This month’s issue features the effects of cow’s milk-derived components on gut and brain development in neonatal piglets, an anthropologist’s perspective of weaning periods in non-human primates, the problems with current recommendations on full-fat dairy intake, and new on-farm technologies to improve fertility rates in dairy cows.

**Lactoferrin and Milk Fat Globule Membrane Improve Gut and Brain Development in Piglets**

- Lactoferrin and milk fat globule membrane (MFGM) are components of milk that have been independently associated with beneficial effects in infants.
- In two new studies, researchers fed piglets with formula containing bovine lactoferrin, bovine MFGM, as well as common prebiotics to test the effects of providing all these components together.
- The studies found that piglets fed the formula containing a mixture of lactoferrin, MFGM, and prebiotics showed improved neurodevelopment, increased body weight, and a decrease proportion of opportunistic pathogens in the gut compared with piglets fed formula alone.
- The results indicate that a combination of lactoferrin and MFGM derived from cows’ milk could provide various beneficial effects when added to infant formulas.

Infants develop rapidly in the first six months after birth, and breastfeeding has been shown to improve various aspects of this early development. Researchers have made efforts to figure out which components of human milk contribute to these beneficial effects. A pair of recent studies find that adding prebiotics and two compounds typically enriched in human milk to piglets’ diets can improve their gut and brain development.

In the new studies, led by Sharon Donovan [1,2] at the University of Illinois, piglets were either fed formula alone, or formula supplemented with prebiotics, the milk protein lactoferrin, and the membrane—called bovine milk fat globule membrane (MFGM)—that encases milk fats and that is rich in bioactive proteins. The researchers found that these additions to the piglets’ diets improved their neurodevelopment, increased their body weight, and decreased the proportion of opportunistic pathogens in their guts.

Both lactoferrin and MFGM have been reported to independently influence brain and gut development [3-5]. “One issue is, most of them have been studied one factor at a time,” says Donovan. “That’s not the way breastfed infants are exposed to these bioactives,” she says. “Basically the goal of this study was to look at these components together, thinking that their modes of action may be different and could therefore potentially have synergistic effects,” says Donovan. The researchers also included a couple of prebiotics that are typically added to infant formulas to their experimental diet. “We were able to show some benefit of the combined ingredients,” she says.

The study was funded by a grant from Mead Johnson Nutrition, which produces infant formula. “They have an interest in assessing the addition of bioactive bovine milk components to infant formulas to basically make formulas more similar to human milk and potentially improve infant outcomes,” says Donovan. Lactoferrin is typically present at much lower concentrations in formula than in human milk, and MFGM is typically absent from formula because of the way formulas are currently made, Donovan says.

Donovan says she expects both lactoferrin and MFGM to be added to formula eventually, and more studies of their effects will help. “Every ingredient added to formula increases the cost, and we also need to make sure that there’s no unforeseen detrimental effect that might occur,” Donovan says. “Our goal is to use the piglet as a preclinical model to help us understand how some of these bioactive compounds are working.”

In one study, Donovan and her group found that piglets given a diet containing lactoferrin, MFGM, and prebiotics were more neurodevelopmentally advanced than piglets without the diet, with differences in gray and white matter concentrations [1]. Donovan suggests that adding these components to formula could potentially also improve neurodevelopment in human infants. A previous study found that infants given formula supplemented with MFGM exhibited higher cognitive scores than infants fed formula without MFGM, and were no different than breast-fed infants [3].

In the second study, the researchers shifted their sights from the brain to the gut. Piglets fed formula supplemented with
lactoferrin, MFGM, and prebiotics experienced increased weight gain, and “we found a number of potential benefits to gut development, and differences in the microbiota,” says Donovan. “One of the things that was good was that the relative abundance of potential pathogens was reduced,” she says.

There has been growing speculation about the role of the microbiome in influencing brain function, and as a result, the researchers also looked for certain neurotransmitters found in the gut, such as tyrosine hydroxylase and vasoactive intestinal peptide. The researchers found that their experimental diet increased the number of cells positive for VIP and TH, indicating that the diet may play a role in influencing the gut-brain-axis. This is one of the first attempts to characterize these neurotransmitters in the gut, and it’s something that Donovan plans to look at in more detail. “We’ve learned a little bit, but we obviously know that we still need to do more work in this area,” Donovan says.

