State of Breastfeeding in the World

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Scientific Evidence for Breastfeeding

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Abstract
The global drive to promote breastfeeding targeted at all 134 million infants born/year on the planet is one of the most pervasive public health interventions. It is, therefore, critical that the breastfeeding field is rooted in sound evidence. Three important scientific pillars of breastfeeding have been: (1) that human milk (HM) is the product of 200 million years of mammalian evolution; (2) that HM composition should be seen as the gold standard for infant nutritional requirements; and (3) that HM has numerous clinical benefits for the infant. I shall look carefully at these areas to help pave the way to a more solid basis for modern breastfeeding medicine. Firstly, I shall look at evolutionary theory for human breastfeeding and consider in general terms the implications for optimal nutritional care of breastfed infants. Secondly, I shall show how HM composition has been incorrectly translated into dietary intake in a large body of past flawed work that resulted in misleading data. Implementing such data as a model for infant formula appears to have increased the risk of obesity and cardiovascular disease (CVD) in formula-fed infants. Finally, most studies that examine the benefits of HM are observational and potentially confounded. So, this body of data needs to be backed by experimental evidence. Here, I shall use preterm infants as a model, since numerous RCTs and physiological studies over 40 years have compared exclusive HM feeding versus cow’s milk exposure. Unexpectedly diverse immediate beneficial effects span the field of neonatology, and long-term programmed effects have been shown for cognition, brain structure, risk factors for CVD, structural development of the heart and lungs, bone health, and atopy. These data add much weight to the evidence, obtained in full-term infants using observational study de-
signs, that HM feeding in early life may fundamentally and permanently change the biology of the organism. Breastfeeding is emerging as a major evidence-based field of medical and public health practice.

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Introduction

Given 7 billion people on the planet and 134 million births/year, the recommendation that all babies should be breastfed constitutes a colossal public health intervention. All public health interventions should be rooted in sound scientific evidence and I shall consider some modern advances in the science and understanding of this important field.

I shall focus on 3 important pillars in breastfeeding medicine: (1) that human milk (HM) is the product of 200 million years of mammalian evolution; (2) that HM composition is the gold standard for infant nutritional requirements; and (3) that HM has numerous clinical benefits for the infant.

Finally, I shall emphasize the great importance of breastfeeding as an evidence-based clinical and public health intervention.

Breastfeeding and Mammalian Evolution

With 200 million years of mammalian evolution, breast milk has evolved major diversity – for instance a 2% concentration of fat in mare’s milk contrasts with over 40% fat in the milk of the harp seal, where the offspring must survive extreme cold. Nevertheless, the application of evolutionary biology to human breastfeeding requires some special considerations with potential implications for practice [1].

Until relatively recently, humans lived in hunter-gatherer societies, but, in a short period, as intelligent primates, humans changed their environment dramatically, whereas our genes are still ancient. The consequent mismatch between our genes and environment is known as “evolutionary discordance.” As Cordain et al. [2] noted for adult humans, the principal phenotypic manifestation of evolutionary discordance is disease. Thus, it is proposed that the high incidence of obesity and cardiovascular disease (CVD) in modern humans is due to the mismatch between genetic adaptation and our modern diet – an example of evolutionary discordance.

The question of relevance here is whether human breastfed infants are affected by evolutionary discordance and how this should be managed to complement the considerable value of breastfeeding identified later in this article. Thus,
modern mothers eat less green leafy plants than our ancestors and presumably have less vitamin K in their breast milk [3]. This may explain the past occurrence of late vitamin K deficiency bleeding in modern breastfed infants – a condition that had a high incidence of intracranial bleeding. Thus, all babies now receive prophylactic vitamin K after birth. A further example is that a consequence of recent migration of human populations into less light-exposed areas of the globe is increased propensity to vitamin D deficiency, which may require vitamin D prophylaxis. An intriguing hypothesis to explain the occurrence of early iron deficiency anemia comes from the observation that piglets put in a concrete pen develop iron deficiency since pig’s milk is relatively low in iron and a concrete pen prevents iron intake from soil [4]. Hallberg [5] speculated that early human infants might have eaten soil to supplement the iron received from human breast milk, but with environmental change and modern public health, modern infants no longer consume iron from soil.

