# MOTHER'S

# MILK

**MANY PARENTS RELY ON INFANT FORMULA TO FEED THEIR NEWBORNS. COULD CELL CULTURE TECHNOLOGY PRODUCE SOMETHING CLOSER TO HUMAN BREAST MILK?**

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On a summer day in 2013, Leila Strickland sat, rapt, in front of her laptop and watched on screen as Mark Post unveiled the first lab-grown hamburger. To create the pinkish, flat patty, Post, a professor of vascular physiology at Maastricht University in the Netherlands, had taken thousands of tissue culture plates full of bovine stem cells, mixed them with fetal calf serum and other nutrients, and waited until they differentiated into muscle cells. This was exciting in and of itself. But Strickland's mind wandered to another potential application of cell culturing: human breast milk.

Like many mothers, Strickland had hoped to breastfeed both her children for the first six months after they were born.

The medical establishment considers breastfeeding the gold standard of infant nutrition, reducing the likelihood of digestive problems, rashes, and—most compelling—necrotizing enterocolitis, a rare but potentially fatal intestinal disease in premature infants.

But like many mothers, Strickland had found breastfeeding difficult. Her first child, a son born three years earlier, had struggled to effectively latch onto her nipple; when he did, she felt searing pain. He began to lose weight. She had spent all day, every day, nursing or pumping to stimulate her milk flow, and still her son cried, hungry. She was now experiencing similar issues with her infant daughter.

As Strickland watched Post from her kitchen table, she began thinking about how she might be able to use a process like his to grow not artificial beef but the cells that produce breast milk. "A pregnant woman could have a needle biopsy of her breast during pregnancy, and I could get the cells growing and producing milk before the baby is born," Strickland wrote excitedly in an email to a friend at the time.

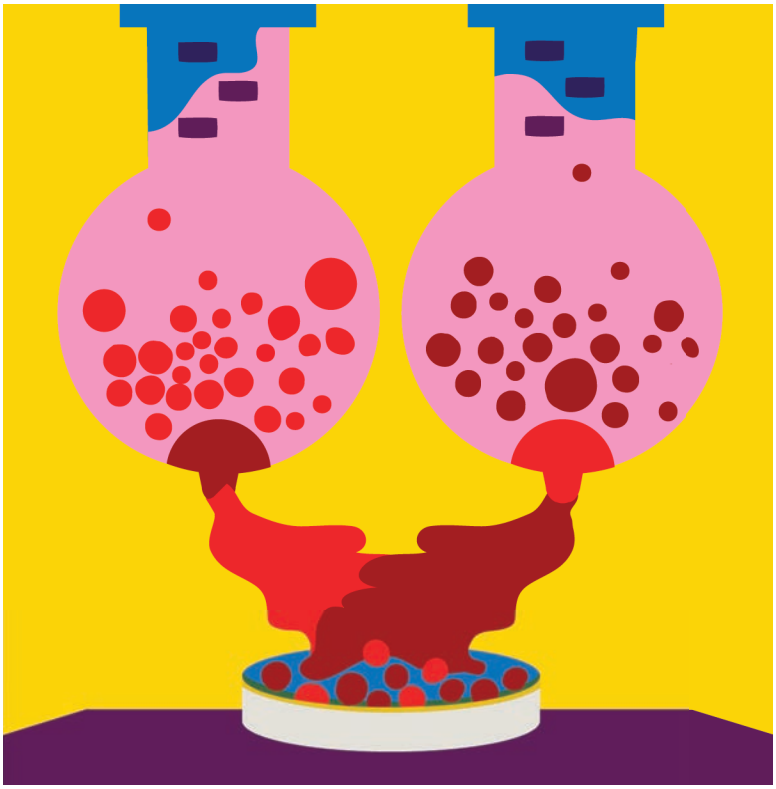
She had earned her doctorate in cell biology and spent several years as a researcher at Stanford before finding work as a medical editor and writer. This was a chance to turn back to the lab bench, with more independence than the average academic. A few days later, she and her husband scrounged together $5,000 in savings and purchased a hulking gray tissue culture hood, a microscope, an incubator, and a centrifuge from eBay for her to experiment with. "It was old dinosaur equipment—most of it probably from the 1960s," Strickland recalls.