The results in piglets are encouraging, and Donovan plans to further characterize the mechanisms of the diet-related changes. “Piglet gut is a very rapidly growing tissue, and typically it’s kind of difficult to increase the growth, because it’s already a system that has its pedal to the metal,” says Donovan. “That suggests that these factors are indeed doing something, because it’s hard to increase a system that’s already growing at its maximal rate,” she says.

The results could have important implications in human infants. “If you have infants that have compromised gut development, or maybe an infant that has had some sort of damage to the gut, then having components that can help in that process can potentially help those infants to recover more quickly,” says Donovan.


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Evolving Motherhood: When to Wean Part I

- In primates, weaning is a process, not an event that happens at a single point in time.
- Growth, tooth eruption, and behavioral observations are proxy methods used to infer weaning.
- Chimpanzees and gorillas—our closest ape relatives—wean between three and five years of age.
- Applying “primate proxies” to humans predicts weaning ages from 18 months to 10 years!

The benefits of breastfeeding are well known, yet however hard some women try, they struggle to produce sufficient milk. For millennia, herbal remedies have been thought to fix this problem. Even Hippocrates—from whose name comes the “Hippocratic Oath”—is said to have advised, “If the milk should dry up give her to drink the fruit and roots of fennel” [1]. To this day, however, there is limited reliable data on whether herbal supplements actually work.

The “evolved” age of weaning is a topic of debate not only among the general public but clinicians and scholars as well. Weaning, however, is not an event—it is a process. When that process begins and how long mothers and infants negotiate milk transfer varies across mother-infant dyads [1,2]. Additionally, adaptations reflect the selection of traits in ancestral populations; changing ecological conditions can lead to a mismatch between adaptations and current ecological conditions. What was once adaptive in landscapes roamed by early humans may not be the best fit in contemporary urban and suburban environments. And lastly, for these types of behavioral biology traits, there is no precise “one size fits all” adaptive threshold.

Discussions of lactation and breastfeeding in humans, particularly duration until weaning, requires consideration of many subjects. Just to name a few topics that immediately come to mind: life history theory, human subsistence patterns, gene-culture coevolution, comparative primatology, population dynamics, cultural relativism, ecology, global health, developmental programming, public policy, economics, equal opportunity, and biopsychology. The complexities of these intersecting topics and their influence on motherhood and infancy are myriad. Oftentimes, research studies are focused within a narrow disciplinary approach, shying away from intersections across social, life, environmental, and medical sciences. Despite these limitations, the current literature provides some opportunity to understand lactation duration and weaning dynamics in primates, shaping what we understand about human weaning.
In primates, weaning is a process, in part, because the “optimal” age of weaning is different from the mother’s and the infant’s perspective. Natural selection has shaped mothers to produce a series of offspring across a reproductive career. Maximizing lifetime reproductive output has favored adaptations to transition from current reproduction to the next reproductive event. The Goldilocks “just right” time point is when weaning doesn’t endanger the infant’s survival or unduly threaten the infant’s well being—but not so long that the mother has appreciably delayed the next reproductive opportunity. An individual offspring, however, is entirely related to himself and only partially related to the mother and the future siblings she’ll produce. This difference of relatedness between oneself and one’s parent and siblings predicts that infants have adaptations to acquire more resources from the mother than she has been selected to provide [3]. From the infant’s perspective, the Goldilocks “just right” time point is later than the mother’s—in order to become stronger and remain buffered from the world for longer. This concept from evolutionary biology is known as parent-offspring conflict, but anyone who has tangled with a weaning tantrum knows what I am talking about.

