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Milk Therapy

Breast-milk compounds could be a tonic for adult ills

Julie J. Rehmeyer

Catharina Svanborg thought that she already knew how remarkable breast milk is. The immunologist had logged hundreds of lab hours documenting ways in which human milk helps babies fight infections. But when the group decided to use cancerous lung cells to avoid the variability shown by normal cells in laboratory tests, Svanborg and her team at Lund University in Sweden were in for a surprise. They applied breast milk to the cancerous lung cells, and all the cells died.
Breast milk killed cancer cells.

"From that moment on, we've been working with it," Svanborg says.

Svanborg's serendipitous discovery of human milk's anticancer power is remarkable, but other researchers have also been finding that breast milk can both protect against and heal a remarkable variety of ailments. Perhaps these properties shouldn't be surprising: Of the thousands of substances that people eat, breast milk is the only one that evolved under natural pressure to keep people healthy.

GOAT GOODS. A transgenic goat named Artemis produces in her milk a human-breast–milk compound called lysozyme. Lysozyme destroys bacteria by drilling through their cell walls.
E. Scharfen

Research teams are now learning to exploit its tricks for purposes well beyond feeding babies. Components of breast milk are being developed as drugs that fight viruses and bacteria. A particular target is diarrhea, which kills about 2.2 million people every year, mostly children in developing countries. Other milk compounds may be added to food to improve digestion. Some milk components might fight medical conditions ranging from arthritis to septic shock.

Although some of these compounds are found in milk from other animals, others occur only in human milk, and the nonhuman versions are generally less potent in people. This presents a challenge, since human-breast milk is not available for sale. So, researchers are developing new sources for the compounds, including genetically modified bacteria, rice, goats, and cows.

The potential for therapies derived from milk is "enormous, absolutely tremendous," says Marian Kruzel, an immunologist at the University of Texas Medical School in Houston.

Good bugs and bad bugs

The protective properties of mother's milk have long been apparent. Breast-fed babies, for instance, get diarrhea half as often as infants who are fed formula do. Decades ago, scientists began wondering how breast milk stops the pathogens that cause diarrhea.

In the 1950s, Lars Hanson, an immunologist at Göteborg University in Sweden, started to solve the puzzle. He found that mothers produce antibodies in their milk and that way pass on to their babies immunities that the women had acquired over their lifetimes.

But the antibodies in breast milk didn't explain all the observations. For example, breast-fed babies have different bacteria in their guts than formula-fed babies do. The breast feeders harbor more of the beneficial, food-digesting bacteria, such as acidophilus and bifidus, as well as less of the coliform *Escherichia coli* and other germs that can make infants sick.

When scientists started analyzing breast milk, they found that the third-largest constituent of breast milk, making up about 1 percent by volume, is a mixture of indigestible sugars known as oligosaccharides. Many of these sugars occur only in human milk.

Initially, the scientists thought that these were useless by-products of milk production. But why would mothers expend so much energy creating compounds that their babies can't use?

In the past few years, scientists have solved this puzzle. David Newburg, of Massachusetts General Hospital in Charlestown and his colleagues genetically engineered mice to produce oligosaccharides in their milk. He then gave their pups campylobacter, a bacterium that causes diarrhea. The pups that drank oligosaccharides didn't get sick.

Unlike the antibodies that mothers pass along to their infants through breast milk, oligosaccharides can protect the baby from pathogens to which the mother has never been exposed.

For a pathogen to infect a person via the digestive tract, it first has to latch on to the sugars that line the gut wall. Oligosaccharides have binding sites that are identical to the ones on the gut-wall sugars, so the pathogens attach to the oligosaccharides instead of to the lining of the gut. Once bound to oligosaccharides, pathogens travel harmlessly through the intestinal tract.

Surprisingly, bacteria that aid digestion prosper in the presence of oligosaccharides. Bruce German, a nutritionist at the University of California, Davis, proposes that only the beneficial bacteria digest some of the oligosaccharides, thereby gaining an advantage over the harmful bacteria. This theory is controversial, however.

German says that the beneficial microbes' advantage is a natural consequence of the coevolution of breast milk and gut bacteria. Oligosaccharides occur in thousands of slightly different forms, and the precise mix of types of oligosaccharides varies from woman to woman. Those who produced breast milk with oligosaccharides that only beneficial bacteria can eat must have had an evolutionary advantage.

German notes that because of this evolutionary process, some bacteria in human digestive tracts are found nowhere else on Earth. "What milk did is recruit an entire life form to protect the infant," German says. "To me, that's pretty inspiring stuff."

German and other scientists want to leverage that protection for babies that aren't breast-fed and for adults too. Oligosaccharides might augment elderly people's weakened natural protection against pathogens. After people have taken strong antibiotics, the sugars could help them recolonize their digestive tracks with beneficial bacteria. Foreign travelers or military personnel who expect to be exposed to unfamiliar pathogens could take oligosaccharides as a preventive measure.

