A bonanza of potent disease-fighting compounds has been discovered in a surprisingly common source—the breasts of every nursing mother on the planet. Human milk, the only substance that evolved to feed and protect us, seems to contain a trove of medicines just now being unlocked by scientists.

“We go down to the bottom of the ocean to find new compounds and test them out against diseases,” says nutritional scientist Lars Bode of the University of California, San Diego. “But if we just look at the natural compounds in human milk, we’ll be surprised at what we find.”

At the forefront of breast milk’s potential lies a diverse set of sugar molecules called human milk oligosaccharides. Although sculpted by 200 million years of mammalian evolution, the sugars don’t feed infants at all. Instead, they play the role of microbial managers, acting as liaisons between the infant’s newly available intestinal real estate and the throngs of microbes that seek to call it home.

These oligosaccharides serve as sustenance for an elite class of microbes known to promote a healthy gut, while less desirable bacteria lack the machinery needed to digest them. And recent research has shown that the sugars act as discerning bouncers as well: The molecules prevent pathogens from latching onto healthy cells, routing troublemakers into a dirty diaper instead. The oligosaccharides also defuse bombs by calming an infant’s emerging immune system so it doesn’t overreact against friendly bacteria.

Oligosaccharides found in human milk might even hold keys to staving off disease in vulnerable children, a notion that
Simply indigestible in addition to nourishing a baby with fats, proteins and ordinary sugars such as lactose, breast milk harbors complex sugars that a newborn largely cannot digest. Some 200 types of oligosaccharides, formed by five simple sugars joined in various structures, help cultivate an infant’s microbial garden and provide many indirect benefits. SOURCE: L. BODE/GLYCOBIOLOGY 2012

Fecal analysis revealed that the babies who were fed breast milk plus an oligosaccharide-consuming strain of bacteria, Bifidobacterium longum ssp. infantis, had more beneficial microbes. “When you put in the breast milk and the B. infantis together, then you get B. infantis colonization,” says Underwood. But when B. infantis don’t get nourished by the oligosaccharides in breast milk, Underwood hypothesizes, “they fade away quickly and don’t get established.”

While the study wasn’t large enough to establish protection against NEC, Underwood hopes that the trial will pave the way for larger tests. Especially in infants whose mothers produce little or no breast milk, bolstering formula with a combination of oligosaccharides and probiotics could help prevent NEC in the most vulnerable infants.

Depending on blood type, the stage of lactation and other factors, the milk oligosaccharide profile varies from woman to woman. This could explain why some infants develop NEC in spite of being breast-fed, Bode says. Reporting in Gut in 2012, his team showed that a specific human milk oligosaccharide helps prevent NEC in rats. In the study, only one oligosaccharide, a branched beauty called disialyllacto-N-tetraose, dampened the disease. And research by Mills and Underwood showed that the milk oligosaccharide content from women delivering at preterm differed from those giving birth at full term. Bode envisions one day mixing NEC-busting oligosaccharides into the breast milk of mothers who lack them and boosting premature infants’ chances of getting out of the neonatal ICU alive.

**Immune tuners**

Beyond feeding bacteria in the gut, the milk oligosaccharides might cultivate a healthy microbiota by dialing down the immune system. Bode argues that a toned-down immune response is crucial for successful colonization of the gut by microbes. The sugars were discovered as “food for bugs,” Bode says, “but I believe they’re so much more than that.”

A tiny fraction of the sugars appear to find their way into a newborn’s bloodstream. Bode and others have detected oligosaccharides in the urine of infants, suggesting that the sugars and their influence could extend well beyond the gut. “Milk oligosaccharides may be able to reduce inflammation throughout the body,” he says. In one study, oligosaccharides reduced interactions between inflammatory immune cells and cells that line blood vessels. “The oligosaccharides,” Bode says, “are able to keep the immune system in check.”

Bode’s team has also produced a slew of studies that demonstrate human milk oligosaccharides’ most provocative power—flushing pathogens out of an infant’s body before they get a chance to wreak havoc.

The researchers reported on September 16 in the *Journal of Pediatric Gastroenterology and Nutrition* that the sugars block the attachment of a nasty strain of *E. coli* to the cells that line the intestine, thwarting the pathogen’s ability to infect neonatal mice. The microbe is responsible for deadly diarrheal diseases that plague infants and children, especially in developing countries where access to clean food and water is lacking.

Milk oligosaccharides that reach the bloodstream may even usher bladder-infecting *E. coli* right out of the urinary tract, the research team has also found.

For more than two decades, Newburg’s group has been compiling a hit list of pathogens that fall prey to milk oligosaccharides, starting with the discovery that the sugars could disarm a toxin secreted by some forms of *E. coli*. “Then we tested the oligosaccharides against various pathogen models—and this...
is my favorite story — it worked against all of them," Newburg recalls. "We thought we'd made a mistake." He and others have since discovered, mostly through cell culture studies, that the sugars may dash the diarrhea pipe dreams of such microbial villains as salmonella, cholera, rotavirus, norovirus, a campylobacter-caused gastroenteritis and multiple strains of E. coli.

Newburg envisions one day giving toddlers oligosaccharide supplements to stave off diseases that tend to creep in following weaning, especially in poor countries where diarrheal diseases abound. But the hunt for potential sources of the sugars has proved challenging.

A better milk mimic

Milk oligosaccharides possess a seemingly endless spectrum of complexity, and researchers are just starting to understand which structures do what. Synthesizing them in the lab is a tedious and expensive process, Bode says. "If you wanted to synthesize and add oligosaccharides to infant formula at the supermarket," he says, "the price would be ridiculous."

