interest in infant nutrition research—notably neurodevelopment—comparative studies are generally confounded.

At least 17 studies (for example, 42–49) have now addressed whether breast-fed and formula-fed infants differ in cognitive outcome or in visual development. A few have failed to observe any differences between these groups. Most have found advantages for the breast-fed group, some even after attempts to adjust for sociobiological confounding. In other cases, such adjustments have eliminated the apparent advantage. Where advantages for the breast-fed group have existed, they have generally been of the order of 0.25 to 0.5 SD of cognitive scores. The advantage has perhaps been less in term infants than in preterm infants.

The problem has been how to get at causation. This pursuit has been revitalized recently by those who cite the cognitive advantage of the breast-fed infants as
evidence in favor of an essential role for dietary LC-PUFAs in neurodevelopment (LC-PUFAs being found in breast milk and not in formula).

In Popperian terms, repeated verification of findings is not an optimal approach; and certainly, there are enough studies showing a cognitive advantage for breast-fed babies, even after adjustment for confounding, for there to be limited value in repeating that exercise.

A more useful approach is to identify novel circumstances in which the causation issue can be examined afresh. One such approach is to study populations in which it is the mothers with lower education and socioeconomic status who breast-feed. Recently, Gale and Martyn (50) published such a study and found that the previously breast-fed group, now in adult life, still performed more highly on cognitive tests despite their social disadvantage. Gale did a subsequent regression analysis and concluded that the apparent breast-feeding effect was associated with dummy (pacifier) use, though this has been debated. More studies of underprivileged breast-feeders might be valuable.

Our own approach has been to explore this issue in premature babies, where the problems of confounding can be tackled in a new way. The two major proposed sources of confounding in this area are: (a) that the breast-feeding effect might be caused by the act of breast-feeding itself affecting mother–infant interaction and hence development and, (b) as discussed above, the sociobiological advantage of modern breast-feeders. We have devised two studies, each of which avoids one of the above types of confounding. The first study (42) involved the follow-up of 300 children from the five-center study described above (Fig. 1) and divided them according to whether or not they had received their own mother’s milk. According to the WISC-R intelligence quotient (IQ) test at 7.5 years, those whose mothers provided breast milk had a 10-point higher IQ. Adjustment for mother’s education (as a proxy for mother’s IQ), social class, and sex reduced the difference to 8.3 points.

This residual 8.3-point difference in IQ at 7.5 years was large, though it might, at least in part, still have been explained by residual social and education confounding. However, the novel circumstance that assists the causation issue here is that we cannot argue that any advantage was conferred by breast-feeding itself, because these infants were too immature to suck and were fed by nasogastric tube. Indeed, an analysis on those babies who received breast milk (for an average of 1 month in hospital) but did not go home breast-feeding showed they still had a near 8-point advantage in subsequent IQ.

The second study (41) was perhaps even more compelling. At the 18-month follow-up, Bayley scores were not different (in study 1, trial A) between children previously fed donor milk versus preterm formula. This was surprising because the term formula versus preterm formula comparison (study 2, trial A) had shown the importance of providing the preterm baby with a formula that met the increased needs of this population. Yet, babies fed donor breast milk, with its low nutrient content for preterm infants (see Table 1), did not appear disadvantaged. We speculated that this might be because donor breast milk contained a factor or factors that
ameliorated the effect of its poor nutrient content. However, a fairer comparison was between donor milk (from study 1, trial A) and term formula (from study 2, trial A), where the diets compared have more similar nutrient contents (Table 1). For clarity, data illustrative of PDI scores have been extracted from Table 3 and placed in Table 4. The comparison between trials of banked-milk-fed and term-formula-fed infants is legitimate because the same preterm formula acted as an internal standard between trials. The babies fed banked milk had a significant near 9-point advantage in PDI over those fed term formula. The novel circumstance of this study is that none of these infants had mothers who chose to provide breast milk, so that the usual sources of sociobiological confounding did not apply, yet the breast-milk-fed group was still advantaged.