For years she struggled to keep the project funded, and she came close to abandoning the idea. But in May 2020, Biomilq, a company she had founded, got $3.5 million from a group of investors led by Bill Gates. Biomilq is now in a race with competitors in Singapore and New York to shake up the world of infant nutrition in a way not seen since the birth of the now $42 billion formula industry.

Breastfeeding has swung in and out of vogue since ancient times—influenced by the evolution of medical knowledge, but also by race and social status. Wet nursing, the outsourcing of breastfeeding to someone other than a baby's mother, goes back at least to ancient Greece. Before the Civil War in America, white enslavers forced Black women to breastfeed the enslavers' children, often to the detriment of the women's own infants.

In 1851, the first modern feeding bottle—an elaborate contraption with a cork nipple and ivory pins that selectively closed inlets to regulate air flow—was invented in France, pushing wet nursing to near extinction. Shortly thereafter, German chemist Justus von Liebig concocted the first commercial infant formula, which consisted of cow's milk, wheat, malt flour, and a pinch of potassium bicarbonate. It quickly came to be considered the ideal infant food.

By the 20th century, formula use had skyrocketed, driven in large part by zealous advertising to doctors and consumers. A 1954 advertisement for Carnation evaporated milk in America shows a radiant mother and infant with text that reads, "8 out of 10 mothers who feed their babies a Carnation formula say: 'My doctor recommended it!'" Later, formula companies began giving hospitals free formula to distribute to new mothers. At the same time, more women were joining the workforce, making sustained breastfeeding more complicated. The perception that formula was just as safe and efficient, if not more so, led breastfeeding rates to plummet. By 1972, 22% of American infants were breastfed—a historic low, down from 77% of those born between 1936 and 1940.



*"I PAID A GUY $20 TO SLICE THE UDDER OFF OF A FRESHLY SLAUGHTERED COW."*

Today, those rates have rebounded, and doctors widely agree that breast milk provides the best nutrition for infants. Most American babies—about 84%, according to statistics from the Centers for Disease Control and Prevention—are breastfed at some point. But only one-quarter are fed solely breast milk for six months, as recommended by the American Academy of Pediatrics and the World Health Organization.

Breastfeeding isn't always easy. As Strickland experienced, babies can struggle to latch on; sometimes the breasts don't produce enough milk; and it can be excruciatingly painful for the mother.

Moreover, many mothers of newborns have to work, and it can be difficult if not impossible to breastfeed or pump milk in the workplace. This, obviously, is harder for women who are poor, and especially in countries like the United States, where there is no mandatory paid parental leave and only a small percentage of working mothers get it from their employers.

The first step Strickland took toward creating breast milk in the lab was less than glamorous. She couldn't afford to buy human mammary cell lines, which can cost hundreds or even thousands of dollars. Instead, she decided to start with cells from cows. To begin her experiments, she needed to find cells—lots of cells—and cheaply.

One weekend in February 2014, Strickland put a cooler, some ethanol, and sterile instruments in the trunk of her car, stuffed a wad of $20 bills in her pocket, and drove down the tree-lined North Carolina interstates to Randolph Packing, a family-owned meat processing company in Asheboro that operated out of a stocky brick warehouse on a residential road.

The manager led her to the processing area, where recently slaughtered cows were strung up by their hooves and moved along a conveyor belt for processing. Trying to keep her eyes locked on the ground, she pointed up at a cow's udder and muttered weakly: "I'd like that piece, please." She went back to her makeshift lab, placed a piece of udder in a petri dish, doused it with amino acids, vitamins, minerals, and salts, and carefully deposited it in an incubator.