One consequence of the major recent change in the diet of humans is that the n-6/n-3 fatty acid ratio in the diet of hunters-gatherers is believed to be around 1:1 whereas with a modern Western diet this ratio is around 15:1, reflecting a relatively low n-3 fatty acid status in modern mothers [6]. The impact of supplementing the diet of a lactating mother with n-3 fatty acids is not established but does at least raise the hypothesis for future testing that nutritional status of the offspring might be further optimized by dietary care of breastfeeding mothers.

In summary, current evidence (see later) shows that breastfeeding is superior to its substitutes on numerous health grounds. Nevertheless, given the evolutionary aspects considered, it is in the interests of population health to identify areas in which nutritional care of breastfeeding mothers or their babies could further improve outcome – a principle already in practice in relation to the use of prophylactic vitamin K and vitamin D in infancy.

**Breast Milk Composition as the Gold Standard for Infant Nutritional Needs**

HM composition has generally been regarded as a gold standard for deriving infant nutritional requirements – for instance in situations where artificial feeding is required. This has certainly been a most helpful concept.

However, for breast milk to be a valid gold standard, it is critical that accurate data are obtained using appropriate methodology. This latter aspect is the one that is discussed in this section since it will be argued that despite intensive work on the composition of breast milk, misleading data have been derived in the past that have misdirected nutrition practice in ways that have had adverse impact on babies and their long-term health.
In 1953, Hoobler et al. [7] were able to summarize no less than 1,500 scientific publications on the composition of HM. In 1977, the UK Department of Health added further to this list: an official publication on the nutrient content of breast milk obtained by complete expression of one breast in mothers from 4 UK cities [8]. These data were proposed to provide a basis for infant nutritional needs and a model for the design of infant formulas. It was at this stage that this and past studies on breast milk composition were challenged as methodologically flawed [9].

One major difficulty in the study of breast milk content is obtaining representative samples of breast milk for analysis. Breast milk fat, and hence energy content, varies greatly during a feed, between breasts, and throughout lactation. Our own data show that during the course of a breastfeed, breast milk fat content doubles, and milk flow, statistically at least, decreases in a curvilinear manner [10]. We suggested that obtaining representative values for milk fat might be best derived by studying milk composition and milk flow during the feeding process, yet this had never been done. In the absence of such knowledge, we hypothesized that milk obtained for analysis in the traditional manner by unphysiological manual or mechanical expression of the breast – so-called expressed breast milk (EBM) – might differ greatly in its fat and energy content compared to the milk obtained by the baby during physiological breastfeeding – termed by Lucas “suckled breast milk” (SBM) [11]. This difference could occur, for instance, if expression of the breast removed more high-fat hind milk than would be obtained by the baby if the breast was not fully emptied during feeding.

In order to study SBM, a milk sampling system was devised by modifying a clinical nipple shield worn on the breast during breastfeeding. The modified nipple shield contained a milk sampling line so that milk could be sampled continuously during a breastfeed, and it also contained a flowmeter in the tip. Initial research using the nipple shield sampling system showed that SBM fat content was around 2.5 g/100 mL versus a figure of around 4.0 g/100 mL obtained in a vast number of prior studies on EBM composition [8, 11]. Thus, if valid, our data suggested that using EBM, it was possible to overestimate milk fat content by 60% compared to SBM obtained during normal feeding. We estimated the energy content of SBM to be 58 kcal/100 mL compared to around 71 kcal/100 mL based on over 1,500 prior publications. This would equate to a methodological error in measuring milk energy content of over 20% when studying EBM versus SBM.

When these data on SBM were published, they were too radically different to those published previously using EBM to be widely accepted. So, to confirm our findings on the energy content of breast milk, we used the doubly labeled water method in a novel way. In this method, 2 naturally occurring stable isotopes:
deuterium (heavy hydrogen, $^2$H) and heavy oxygen ($^{18}$O) are given orally producing enrichment of these isotopes in body fluids. Decline in these isotope enrichments back towards baseline is measured in urine or saliva over several days. The slope of the decline in $^2$H can be used to measure water output (since hydrogen is lost as water), which in steady state reflects water intake, and, from this, milk volume intake can be derived. The decline in $^{18}$O is faster since oxygen can be lost in both water and carbon dioxide. Hence, the difference in the decline in $^2$H and $^{18}$O is the CO$_2$ production rate, from which energy expenditure can be derived – and hence metabolizable energy intake. Thus, over several representative days, milk volume intake and energy intake can be estimated, and, by dividing the latter by the former, the energy content of breast milk is derived without any recourse to breast milk sampling. This approach produced values for energy content of breast milk according to postnatal age of 57–61 kcal/100 mL, thus confirming our previous values using the nipple shield system [12]. Later work has confirmed our finding that breast milk energy content had been greatly overestimated in past EBM studies.