These two studies were done on preterm infants, and although they provide perhaps more compelling evidence than previously for an effect of breast milk itself on later cognitive function, it is possible that the findings cannot be extrapolated to the term infant born during a less rapid stage of brain growth. It should be emphasized, however, that if there is a breast milk advantage, it cannot necessarily be ascribed to the presence of long-chain polyunsaturated fatty acids—there are indeed many candidate factors in human milk (thyroid hormone, growth factors, and so on) that might exert a biological effect (42). Demonstration of a clear long-term effect on neurodevelopment of any of these candidate factors in a randomized formula supplementation study would provide important collateral evidence for any beneficial effect of breast milk. Because the cognitive advantage of breast-fed versus formula-fed babies has been seen during midchildhood, when cognitive tests are predictive of those in adulthood, supplementation studies in formula-fed babies would need to have at least a several-year follow-up period. Currently, the trials of LC-PUFAs, important in this regard, are generally small, with relative short-term follow-up, and do not yet contribute convincingly to the intriguing question about breast milk and long-term cognitive function.

REFERENCES


LONG-TERM OUTCOME TRIALS


DISCUSSION

Dr. Aeschlimann: I have a comment about safety. You say assessment of safety needs an adequate sample size, but it is necessary to be precise about the sample numbers. If you have only 30 infants in a trial and see no adverse reactions, you can only say with 95% confidence that the incidence of adverse reactions is less than one in ten; and if you have 3000 people with no adverse reaction, you can only say that the incidence is less than one in 1000.
**Dr. Lucas:** Recent test cases in court, for example the Dehendorf case, show that it is almost impossible to have a large enough safety trial to pick up all the rare effects. Nevertheless, I think that we have to do a realistic job here, and in situations where safety issues are testable. For instance, several of the potential effects of LC-PUFAs in premature babies, such as infection and necrotizing enterocolitis, are not so rare that we can’t reasonably test the hypothesis that there is a differential incidence between groups—and we should do it. There are many more postmarketing questions that need to be addressed as far as minor safety is concerned, but I would still say that not only are we bad at looking at premarketing safety in clinical trials, we are equally bad, if not more so, at looking at postmarketing surveillance techniques to examine safety.

**Dr. Haschke:** Without going into details, could you comment a little more on the long-term outcome in the LC-PUFA studies? You mentioned you had 2000 infants in different studies, with different designs of course. Could you give us a preliminary idea of the outcome of those studies? We are struggling with studies with a sample size of 50, and we are discussing effects in the very short-term range.

**Dr. Lucas:** We have six LC-PUFA studies at various stages. The first one to be completed has over 400 subjects in it, but we are only doing a preliminary analysis on it at the 9-month follow-up; our targeted follow-up is 18 months. I can say at this very preliminary stage—because we have now been allowed to do an analysis although we have not actually broken the code—that there is no impact on development and growth between LC-PUFA-supplemented infants and non-supplemented infants, using both AA and DHA, at 9 months. However, we clearly need to look at our 18-month follow-up data before drawing any definite conclusions. At 18 months, test scores are verging on showing reliable correlations with later scores, although by no means definitively; for example, the correlation coefficient between the Bayley score at 18 months and the WISC-R score at 7½ to 8 years would be about 0.5, but it is obviously better in populations than in individuals. If we find differences at 18 months, then clearly they need to be followed up; if we fail to find differences at 18 months, we still need to do longer-term follow-up because the early tests may not be sophisticated enough to pick up effects. So in these studies, we really are committed to follow-up into childhood, but we may get some important clues in the second year of life.

**Dr. Haschke:** My second question is related to long-term outcome in growth. Was there any long-term effect on growth, in particular in those infants who were fed breast milk versus the preterm formula?

**Dr. Lucas:** We have failed to find a consistent relationship between early growth and later neurodevelopment up to 7½ to 8 years. We have also found absolutely no relationship between early diet, which has a profound effect on neonatal growth, and body size up to 7½ to 8 years later. So it appears that early neonatal growth is far less predictive of anything than we might have imagined.

**Dr. Tsang:** You have identified an important problem, but it is a moving target. You just told us that your banked breast milk is no longer being used, your term formulas are no longer being used, and your preterm formulas are not the same, so all three things you studied are no longer in existence. Because of the long duration of your studies, every time you present your data, they are out of date and no longer relevant. How do you face this new challenge?