In a message to her parents, the next day, she wrote: "I went to the slaughterhouse yesterday and paid a guy $20 to slice the udder off of a freshly slaughtered cow… It's safe to say I won't be eating any beef for a while. Came in this morning and found that the cells are growing! A cow died yesterday morning, but a piece of her is still alive in my lab!"

Breast milk derives from two types of cells in the milk ducts and alveoli—small sacs in the mammary gland where milk collects. Luminal epithelial cells absorb nutrients from the bloodstream and convert them into milk. Beside them, lining the ducts and alveoli, are smooth, muscle-like myoepithelial cells. When an infant starts suckling, it prompts the myoepithelial cells to contract, pushing milk from the luminal cells, through the ducts, to the baby's mouth.

For three years, Strickland brought her laptop to her tiny rented lab space so she could run experiments with her cow udder cells between writing and editing assignments. Her biggest triumph was persuading the luminal epithelial cells to form a continuous layer that could maintain the compartments critical for synthesizing milk. She figured out which surfaces promoted the healthiest cell division and how the density of cells affected their growth rate. None of these findings were novel, but she was pleased to be learning the techniques needed to ultimately move on to human cells.

By 2016, Strickland had run out of money and had to put the endeavor on hold. But the idea never left her. Eventually, in 2019, as more and more cultured-food businesses began trying to make everything from meat to fish to chicken nuggets in a lab, several friends convinced her to revive her plan.

Strickland recruited two other scientists to work with her. In August 2019, they were accepted to IndieBio, a prestigious biotech accelerator in San Francisco that gives startups $250,000 of seed funding and other support. She quit her day job and began to work on the project full time.

There was a problem, however. Strickland and her two partners all came from similar backgrounds, with extensive scientific experience but limited business bona fides. As the team prepared to move to California for four months, it became clear they were not a good fit.

Around the same time, a friend introduced Strickland to Michelle Egger, a food scientist in her late 20s. Egger had been fascinated with milk since she was a child growing up in Minneapolis, where she once placed second in a youth butter carving competition at the Minnesota state fair. After college at Purdue, Egger got a job in the dairy department of General Mills, where she worked for three years before enrolling in business school at Duke. She was in her second year when she first met Strickland.

Egger was excited by Strickland's proposition. Most infant formulas consist of environmentally intensive dairy products that require ample water to manufacture and prepare. Palm oil is another common ingredient. One study in 2015 suggested that producing one kilogram of milk formula generates the equivalent of four kilograms of carbon dioxide emissions. Strickland's approach had the potential to be much more efficient.

Things were hard at first. The change to the team caused Biomilq to lose its spot at IndieBio. It applied for, but failed to secure, several research grants. Worried that Biomilq would run out of money, Strickland started speaking to her old boss about returning to the job she'd left. Egger also quietly began to look for jobs.

Biomilq was on the brink of shuttering when Strickland and Egger were promised $3.5 million in funding from a group of investors led by Breakthrough Energy Ventures, which Bill Gates had established to back technologies that could reduce carbon emissions. Upending the formula industry held the promise of doing just that. As the spring of 2020 gave way to summer, the money arrived in Biomilq's bank account.

Biomilq is not the only company aiming to make a new kind of baby formula. Using a broadly similar approach, TurtleTree Labs in Singapore eventually hopes to "replace all milk currently on the market," according to cofounder Max Rye. In addition to other projects, the company is working to create "fortifiers" that can be added to formula to duplicate the properties of breast milk. Some formulas are already fortified with proteins and carbohydrates derived synthetically or from cow's milk. Another cofounder, Fengru Lin, explains that, in contrast to Biomilq, TurtleTree plans to work with the formula industry and hopes to get its products to market in 2021.

Meanwhile, Helaina, a company based in New York, will emulate breast milk through fermentation. Laura Katz, the company's founder, plans to use microbes to synthesize the milk's constituent compounds—proteins, carbohydrates, and fats—and then recombine them into a nutritious liquid. Since similar processes have already won approval from the US Food and Drug Administration for products like Impossible Burgers, which are made from fermented soy protein, she hopes to face fewer regulatory hurdles than her competitors. Like Strickland and Egger, she is motivated by indignation at the lack of options for new parents.