One importance of these findings is that formula manufacturers based their products, and still do, on the composition of EBM, which emerges as the wrong model.

In addition to errors in prior estimation of breast milk fat and energy, breast milk protein content was also overestimated by using analytic methodology developed by the dairy industry. In cow’s milk (CM), there is little nitrogen that is not part of protein so that it is possible to estimate protein content by multiplying nitrogen content by a constant (6.38) [13]. This was used inappropriately for human breast milk in which there is a high content of nonprotein nitrogen (e.g., urea), which should not be counted as protein. Thus, more recent work shows that the true protein content of breast milk is significantly lower than previously thought [14], and this is one reason why infant formulas have substantially higher protein content than breast milk.

Thus, as a result of flawed methodology for breast milk compositional analysis, a generation of babies were fed on formulas modeled on EBM composition unphysiologically high in fat, energy, and protein. This constituted an inadvertent experiment in early overfeeding, and animal studies since the 1960s show early overfeeding increases later cardiovascular risk factors [15].

The higher nutrient intake of the formula-fed infants is believed to be a major factor in the faster early growth of formula- rather than breastfed infants. So, does it matter that formula-fed babies grow faster? In 2004, based on our nutritional intervention trials and animal evidence, we published our postnatal growth acceleration hypothesis, which proposes that faster early growth increases the risk for later obesity and CVD [15]. In that publication, the known in-
increased risk of obesity and cardiovascular risk markers with formula feeding was proposed to relate to the faster growth rate. Since then, over 60 studies, including randomized trials, have supported the postnatal growth acceleration hypothesis.

Thus, flaws in research on breast milk composition were indirectly partly responsible for the major modern epidemic of CVD and obesity – a salutary example of the importance of methodology in science. The field has now become a priority for research on both breastfeeding and formula feeding.

The Benefits of Breastfeeding Revisited

Arguably, the main platform for the global promotion of breastfeeding is the scientific evidence for its clinical benefits. However, with few exceptions, the comparison of breast- and formula-fed babies has not been based on randomized trials that would prove causation, but rather on observational associations.

Initially, the main outcomes of interest were infection and cognition, but these outcomes are potentially highly confounded by the differences in the populations (statistically) that choose to breastfeed or formula feed. As an example, cognitive benefits in breastfed babies have been described in a number of studies since 1929, but in 2006, Der et al. [16] concluded from a meta-analysis and study of sibling pairs that there was no cognitive benefit due to breastfeeding, and the previous positive findings were explained by the higher maternal IQ in those who chose to breastfeed. This study emphasizes the ever-present potential for confounding in epidemiological studies where there are major demographic differences between the groups compared, though the study by Der et al. [16] was also nonrandomized.

Today, a wide variety of beneficial outcomes has been linked beneficially to breastfeeding [17], including CVD and obesity risk, atopic disease, IQ, brain size, infection, cancer, sudden infant death, celiac disease, and type I and II diabetes – but again these beneficial outcomes have only been epidemiologically associated with breastfeeding and not determined experimentally, leaving uncertainty over causation.

The challenge then is how better-quality evidence can be obtained, given the constraint that randomized trials, for instance comparing the outcome of breastfeeding versus formula feeding, are generally precluded on ethical grounds.

The Preterm Infant as a Model

The area I shall focus on here is the use of the preterm infant as a model. Whilst accepting that the spectrum of diseases and the sensitivity to early nutrition is somewhat different in preterm and term infants, neonatal care is an
area where it has been ethically possible to conduct numerous strictly randomized trials of EHM feeding versus exposure to CM. My argument is that if a wide range of important outcomes in preterm human infants are favorably impacted by HM feeding, this would indicate that the weaker observational data on the benefits of breastfeeding in full-term infants are more likely to be causal – especially when the same outcomes (e.g., infection, allergy, cardiovascular risk, or cognitive development) can be studied in both the preterm and term populations.

*Preterm Trials Comparing Exclusive Human Milk Feeding versus Exposure to Cow’s Milk*

There are 3 categories of randomized controlled trials (RCTs) that provide evidence on the benefits of HM or adverse impact of CM.