While nursing patterns reflect a conscious behavioral negotiation between mother and infant, some lactation adaptations, such as milk composition, are operating beyond conscious control of mother or infant. Fundamentally, the divergent genetic interests are predicted to cause a gap between maternal and infant adaptive optima. Mother’s physiological optima for milk production—protecting her condition for future reproduction—will likely be less than baby’s optima for milk consumption that sustains maximal growth. The milk a mother synthesizes will fall somewhere between what is optimal for her lifetime reproduction and what is optimal for an individual baby’s development. This means that, while breastfeeding is the optimal form of infant feeding compared to other available options, breast milk is not necessarily optimal or maximal for infants.

Evolved weaning in humans

Estimating expected age(s) of weaning for humans as a function of our primate heritage presents highly variable predictions. Values for “age at weaning” across primate species are derived from behavioral observations, inferred from developmental milestones, or measured from biological samples, and they all provide different age predictions for human weaning. Indeed, in many ways we are setting off on a Highway to the Danger Zone. Here I present empirical data, in part because the aggregated life history tables within the order Primates reflect substantial variation in methods, timing of study, ecological conditions, and statistical covariates [4]. Humorously, Lee headed a section in a review and meta-analysis with “Data Sources and Their Problems” [5].

Relying on behavioral observations depends on how weaning is operationalized. Weaning can be the introduction of non-maternal foods—even though many mammals have a period of complementary feeding of mother’s milk and solid foods [6,7]. Perhaps the date of last nipple contact or suckling bout, but sometimes milk isn’t transferred, or milk is transferred in very, very small volume. Night-time nursing may account for much of the milk transfer, [8,9] especially as lactation progresses. A recent study reported weaning age in wild mountain gorillas as intermediate from the month last suckling was observed and the next month for which no suckling was observed [10]. Based on observations of 29 infants, the mean weaning age of mountain gorillas was 40 months, but ranged from 35–50 months. Infants were weaned later if their mothers were first-time mothers or if they lived in multi-male social groups. Observations of wild chimpanzees suggest that offspring are weaned between 4 and 5 years of age [11]. Orangutans likely wean their young even later. But patterns in humans are hard to compare with non-human primates, because behavioral observations during daylight hours are very different than asking human mothers when they weaned their infants.

Weaning age may be more influenced by developmental milestones, rather than a particular age. Lee and colleagues suggest that weaning is “ecologically sensitive” and occurs as infants triple or quadruple their birth weight, rather than at a particular age [12,13]. Weaning, therefore, depends on how fast the infant grows. This, in turn, depends on the volume and energy density of milk a mother produces, which is highly variable among individual mothers. However, getting the birth weights of wild primates presents serious challenges, hence most of the data showing this pattern come from captivity. Within the captive setting, ample food and health care accelerate growth and maturation rates, which lead to earlier weaning. Similarly, the ample food and low infectious disease burden in the United States, may contribute to US infants tripling their birth weight within 18 months [14] and quadrupling their weight in 30–33 months (CDC Growth
Tooth eruption patterns have been used to infer when primates become nutritionally independent—assuming that adult diets rely on the eruption and occlusion of molars (particularly first molars) [15]. Gorillas, chimpanzees, and orangutans [16] have their first molar erupt typically ~3.8–4.6 years of age, substantially earlier than humans. In humans, 1st molar eruption occurs around 5.5–7 years of age [17,18], after most humans have been weaned. But research demonstrates that inferences from tooth eruption schedules for weaning at the species level have notable limitations [19–21]. In part, this is because average tooth eruption patterns were linked to averages for “weaning age” at the species level, but that tells us little about the variation WITHIN species. Indeed, in a recent study of wild-living chimpanzees, Smith and colleagues [19] found that “first molar emergence in these chimpanzees does not directly or consistently predict the introduction of solid foods, resumption of maternal estrous cycling, cessation of nursing, or maternal inter-birth intervals.”