**Dr. Lucas:** I totally disagree that it is irrelevant! The issue that we need to address, which is unknown, is whether early nutrition *per se* matters for long-term outcome. If we decide that feeding babies suboptimally makes a difference to long-term outcome, then that is of
immediate clinical importance in 1996 because premature babies are frequently fed subopti-
mally—they may not be fed on term formulas or banked breast milk, but they are frequently fed suboptimally. So we are establishing whether nutrition matters. Now obviously in these long-term studies, you will have some degree of redundancy if you like. Nevertheless, as we discover that more medium-term outcomes have predictive value for later outcomes, then we can get much closer to our target in subsequent studies. Neonatal intensive care has been extremely fast moving over the last 20 years, and it is likely to stabilize in the next few years. I think we will very shortly be getting data that are of current relevance.

*Dr. Hamburger:* At the very least, you have convinced people that it is worth paying for long-term study!

*Dr. Lozoff:* Many of us in this room are physicians, and we have generally been quite content to use outcome measures such as Bayley or IQ tests, but if we were to present these data to behavioral scientists, they would be horrified. They would say these are very crude measures, they tell us nothing about process, they don’t correlate with function, IQ measure-
ments are horribly confounded by measurement and culture bias, and we don’t know what intelligence is, and so on.

*Dr. Lucas:* These are all valid points. First, what psychologists are generally interested in is cognitive measures in an *individual*, but what we are looking at is differential effects on cognitive function between large randomized *populations*. That cancels some of their criti-
cisms. In populations, intelligence quotient is certainly correlated with academic performance, and I don’t think any of us, or even your most critical psychologists, would like to lose 5 IQ points as a result of early diet. I have presented data on the Bayley and IQ tests simply because I felt they would be most amenable to a general audience. We are in fact doing a lot more sophisticated testing on these children and have done all the way through; in our adolescent follow-up, we will be able to do some really very sophisticated tests on these children. So I agree with you, but nevertheless I think that the Bayley and WISC-R IQ have such general acceptance that they are worth measuring—but other things as well.

*Dr. Whitehead:* You said at the beginning of your talk that your hope was there would be a lifetime follow-up on your work. What do biomedical scientists like yourself, who are interested in this kind of topic, need in order to ensure that such a follow-up does occur, because if it does not occur, then we are not delivering the goods that science expects us to deliver.

*Dr. Lucas:* This is a practical issue. I would make the general point that we have heard some important comments from statisticians, and the statistics of these clinical trials are of course very important, but the practical aspect of running these trials is really the major problem. The one outstandingly important practical issue here is how to hang on to your patient population. In certain countries, that is relatively straightforward—in Scandinavia, it is straightforward, and in Britain, it is relatively straightforward—because people are tagged by being part of the national health service. We use a number of other tagging techniques, such as keeping ourselves informed on addresses of relatives and friends, so that if subjects move, we can contact people who would know and care where they have gone to—of course, with their permission. This is just one of a number of different techniques that one might use. You have to look at the population you are studying and decide how feasible it is going to be to achieve reliable follow-up. In Britain, we achieved 98% follow-up of subjects at 7½ to 8 years, who were diffused all over the country. That encouraged us to believe that we could keep tabs on this population. It is slightly more difficult if they move overseas, but still not impossible.

*Dr. Hamburger:* It’s almost impossible in the States.
Dr. Pohlandt: You haven’t had time enough to outline all your work, but I think it is important to indicate which variables have been primary ones and which secondary ones, and also what questions you asked after finishing the studies—for example, what about necrotizing enterocolitis?

Dr. Lucas: Anticipating that question, which is a very important one, the three variables I presented to you were absolutely key variables at the outset of our trial: trial size was calculated for differences in neurodevelopmental outcome; growth was obviously a key measurement in the neonatal period to establish that we were looking at differences in nutritional status in the short term, and necrotizing enterocolitis and death were the two most important outcomes in terms of safety. So I haven’t fudged the outcomes to provide a story! There are several other outcomes that we have reported that are genuinely secondary outcomes of the study and, therefore, are much more hypothesis-generating than necessarily definitive. I think it is extremely important that investigators in studies like this make it very clear whether a hypothesis is a post hoc one or a primary one.

