ELEMENTS

BREAST-FEEDING THE MICROBIOME

By Ed Yong, JULY 22, 2016

This is an edited excerpt from "I Contain Multitudes: The Microbes Within Us and a Grander View of Life," which will be published on August 9th by Ecco, an imprint of HarperCollins Publishers.

The Foods for Health Institute, at the University of California, Davis, has the appearance of a Tuscan villa, its terra-cotta-walled buildings overlooking a large vineyard and a garden that bursts with summer vegetables. It is led by a chemist named Bruce German, and if there were a world title in extolling the virtues of milk he would surely hold it. At our first meeting, he spent half an hour monologuing on the subject, bouncing on an exercise ball and kneading a tattered shred of bubble wrap as he spoke. Milk, he said, is a perfect source of nutrition, a superfood that is actually worthy of the label. This isn't a common view. The number of scientific publications about milk is tiny, compared with the number devoted to other bodily fluids—blood, saliva, even urine. The dairy industry has spent a fortune on extracting more and more milk from cows, but very little on understanding just what this white liquid is or how it works. Medical-funding agencies have generally dismissed it as irrelevant, German said, because "it doesn't have anything to do with the diseases of middle-aged white men." And nutritionists have looked at it as a simple cocktail of fats and sugars, one that can be easily duplicated and replaced by

formulas. “People said it’s just a bag of chemicals,” German told me. “It’s anything but that.”

Milk is a mammalian innovation, common to platypuses and pangolins, humans and hippos, its ingredients varying according to what each species needs. Human milk is a particular marvel. Every mammal mother produces complex sugars called oligosaccharides, but human mothers, for some reason, churn out an exceptional variety: so far, scientists have identified more than two hundred human milk oligosaccharides, or H.M.O.s. They are the third-most plentiful ingredient in human milk, after lactose and fats, and their structure ought to make them a rich source of energy for growing babies—but babies cannot digest them. When German first learned this, he was gobsmacked. Why would a mother expend so much energy manufacturing these complicated chemicals if they were apparently useless to her child? Why hasn’t natural selection put its foot down on such a wasteful practice? Here’s a clue: H.M.O.s pass through the stomach and the small intestine unharmed, landing in the large intestine, where most of our bacteria live. What if they aren’t food for babies at all? What if they are food for microbes?

This idea dates back to the early twentieth century, when two very different groups of scientists made discoveries that, unbeknownst to them, were closely connected. In one camp, pediatricians found that microbes called *Bifidobacteria* (“Bifs,” to their friends) were more common in the stools of breast-fed infants than bottle-fed ones. They argued that human milk must contain some substance that nourished the bacteria—something that later scientists called the bifidus factor. Meanwhile, chemists had discovered that human milk contains carbohydrates that cow milk does not, and were gradually whittling this enigmatic mixture down to its individual components, including several oligosaccharides. The parallel tracks met in 1954, thanks to a partnership between Richard Kuhn (chemist, Austrian, Nobel laureate) and Paul Gyorgy (pediatrician, Hungarian-born American, breast-milk advocate). Together they confirmed that the mysterious bifidus factor and the milk oligosaccharides were one and the same—and that they nourished gut microbes.

By the nineteen-nineties, scientists knew that there were more than a hundred H.M.O.s in milk, but they had characterized only a few. No one knew what most of them looked like or which species of bacteria they fed. The common wisdom was that they nourished all Bifs equally, but German wasn't satisfied. He wanted to know exactly who the diners were and what dishes they were ordering. To do that, he took a cue from history and assembled a diverse team of chemists, microbiologists, and food scientists. Together they identified all the H.M.O.s, pulled them out of the milk, and fed them to bacteria. And, to the researchers' chagrin, nothing grew.

The problem soon became clear: H.M.O.s are not an all-purpose food for Bifs. In 2006, the team found that the sugars selectively nourish one subspecies, *Bifidobacterium longum infantis*. As long as you provide *B. infantis* with H.M.O.s, it will outcompete any other gut bacterium. A closely related subspecies, *B. longum longum*, grows weakly on the same sugars, and the ironically named *B. lactis*, a common fixture of probiotic yogurts, doesn't grow at all. Another probiotic mainstay, *B. bifidum*, does slightly better, but is a fussy, messy eater. It breaks down a few H.M.O.s and takes in the pieces it likes. By contrast, *B. infantis* devours every last crumb using a cluster of thirty genes—a comprehensive cutlery set for eating H.M.O.s. No other Bif has this genetic cluster; it is unique to *B. infantis*. Human milk has evolved to nourish the microbe, and it, in turn, has evolved into a consummate H.M.O.vore. Unsurprisingly, it is often the dominant microbe in the guts of breast-fed infants.