Something that potentially provides insights into an adaptive timing of weaning is the production of lactase. Baby mammals are able to digest mother’s milk because they produce the enzyme lactase. This lactase enzyme breaks down lactose, the primary sugar in mammalian milk. The gene expression that controls the production of lactase shuts down during development as infants transition into juveniles. As lactase production declines, so does the ability to digest milk, with varying degrees of intestinal distress and stool liquidity. Scholars have hypothesized that the genetically programmed down-regulation of lactase is an aspect of the push-pull of parent-offspring conflict—if kiddo can’t digest mother’s milk, kiddo isn’t demanding it, and mother can allocate milk and energy to the next kiddo [22]. But many humans have “lactase persistence genes” that express well into adulthood allowing humans to digest milk after weaning. Notably, not all humans have genes for lactase persistence. Where reported, the timed onset of declining lactase production occurs around 2 years of age. As stated by Wang and colleagues, “genetically programmed down-regulation of the lactase gene is detectable in children from the second year of life, although the onset and extent are somewhat variable” [23]. However, the end of any lactase production occurs by age 5 or as maybe as late as age 10, depending on the population being studied [24]. Which means that human kiddos without lactase persistence have a pretty wide and variable window for digesting mother’s milk—2–10 years.

### Takeaways of comparative primate weaning

These proxies—behavioral observations, growth thresholds, tooth eruptions, cessation of lactase production—remain imperfect, and suggest highly variable predicted ages for human weaning. Rather than relying on proxies of weaning, more accurate methods to directly investigate lactation curves and milk transfer are emerging. Researchers can measure isotopic signatures of milk consumption in feces and teeth, but very few species have been described, so broad comparative analyses aren’t currently possible [25–27]. New data will allow for more comprehensive analyses, but humans are exceptional in many ways when compared to non-human primates. The most exciting insights into human weaning may come not from primate proxies but from cross-cultural comparisons into the complex biocultural weaning of the human species. **FIND OUT MORE IN NEXT MONTH’S ISSUE OF SPLASH!**

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9. McKenna, J. J., & Gettier, L. T. (2016). There is no such thing as infant sleep, there is no such thing as breastfeeding, there is only breastfeeding. Acta Paediatrica, 105(1), 17-21.
The basic dogma has always been that saturated fats in diets raise LDL, which in turn increases the risk for CVD. But this...
The dogma has recently been questioned because numerous prospective studies have failed to find any association between saturated fat consumption and subsequent development of CVD [2-5,7,9,10].

One of the key sticking points of those that question the dogma is the emphasis on LDL levels to assess CVD risk. Many have argued that looking at only one biological measurement is too reductive [2,4,5,7,9,10]. For starters, they point out that there is a “good” cholesterol, high-density lipoprotein (HDL), responsible for removing lipids from the arteries. Individuals with high LDL levels but with correspondingly high levels of HDL would have a different CVD risk than those with high LDL but low HDL. Indeed, low HDL levels are more indicative of CVD risk than are high LDL levels [2-4].

Furthermore, there are actually two types of LDL molecules, large and small. The small LDL molecules are more likely to lead to clogged arteries and inflammation than the large LDL molecules. Considering just one measurement of total LDL, therefore, obscures the variation in the type of LDL molecules that are present and their potential effects on heart health.

The relationship between saturated fats and cholesterol is much more complicated than it is often depicted. It turns out that while some types of saturated fats in the diet do increase LDL, other types increase the large (and less worrisome) LDL molecules to a greater degree than small LDL, whereas other saturated fats increase HDL [2-5,7]. Moreover, saturated fats have several other physiological influences in the body unrelated to blood lipids and cholesterol, many of which may be positive for overall health [2,5]. Thus, statements from the DGA to limit all saturated fats result in making villains out of nutrients (and the foods that contain them) that may actually be nutritional good guys.

**Dairy fats: Guilty by association**

A prime example of this nutritional stereotyping is the DGA’s recommendation to avoid full-fat dairy products, including milk, cheese, and yogurt, in favor of their low- or fat-free counterparts. The message this sends to consumers is clear: as a source of saturated fat, full-fat dairy products are inherently unhealthy. Or are they? This question has received much scientific scrutiny, and the current consensus is that there is no clear evidence that dairy foods increase the risk for CVD [2-5,7]. Indeed, research results often point in the opposite direction, suggesting improved heart health and other health benefits from full fat dairy foods.