1. Historical trials [18] comparing EHM feeding versus CM-based products (used either alone or in combination with HM). In these trials, the HM arm received no CM since this was the era before the development (in the later 1980s) of CM-based breast milk fortifiers. The largest of such trials was by Lucas et al. on over 500 infants but at least 5 other smaller RCTs of this nature were done by other investigators.

2. The historic fortifier trial of Lucas et al. [19] tested the clinical impact of adding CM-based fortifier to breast milk versus no fortification (which was ethical at this time when fortifiers were just being introduced into practice).

3. A third RCT category has a long history, as explained here. In the late 1970s, the first evidence began to emerge that HM protected against necrotizing enterocolitis (NEC) and sepsis. However, extensive research showed that HM alone did not meet the needs of preterm infants for protein and other nutrients needed to fuel the rapid growth of the preterm infant, notably the growth and development of the brain. In response to this, CM-based special preterm infant formulas were devised in the 1970s (CM-based HM fortifiers came later in the 1980s) – but by the late 1970s evidence began to accumulate that CM products had adverse effects. In response to this, Lucas et al. [20] developed the concept of lacto-engineering whereby donor breast milk (DBM) was separated and reconstituted to produce HM-based formulations enriched in HM protein and fat that met nutritional needs of preterm infants and allowed total exclusion of CM. The HIV epidemic in the 1980s closed down HM banks, but with the more recent re-emergence of milk banking the opportunity arose for commercial production of HM-based fortifiers and preterm formulas allowing preterm infants to receive an exclusive HM (EHM)-based diet. In the USA, many level 3 or 4 neonatal intensive care units have used these HM-based products providing a new opportunity to do RCTs.
and quasi experimental studies comparing current practice using diets containing CM versus feeding an EHM diet with these modern lacto-engineered products.

**Necrotizing Enterocolitis and Systemic Sepsis**

In term infants, breastfeeding is associated epidemiologically with significant reduction in infection. In preterm infants, more serious infective/inflammatory conditions – notably NEC and proven systemic sepsis – are common, and RCTs and related studies can be used to test the impact of HM versus CM as a model. At least 7 RCTs including trials from the prefortifier era [18] and 2 trials of lacto-engineered products examined the impact on NEC [21, 22]. In all, 6 trials of HM/CM exposure were included in a Cochrane meta-analysis [18]. Collectively, the RCTs show around a 3-fold increased risk of NEC with CM exposure. Further to this, at least 8 quasi-experimental studies have been done on around 4,000 (published in full [23] or in abstract form) that examine the impact of introducing an EHM diet with lacto-engineered products; the incidence of NEC was on average 3 times higher when infants were exposed to CM compared to those fed the EHM diet. With regard to sepsis, 3 historic RCTs from India showed exposure to CM increased the risk of major infection [24]; and the quasi-experimental study on 1,600 babies before and after introducing an EHM diet using lacto-engineered products showed a major fall in the incidence of late-onset sepsis from 30 to 19% [23]. We conducted 2 further RCTs with NEC or sepsis as a combined outcome – our fortifier trial [19] and an unpublished analysis of our historic trial comparing preterm formula with DBM; in both cases, NEC or sepsis was doubled in the CM limb. The US trials on lacto-engineered products showed NEC, NEC surgery, and sepsis were dose related to the amount of CM in the neonatal diet [25], in accord with our own data from the UK [26].

Thus, at least 12 RCTs and 8 quasi-experimental studies show that HM has a major protective effect against infective/inflammatory conditions that provide support for a causal role of breastfeeding in protecting against infection in term infants.

The clinical importance of NEC and sepsis is emphasized by the evidence that these are accompanied by an increased risk of cerebral palsy and lower cognitive performance [27].

**Mortality**

The US trials (combined) of lacto-engineered products show that death rate was 4 times higher in those exposed to CM versus an EHM diet comprising modern lacto-engineered products [25].
**Retinopathy of Prematurity**

A recent RCT in Canada has been presented in abstract form based on infants with a 100% base diet of HM but randomized to a standard CM-based HM fortifier or a HM-based HM fortifier. The group exposed to the CM fortifier had a significant 6-fold increase in potentially blinding retinopathy of prematurity. In all, at least 7 further studies (5 of them included in a systematic review) showed collectively in around 4,000 subjects a major increase in retinopathy of prematurity with CM exposure compared to EHM [23, 28].

**Cardiorespiratory Impact**

In a quasi-experimental 4-center study by Hair et al. [23], comparing CM exposure with an EHM diet, the EHM group had significant reductions in need for ventilation, bronchopulmonary dysplasia, and patent ductus arteriosus. Assad et al. [29] found a 73% increase in bronchopulmonary dysplasia in those exposed to CM rather than an EHM diet.