B. infantis earns its keep. As it digests H.M.O.s, it releases short-chain fatty acids, which feed an infant's gut cells. Through direct contact, *B. infantis* also encourages gut cells to make adhesive proteins that seal the gaps between them, keeping microbes out of the bloodstream, and anti-inflammatory molecules that calibrate the immune system. These changes only happen when *B. infantis* feeds on H.M.O.s; if it gets lactose instead, it survives but doesn't engage in any repartee with the baby's cells. In other words, the microbe's full beneficial potential is unlocked only when it

feeds on breast milk. Likewise, for a child to reap the full benefits that milk can provide, she must have *B. infantis* in her gut. For that reason, David Mills, a microbiologist who works with German, actually sees *B. infantis* as part of milk, albeit a part that is not made in the breast.

It is unclear why human breast milk stands out among that of other mammals. It has five times as many types of H.M.O.s as cow's milk, and several hundred times the quantity. Even chimp milk is impoverished compared with ours. Mills suggests a couple of possible explanations for this difference. One involves our brains, which are famously large for a primate of our size, and which grow incredibly quickly during our first year of life. This fast growth partly depends on a nutrient called sialic acid, which also happens to be one of the chemicals that *B. infantis* releases while it eats H.M.O.s. It is possible that, by keeping this bacterium well fed, mothers can raise brainier babies. This might explain why, among monkeys and apes, social species have more milk oligosaccharides than solitary ones, and a greater range of them to boot. Living in larger groups requires remembering more social ties, managing more friendships, and manipulating more rivals. Many scientists believe that these demands drove the evolution of primate intelligence; perhaps they also fuelled the diversity of H.M.O.s.

An alternative idea involves diseases. In a group setting, pathogens can easily bounce from one host to another, so animals need better ways of protecting themselves. H.M.O.s provide one such defense. When a pathogen infects our guts, it almost always begins by latching onto glycans—sugar molecules—on the surfaces of our intestinal cells. But H.M.O.s bear a striking resemblance to these glycans, so pathogens sometimes stick to them instead. They act as decoys, drawing fire away from a baby's own cells. They can block a roll call of gut villains, including *Salmonella; Listeria; Vibrio cholerae*, the culprit behind cholera; *Campylobacter jejuni*, the most common cause of bacterial diarrhea; *Entamoeba histolytica*, a voracious amoeba that causes dysentery and kills a hundred thousand people every year; and many virulent strains of *E. coli*. H.M.O.s may even be able to obstruct H.I.V., which might explain why more than half of

infants who suckle from infected mothers don't get infected, despite drinking virus-loaded milk for months. Every time scientists have pitted a pathogen against cultured cells in the presence of H.M.O.s, the cells have come out smiling.

The team at the Foods for Health Institute has set up an impressive milk-processing facility in its mock-Tuscan building. In the main lab, which Mills runs with the food scientist Daniela Barile, there are two huge steel drums in which milk is stored, a pasteurizer that looks like an espresso machine, and a riot of other equipment for filtering the liquid and breaking it down into its components. When I visited, hundreds of empty white buckets were stacked on a nearby rack. "They're normally full," Barile told me. The full buckets are kept in a huge walk-in freezer, which is chilled to an intensely uncomfortable -25.6 degrees Fahrenheit. On a nearby bench, there's a row of Wellies ("When we process, there's milk all over," Barile said), a hammer for chipping ice ("The door's not closing properly"), and, inexplicably, a ham slicer (I didn't ask). We popped our heads inside. White buckets were arrayed on pallets and shelves, containing some six hundred gallons of milk between them. A lot of this was cow's milk, donated by dairies, but a surprising amount came from humans. "Lots of women pump milk and store it, and once their kid weans, they think, Now what do we do with it? People then hear about us and we get donations," Mills said. "We got eighty litres, collected over two years, from someone random at Stanford University, who said, 'I have all this milk. Do you guys want it?' " Yes, they did. They need all the milk they can get.

About twenty miles east of the Institute, at U.C. Davis Children's Hospital, a pediatrician named Mark Underwood is making practical use of the findings of German and his team. Underwood heads the hospital's neonatal intensive-care unit, which can accommodate as many as forty-eight premature babies at a time. The youngest are born at twenty-three weeks; the lightest weigh just over a pound. They are usually delivered through C-sections, put on courses of antibiotics, and stuck in a supremely sanitized environment. Bereft of the usual pioneering microbes, they grow up with a very strange microbiome: low on the usual Bifs and high in opportunistic pathogens that grow in their place. The preemies are the epitome of microbial

imbalance, or dysbiosis, and their strange internal communities put them at risk of an often fatal gut condition known as necrotizing enterocolitis. Many doctors have tried to prevent NEC by giving probiotics to premature babies, with some success. But Underwood, after talking to people like German and Mills, thinks that he can do better by infusing the infants with a combination of *B. infantis* and breast milk. "The food you feed these bugs is as important as the bugs themselves in getting them to grow and colonize a fairly hostile environment," he told me. If the treatment works, breast milk could do for preemies what it does for their full-term brethren, nourishing baby and bacteria, infant and *infantis*, and preparing them for life ahead.

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