Research results on the link between dairy and CVD risk come almost exclusively from prospective studies. The study design is quite simple—researchers identify their study cohort and follow them for an extensive period of time (often several decades) to see which study participants develop particular traits (such as a stroke, heart attack, or hypertension). Dietary data are collected along the way, and at the end of the study they can compare what individuals consumed to their health outcomes. Although these studies do not prove a cause and effect, they usually have very large study cohorts, allowing the researchers to demonstrate patterns that are strongly suggestive of a link between diet and health outcome.

For example, de Oliveira Otto et al. [2] followed 5200 study participants (ages 45–84 years old) from 2000 to 2010 to assess the relationship between their intake of saturated fat from dairy and red meat with outcomes related to CVD (e.g., hypertension, heart attack). Participants with a higher intake of dairy saturated fat had a lower risk of CVD, whereas red meat saturated fat was associated with a higher CVD risk. Dairy’s benefits are demonstrated even more clearly by their finding that substituting just 2% of energy from meat saturated fat with energy from dairy saturated fat lowered the risk of CVD by 25% [2]. Two percent of energy is not a major lifestyle change (perhaps just a hundred calories), and yet the impact on heart health is profound.

De Oliveira Otto and colleagues believe that the food-based effects of saturated fat are related to several unique attributes of dairy fat [2]. First, they point out differences in the types of fatty acids present. Saturated fats are chains of carbons, and chain length may influence their metabolic properties. Compared to red meat, dairy has a higher proportion of short-chain fatty acids (fewer than 10 carbons in length) and medium-chain saturated fats (10 and 12 carbons), both of which are believed to raise HDL levels more so than fatty acids with 14 or 16 carbons [2]. Additionally, dairy has a higher proportion of odd-chain saturated fats, which have demonstrated effects on both heart health and decreased risk of type 2 diabetes [2,5].

Numerous studies also suggest that the heart health benefits of dairy may have little to do with the fatty acids present, and more to do with the other nutrients that make up dairy foods, including calcium, potassium, phosphorus, and even naturally-occurring trans fats [2-7,11]. Take calcium, for example. This essential mineral is well known for its positive influence on blood pressure, but it may also relate to the way that dairy fats are digested [4]. Calcium can bind many of the saturated fats present in dairy to create calcium soaps that are not soluble and are therefore not removed from the digestive tract into the blood stream [4]. In doing so, it is as if these fats were never consumed in the first place.

In fact, the way that all milk fats are "packaged" may have a large influence on their digestion and ultimate effects on health [4,6]. Fat in milk is present as a milk fat globule; in between the fat and the digestive tract are three layers of membranes made up of phospholipids and proteins, each of which affect the way in which the milk is digested. They also have their own positive health effects, including lowering small particle LDL [6].

Milk fats unique travel accommodations through the digestive tract further distinguishes them from saturated fats from other food sources. Taken together with the types of saturated fatty acids present and the nutritional benefits from the
In a 2011 paper, Astrup and colleagues [3] asked, “Should advice on saturated fatty acid intake be based on food rather than on types of fatty acids?” The scientific evidence replies with a resounding “yes.” And this is because foods actually are the sum of their parts.

Nutrition science calls this way of thinking “the food matrix” [2,3,6,11]. Although it sounds like something out of a sci-fi movie, the food matrix approach simply means considering the complexity of food rather than simply looking at one particular nutrient. On paper, five grams of saturated fat in a cup of whole fat milk may seem like an unhealthy nutritional choice. But that cup of milk is more than just those grams of saturated fat. Milk contains a unique combination of essential nutrients and high quality proteins, all of which have demonstrated health benefits, including bone growth, bone quality, lean body mass maintenance, and insulin resistance. And on closer inspection, those five grams of saturated fat might not be so terrible either; a higher proportion of shorter chain fatty acids, fat-binding calcium, and fat presented in the milk fat globule means milk fat is not metabolized in the same way as saturated fat from other dietary sources such as red meat or palm oil [2].