Dr. Uaay: Your studies are multicenter, and I think it is very important to get an idea of how homogeneous the centers are. In our experience with necrotizing enterocolitis, we find some centers with rates as low as in your breast milk group, while others have values of 20% or 30% in babies under 1500 g. So how important is it to have a homogeneous group of centers to test these variables?

Dr. Lucas: What is important, as has been suggested by statisticians here, is that you have a separate randomization in each center. That is absolutely critical because, otherwise, you could have really quite serious bias if you don’t have balanced groups from each center. Of course, there are center variations in necrotizing enterocolitis; that is well established. You can’t pick up significant differences within individual centers often—that is the whole point of having multicenter studies; but for most of the factors that have shown up as differences in the overall population, we found the expected trends in individual centers when we have done the appropriate analysis. The strength of having many centers is that, provided your nutritional intervention is stereotyped, then the fact that you get an outcome difference despite minor variations in practice between centers gives your answer a robustness and a generalizability for other centers.

Dr. Yolken: I wonder if you could comment more on the feasibility of doing studies in a naturally occurring breast-fed population versus a formula-fed population, where you can’t totally randomize the groups. Do you have studies like that?

Dr. Lucas: There have been about 17 studies comparing breast-fed and formula-fed babies, most of them showing an advantage for the breast-fed group. But all of them are potentially confounded, even after adjusting for confounding factors, so what you don’t want is repeated verification; more and more studies showing the same thing would be useless. What we need to do is to find circumstances that get around the confounding problems. We have done two studies that avoid the conventional confounders: one used breast milk taken from a donor population, in cases where the mother chose not to provide breast milk herself; the other used premature babies, where there was no breast-feeding, so you get rid of the bonding effect of breast-feeding, and you are just looking at the effect of milk given down a tube. Another way would be to look at populations in which the higher socioeconomic group has chosen to bottle-feed rather than breast-feed and see if you still get the breast-feeding advantage. That may be the way forward; obviously, you can’t randomize.

Dr. Lozoff: In relation to your measures for outcome, I would completely agree that those of us who are doing research in clinical nutrition are charged with asking what is important for function. It seems that there are two very different approaches, one looking at very specific
mechanisms and parts of the central nervous system, which guided the choice of measures, and the other—as in the work you presented and similar to what I have been doing—taking very crude overall measures. I wonder what your thoughts are about these almost polar opposites.

Dr. Lucas: The choices are probably slightly too stark, in the sense that there have been a huge number of studies on the impact of malnutrition on experimental animals, and also a fair amount of work done on human brain development, which could guide you in this area. For instance, we know that new neurons are being formed in the posterior parts of the brain—in the cerebellum, for instance—during the prenatal period, whereas most neurons are formed earlier in gestation. So we would expect those to be particularly vulnerable in premature babies, and that is why we have put quite a lot of dominance on psychomotor tests in our 9- and 18-month follow-ups, because we felt that we would be most likely to pick up differences in coordinating functions. You appreciate that the Bayley psychomotor test is highly dominated by coordinating and balancing skills. That hypothesis turned out to be true, and we did see our biggest effects on the Bayley psychomotor rather than mental development at that stage. However, because this is an exploratory area, we need to have fairly broad-based tests that are going to pick up differences in function. We are now adopting a much more sophisticated approach, looking at brain imaging and so forth in these populations.

Dr. Uray: From the information that you provided, and other studies provide, about the effect of human milk versus formula, what do you think are the nutrients involved? Of course, I like the LC-PUFA hypothesis, but have you tested other hypotheses, for example thyroid hormone?

Dr. Lucas: We haven’t tested other hypotheses. We are testing the LC-PUFA hypothesis because we consider it to be plausible—it does need to be tested as a possible cause of differences between breast-fed and formula-fed babies, but there are so many other differences, and in particular, the nonnutrient differences as you point out. There is a mass of hormones and growth factors in human milk not present in formula, somewhere between 35 and 50 at the last count, including thyroid hormone, for instance, which you mention, and which has a very potent effect on neurodevelopment. So there are a long list of things to look at, but we are particularly involved with LC-PUFAs at the moment.

Dr. Rey: Can we say that there is no advantage to adding LC-PUFAs to preterm formula according to your data because the IQ at 7 years was exactly the same in banked breast milk and preterm formula without LC-PUFAs?