But for premature infants, caregivers may be willing to invest in the costly sugars to help prevent diseases such as NEC, he says. Because synthesis is still cost-prohibitive, Bode suggests using donor breast milk in cases when the mother's milk is unavailable. Frozen, pasteurized donor milk from breast-milk banks is far superior to infant formula for such a use, provided processing leaves the oligosaccharides intact.

Neonatologist Underwood agrees, but says, "the truth is, there's probably not enough donor human milk to go around." While Europe has more than 200 milk banks and Brazil has a similar number, the United States has only 13. Though donor milk is becoming more common in neonatal ICUs around the country, Underwood says, general availability, especially for full-term infants, seems a long way off. "There's a tremendous amount of capacity in the world," Underwood says, "but the U.S. and Canada are very slow to develop milk banks. They're expensive, and the regulations are tremendous."

Formula companies already sell an easy-to-synthesize oligosaccharide called galacto-oligosaccharide as an additive to infant formula, a product scientists once thought similar to the oligosaccharides found in human milk. But now they know better, Bode says. "The oligosaccharides that are currently in formula are structurally very different from those in human milk," he says. While the synthesized oligosaccharide has been shown to promote the growth of some beneficial bacteria and to offer protection against certain pathogens, the additive falls short when compared with the benefits of the full spectrum of oligosaccharides found in breast milk.

Bode is working to help companies develop better oligosaccharides to add to infant formulas. Although breast-feeding is always the best option, he says, certain circumstances such as low milk supply, illness or the stresses of returning to work may prevent some mothers from breast-feeding. "It's a little bit romantic to think that formula will disappear from the surface of the planet at some point," Bode says. "I'd rather help make something better if it's going to be used anyway."

While Bode hopes that new synthesis techniques or increased donor milk supply will one day meet the demand for oligosaccharides, at least in the neonatal ICU, Mills and his colleagues at UC Davis are betting on dairy cows.

With easy access to a barn full of cows, these scientists have a ready supply of bovine milk at their disposal. The researchers also have a partnership with a cheese producer that sends them regular shipments of various dairy by-products such as whey — a source of oligosaccharides.

Mills and colleagues are hoping to convince the dairy industry to siphon off "waste products" for the production of oligosaccharides. The sugars are at least 20 times more abundant in human milk than in bovine milk, and many of the oligosaccharide

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structures in human milk are absent or exist in only trace amounts in bovine milk. “On the other hand,” says Mills, processors go through 13 million gallons of cow’s milk per day, “so you could have truckloads of it.”

That helps motivate Barile to keep digging through dairy products in search of more sugars. In 2009, she reported finding 15 distinct oligosaccharides in whey permeate, a substance Barile calls “a by-product of a by-product.” The discovery was initially exciting, Barile says. But the bovine oligosaccharides lack fucose, a monosaccharide that in human milk adorns up to 70 percent of oligosaccharides, tending to lend them pathogen-blocking powers.

Convinced that the fucosylated sugars must exist in bovine milk, even if in trace amounts, Barile’s team refined its separation techniques. As reported in the June Glycobiology, the team eventually identified 50 different oligosaccharides in bovine milk, including structures with fucose. A disease-busting sugar called 2’-fucosyllactose, or 2’FL, that represents through 13 million gallons of cow’s milk per treatment well, and the team is in the process of screening the structures there is far superior to anything that the biotech industry can currently produce, she says. “Maybe in 20 years, technology will catch up, and we’ll have a better understanding of which structures are important.” Until then, she thinks that relying on the natural diversity of structures in bovine milk is a safer bet than cherry-picking some human ones for industrial production.

Newburg’s approach couldn’t be more different. Rather than milking cows (or humans), he manipulates microbes. By adding just the right mix of genes to bacteria or yeast, he hopes to produce oligosaccharides in huge batches through fermentation. In 2002, Newburg cofounded a small company, Glycosyn, with the goal of designing microbes that produce the sugars.

“That’s the way to make it most cheaply,” Newburg says. “Fermentation technology is something you find in every country, no matter how poor it is.” After designing strains of microbes that pump out the oligosaccharides, Newburg envisions inexpensively making oligosaccharides in the countries that need them most.

But before that can happen, Newburg’s team must get the microbes on board. “It’s actually quite difficult,” he says. “You try something, and then you fiddle with it and try it again.”

Newburg has set his sights on none other than 2’FL. The molecule holds promise against cholera, campylobacter gastroenteritis and certain E. coli infections. “So it’s an obvious first target,” he says. He expects his team to produce a 2’FL-producing microbe fit for distribution within the next few years, and microbes that make other oligosaccharides are also in the works.

Newburg imagines milk oligosaccharides supplanting the use of antibiotics in some cases. Unlike antibiotics, which breed resistant strains of bacteria, “human milk oligosaccharides have been ‘used’ for millions of years without resistance,” he says. “It could be a game changer.”

Whether derived from a chemistry lab, donor’s milk, dairy products or microbes, scientists hope to deliver the benefits of milk oligosaccharides to children living on life’s vulnerable edges: those born too early and those freshly weaned. Even adults who have had their gut microbiota ravaged by antibiotics or their immune systems pummeled by chemotherapy may, like infants, benefit from the nurturing effects of the oligosaccharides. But researchers will likely never fully re-create nature’s potent elixir or unlock all of its mysteries. Breast, so the saying goes, may always be best.

Explore more

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