The American public has embraced a false dichotomy due to marketing that categorizes all saturated fats as the bad fats and unsaturated fats as the good fats. Thus, it may not be an easy task to convince consumers that some foods with saturated fats may have been given a bad rap. But informing consumers about which foods are healthy or which should be limited instead of simply lumping together all food sources of saturated fats may help break the stigma attached to full-fat dairy.


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Automated Dairy Farming Gathers Momentum

- Automated systems are soon set to change the face of dairy farming.
- Currently, timing of artificial insemination (AI) is a major factor in fertility rates.
- Body temperature varies with estrus cycle and ovulation.
- Infrared technology detects whole body temperature profiles.
- Thermography is shown to be a viable method to automate estrus detection in cows.
- Automated farm systems will help take guess work and hard labor out of dairy.

The Dairy Science Unit at The University of Sydney has been developing future dairy concepts and practices for over 10
years. Along with collaborators and partners in industry, the focus has moved from sustainable farming practices to the development of large herd, automated milking systems in pasture based settings, and increasingly expanded automation of dairy farming theme (see e.g. [1]). This is a trend that is emerging in agriculture on a global scale, and dairy stands to benefit enormously from this revolution.

The program at The University of Sydney aims to evaluate new and emerging technologies for practical on-farm use. A recent report from Talukder et al. [2] highlights the approach and some of the technologies within the scope of these developments. The study tackled the issue of fertility in dairy cows. Fertility rates have been declining in dairy cows over many years, so there is a lot of interest in understanding the factors contributing to the decline and devising solutions.

Fertility in dairy cows is closely associated with timing of insemination, and when the majority of inseminations are artificial, the opportunity for failed conception increases with herd number and the logistics of servicing. The goal of the farmer is to ensure viable semen is present in the oviduct at the time of ovulation. Accurate methods to detect and predict stage of estrus and ovulation are central to improving calving rates.

The study by Talukder et al. [2] examined the potential of using infrared cameras to detect estrus in dairy cows. This was a preliminary study, but it was large enough to assess the opportunities and feasibility of moving to a larger scale analysis. The scientists induced estrus using hormone treatment in 20 cows. They knew that the onset of estrus is associated with changes in body temperature and a detectable change in body surface or skin temperature. This is the basis of some methods that are currently in practice. Thermal detection is possible using infrared radiation detected with the use of specialized cameras.

The potential advantage of using digital technology is that capture can be automated. For example, the cameras can be placed in a location on-farm where all cows are known to pass. This can be on the approaches to the milking parlor, or in lanes that lead between paddocks. Because the capture is digital and can be transmitted wirelessly to a control center along with the cow’s identity, it is possible to incorporate this information into individual cow profiles that are monitored remotely by the farmers, and flag or alert them to specific management criteria.

There are two measures that broadly allow the evaluation of monitors like thermal detection. The specificity of the measure indicates how many measures are correct. The sensitivity of the measurements indicates the capacity of the monitor to accurately capture small changes. The scientists designed the study to assess sensitivity and specificity by comparing them to those determined by standard measures of estrus and ovulation. They developed an algorithm to predict the timing of ovulation.

The data showed that the infrared camera method is very sensitive for detecting changes in body surface temperature. A rise of just 1oC was detectable by the camera. However, the specificity and predictive value of the technique was dependent on the temperature threshold that was set as the indicator. The capacity to predict ovulation in this case peaked at 73%, which is lower than that measured by current standard methods. However, there is a lot of scope for expanding the study and building on how measurements are collected and algorithms are used for prediction.

One alternative is based on using alternative sensor technology coupled to intelligent systems for training or machine learning. An example of this is the use of sensors that identify tell-tale movements or ruminant activity in cows. Algorithm based interpretation of these measurements may accurately determine health indicators and calving with impressive accuracy [3].

The future of the dairy farm is an environment rich in data, in which farmers and the profitability of their farms will be optimized through automation. The system will increase the capacity for attention to management of production and health of each cow. Farmers will be increasingly technology expert controllers, overseeing information networks from remote locations. A small army of autonomous mobile and static robots will perform the monotonous and routine tasks, and in doing so, contribute continuous feedback to a farm operations control center.

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