Dr. Lucas: This is a rather unfair comparison because banked breast milk is nutritionally insufficient for premature babies compared with preterm formulas, so you could be looking at counterbalancing effects. The more realistic comparison is between banked breast milk and term formula, which I showed you, where the nutrient contents are much more similar. There we got a very large difference between groups, and we need to explain it. One possible explanation is LC-PUFAs, but the difference could be related to any number of other factors present in human milk.

Dr. Guesry: I think that to compare own mother’s milk with preterm formula is also unfair, because when a mother takes on the burden of coming every day for weeks to provide her own milk for her baby in the neonatal unit, this probably means she will give better care over the rest of the 7 years of observation. We have to be very careful in looking at all these factors.

Dr. Lucas: No one could agree more with that than I. All the studies that compare mother’s own milk with formula are confounded, including my own, as I pointed out in my paper. The one bit of confounding that wasn’t present in that particular study was that you couldn’t say that the advantage was caused by breast-feeding, because the babies received human milk down a tube not from the breast. We did adjust for mother’s education, which is a proxy for maternal IQ; we did adjust for social class; but we didn’t adjust for positive health behavior, which you have just described, and it could easily be the explanation of our results. That is
why it is so important to identify circumstances that get around the confounding, such as the comparison of banked breast milk with term formula, where there is a similar nutrient content and two populations whose mothers have chosen not to provide breast milk. So you have taken out all the positive health behavior. The fact that there is still an advantage to banked breast milk over term formula does at least provide a challenge.

Dr. Rey: I would like your opinion on the long-term effects of malnutrition in infancy. You know about the many papers published by Barker, and the last one was very strange, because he found that the rate of suicide was higher in people with a smaller increment in weight in the first year of life. He found that the group who committed suicide had a weight at 1 year that was 395 g less than the control group (1). I think this is very puzzling. Are you afraid that your children fed with term formula will commit suicide in the future?

Dr. Lucas: From the 1960s onwards, we have had very powerful data from animals suggesting that early diet affects long-term outcome in a variety of species, so the question is whether this is true for humans. There are two approaches that we could adopt to find out. One is the epidemiologic approach, which has been adopted by Barker, that is, to try to find nutritional markers in early life and relate them to long-term health outcomes; the other approach is the experimental intervention approach, which is the one we have adopted. The advantage of Barker’s approach is that you can look at the extremes of life very quickly without doing a long-term experiment. The disadvantage is that it doesn’t prove cause; we have no idea whether the relationship between birth weight and long-term systolic blood pressure that he has shown, for example, is causally related to maternal and hence fetal nutrition, which is what he hypothesizes. The advantage of the approach we have adopted is that we can get a cause; the disadvantage is that it takes a long time to get the answer. I think in the end Barker’s epidemiologic studies are hypothesis-generating. If we want to change public health policy, however, it has got to be on the basis of intervention studies.

Dr. Haschke: Can you also comment on the calcium and phosphorus status in the infants receiving banked breast milk? Did they receive calcium and phosphorus supplements? If yes, what was the outcome? If not, can you also compare the incidence of rickets and abnormal bone structure?

Dr. Lucas: In the early 1980s, we did not give multinutrient fortifiers in breast milk—those products did not exist in Britain. The only supplement that we added to human milk was phosphorus, a small amount bringing the concentration up from 15 to 30 mg/100 ml. Despite doing that, the babies fed on human milk did very badly in terms of short-term bone mineralization; they had a very high incidence of high alkaline phosphatases, and they grew less well in terms of linear growth, not only in the neonatal period, but also for the first 18 months of life. What was fascinating was that when we took a pilot population at 5 years of age and looked at bone mineralization using a rather unsophisticated technique (single-photon absorptiometry), we found that babies who had been randomly assigned to the preterm formula had a lower bone mineral content than babies who had been randomly assigned to banked breast milk after adjustment for body size. That raised the hypothesis that despite the short-term deficits, there might be some value in human milk in long-term bone mineralization. We are currently testing that hypothesis in several hundred children now, and they have reached 12 years of age, but I can’t tell you the answer yet. However, we are now doing much more sophisticated studies including bone turnover.

REFERENCE