"I think the best thing we can do is support women to breastfeed," Katz says. But if that's impossible, mothers "deserve something better than current infant formula." She adds, "I see all this innovation happening in cell-based meat production for people who just want to eat a burger, but the products that we feed babies have stayed static over the past 20, 30 years."

None of these propositions will be scientifically simple, in part because relatively little is known about breast milk. Most studies of human mammary epithelial cells tend to focus on their role in breast cancer rather than milk production.

As for the milk itself, it's a rich and bewildering stew of thousands of chemicals. "We know nutritionally about the proteins, the carbohydrates, and the fat in there. We know about some particular bioactive molecules in there, like oligosaccharides [complex sugars that feed healthy bacteria in a baby's gut], IgA [the main antibody found in breast milk], bile-salt-stimulated lipase [an enzyme that aids in the digestion of fats]—these things that people always bring up as being good in breast milk," says Tarah Colaizy, the research director of the Human Milk Banking Association of North America, who also teaches at the University of Iowa. But, she notes, breast milk also contains short strands of RNA, whose presence was only discovered in 2010, and whose role in infant development is not yet well understood.

That's why Strickland and Egger plan to use mass spectrometry, a technique that measures the mass of different molecules within a sample, to study how the proteins, oligosaccharides, and fats contained in their product compare with the constituents of human milk pumped from a breast. But

another challenge looms even larger: how to standardize a substance that is unique to every mother.

Breast milk changes in composition as a child grows. For the first few days after giving birth, mothers produce colostrum, a thick, yellow, concentrated milk packed with compounds like the antibody IgA and lactoferrin, an abundant protein that boosts a baby's immunity. Soon, colostrum is replaced by "transitional milk," which is thinner but contains more fat and lactose. After about two weeks, a mother's milk is considered "mature." But even then, it can change in composition over the course of a single feeding. Hindmilk, or the last milk left in a breast, has a higher fat content than the milk that is produced earlier on, which is why women are often counseled to empty one breast before switching to the other.

Though Egger and Strickland admit they won't be able to replicate this complexity, nor all the antibodies and microbes in any given woman's milk, they say their product will be more personalized than those of their competitors. Just as Strickland envisioned back in 2013, they plan to work with pregnant women, taking samples of their mammary epithelial cells and culturing them to create individualized milk for use when their babies arrive. After that, they hope to create a more economical generic option using donor cells. Both, Egger insists, will be better than formula.

***"I SEE ALL THIS INNOVATION IN CELL-BASED MEAT PRODUCTION ... BUT THE PRODUCTS THAT WE FEED BABIES HAVE STAYED STATIC."***

The Biomilq researchers are now working from a whitewashed lab space in Durham, North Carolina, that they share with several other biotech startups. In a freezer set to -80 °C (-112 °F), they store test tubes full of cells from a number of different donors. Some of them, like those from a 27-year-old woman who donated her mammary tissue after a breast reduction surgery, have been "immortalized"—manipulated to proliferate indefinitely.

Strickland and Egger have already produced a liquid containing both lactose and casein—the main protein and sugar compounds found in breast milk. They are now testing it to see if they can detect other components, like oligosaccharides and lipids. They are currently tinkering with their equipment and the nutrients they use to grow the cells to see what combination gets them closest to matching the composition of natural breast milk; they estimate it will take about two years to come up with a good enough match.

One Friday morning in September, Strickland took a test tube containing 3 million cells, warmed it between her hands, and spread the contents over a plastic tissue culture plate. A colleague then doused the plate with a warm yellow liquid containing 53 different salts, vitamins, minerals, and amino acids. Once the plate's surface was mostly covered with duplicating cells, they planned to move the cells into a small bioreactor, a plastic device with clear tubes emanating from its sides that encourages growth. After about a month, the cells would begin to secrete a substance similar to breast milk. There's only one small problem, Strickland says. "We don't yet know what to call it."

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