**Cognitive Development**

In preterm infants, numerous observational studies have shown that use of HM in neonatal care is associated with higher IQ or DQ but, like the studies in full-term infants, such data do not prove causation. However, the opportunity to study this using an experimental design arose with our own RCTs in neonates whose mothers had elected not to provide their own breast milk (thus eliminating the potential confounding relating to mother’s choice to provide breast milk). These two trials compared as sole diets: (i) DBM versus preterm formula (PTF), and (ii) term formula (TF) versus PTF. The first of these trials, DBM versus PTF, compared HM with CM, but the CM arm (PTF) provided much higher protein and energy intakes. Nevertheless, the HM (DBM) group was not disadvantaged in later cognitive scores, suggesting that breast milk had factors that ameliorated the poor nutrient intake. In order to remove the major nutritional difference between these groups, we elected to compare DBM from trial (i) with TF from trial (ii) since these were diets both suitable for term infants. This cross comparison of RCTs was justified since both trials used the same PTF, thus constituting an “internal standard.” The HM (DBM) group had a significant 7-point advantage in the Bayley psychomotor index compared to the TF, providing compelling experimental evidence that HM promoted better cognitive development than seen in the CM (TF) group.

This finding is consistent with a rare RCT done in term infants – the Belarus trial – a cluster RCT done on over 17,000 mother-infant pairs. The intervention in breastfed infants was active breastfeeding promotion compared with no active promotion in the breastfed control group. A significantly longer duration of
exclusive breastfeeding was achieved in the intervention group, which showed a 7.5-point advantage in verbal IQ at 6.5 years [30].

These two pieces of experimental evidence give weight to the view that studies that show an association between breastfeeding and superior cognitive outcome are causal.

**Cardiovascular Risk Factors**

Many epidemiological studies link breastfeeding to CVD risk factors. In our large historic RCT of EHM versus CM exposure in preterm neonates, we found at the 16-year follow-up that the EHM group had favorably reduced the LDL:HDL cholesterol ratio, diastolic blood pressure, insulin resistance, and metabolic tendency to fatness (leptin resistance) [31–33]. Thus, early HM feeding in a strictly randomized trial reduced 4 key risk factors for CVD. The effect size was large; for instance, the impact of early HM feeding on later cholesterol alone would be expected in adults to reduce CVD by 25% and death by 13–14%. These data add weight to the causal nature of a protective role of breastfeeding for future obesity and CVD.

**Atopic Disease**

The relationship between breastfeeding and later atopy has been observational and uncertain. In our historic RCT comparing EHM with CM exposure, those with a family history of atopy fed an EHM diet had a major reduction in eczema, food and drug reactions, and wheezing at the 18-month follow-up [34]. Thus, strict experimental evidence confirms that HM, at least in those with a family history of atopy, is protective against future development of atopic phenomena.

**Conclusion**

Clearly, the HM-fed preterm infant is not a perfect model for the breastfed term infant, and some outcomes considered above would not occur in term infants. Nevertheless, it is a very useful model and conceptually, experimental studies in preterm infants add much weight to the view that breast milk is likely to have broad and important causal effects on short- and long-term outcomes in healthy full-term infants.

**Further Models**

Given the difficulty in providing an evidence-based underpinning for the impact of breastfeeding on clinical outcome, it is important to explore creatively further opportunities for experimental studies. In this paper, I have considered the value of RCTs in preterm infants and noted the inventive Belarus study on breast
milk and cognitive development in term infants. One potentially promising area is the use of RCTs to study the impact on outcome of individual components of breast milk, for instance, HM oligosaccharides.

**Overview**

It has been an objective in this paper to examine some of the general principles that underlie the science of breastfeeding medicine in order to help strengthen this important field, in the interests of improving infant, child, and population health. The critique in the 3 sections of this paper – on human evolution, HM as a gold standard, and the proposed benefits of breastfeeding has significant, practical clinical and public health implications. Breastfeeding and indeed the use of HM in neonatal intensive care is entering a new era of quite unexpected importance for human biology and health.

**Disclosure Statement**

Alan Lucas has taken part in educational events organized by infant food, breast milk and feeding device companies for which he has received an honorarium and expenses. He has provided medical scientific advice to breast milk companies for which he has received consultancy payment.

**References**