Newburg expects that as bacteria continue to develop resistance to antibiotics, oligosaccharides will be increasingly important for fighting pathogens. "This is a totally different type of defense against pathogens that mammals have been using for thousands of years, and it still works," Newburg says.

He suggests that bacteria can't evolve a resistance to oligosaccharides because if they change in such a way that they no longer bind to the oligosaccharide, they also can't bind to the cell wall to infect their targets. "The mechanisms for protection in milk are so exquisite," Newburg marvels.

Procuring a supply of oligosaccharides for preventive or therapeutic treatments presents a challenge. Newburg is working to genetically engineer *E. coli* bacteria to produce the sugars.

"What motivates me personally is the large number of babies in the Third World who have diarrhea," Newburg says. Oligosaccharides added to formula could protect babies who don't receive breast milk.

Bioengineering milk

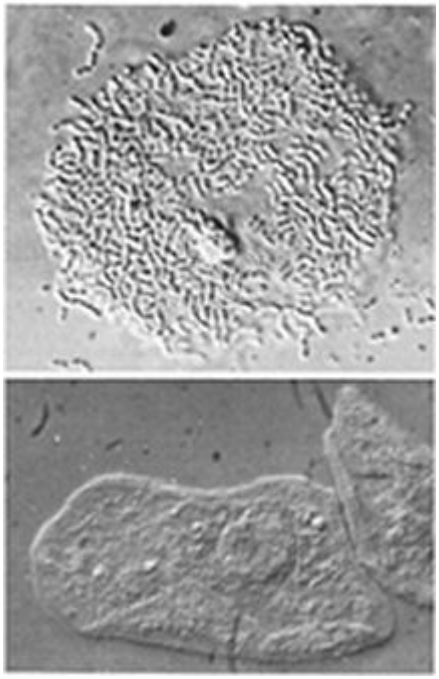
Getting bacteria to produce human oligosaccharides would be only the first step toward Newburg's vision. For protection against infections, people would have to eat substantial amounts of oligosaccharides regularly. So, to make supplements for adults

or for baby formula, bacteria would need to produce oligosaccharides in large quantities and at low cost.

On the other hand, genetic engineering of larger organisms has already produced inexpensive and abundant supplies of two other human-breast–milk compounds: lysozyme and lactoferrin.

In 1998, scientists genetically engineered a goat to excrete lysozyme in its milk, and in 2002, another team created one variety of rice that produces human lysozyme and another variety that yields human lactoferrin. Also in 2002, a team engineered a cow to produce human lactoferrin. As a result, researchers are for the first time performing large-scale clinical trials of lactoferrin and lysozyme.

Lactoferrin is a dazzlingly multitalented protein. In breast-fed babies, it can appropriately suppress inflammation or boost immune activity. It also fights viruses, bacteria, and fungi. Even after the protein has broken down in the gut, the fragments fight urinary-tract infections as they are expelled from the body.



ATTACK THWARTED. Bacteria that can cause pneumonia attack a throat cell (top) by attaching to sugar chains on the cell. In a solution of oligosaccharides—indigestible sugars contained in breast milk—the pneumococci bind to the sugars and don't latch on to the throat cell (bottom).
B. Andersson

Because lactoferrin lowers the immune system's inflammatory overreactions, it may be useful against arthritis, multiple sclerosis, and septic shock. In 1998, when researchers treated piglets with lactoferrin before inducing septic shock, the compound reduced mortality to less than one-fourth of that in untreated piglets. In 2001, another group showed that treating rats in septic shock with lactoferrin dramatically reduced blood-toxin concentrations.

The many claims for lactoferrin's capabilities "may look suspicious," admits Michal Zimecki, an immunologist at the Polish Academy of Sciences in Wroclaw. Lactoferrin "seems like a golden bullet, but it really is so."

Lysozyme is, by comparison, a one-trick pony: It chews up bacterial cell walls. However, its trick is fine-tuned. Lysozyme selectively destroys deleterious bacteria, usually leaving the beneficial ones unharmed.

At a clinic in Peru, Bo Lönnerdal, a nutritionist at the University of California, Davis, recently conducted a trial of a combination of lactoferrin and lysozyme against diarrhea. The standard treatment for acute diarrhea in children there is simple rehydration with a solution of sugar and salt.

Lönnerdal added his two compounds to the solution given to half the children treated. Those who received lactoferrin and lysozyme, he found, recovered more quickly and were less prone to a repeat bout of the disease. The study is scheduled to appear in an upcoming *Journal of Pediatric Gastroenterology and Nutrition*.

Killer milk

As outlandish as lactoferrin's potential may seem, it is perhaps even stranger to think that breast milk components could cure cancer.

Once Svanborg and her team had established that something in breast milk was killing human cancer cells in the lab, they isolated the assassin. It turned out to be the protein alpha-lactalbumin. But the compound becomes lethal only when exposed to acid, as it is in a stomach and was in the lab. The acid unfolds the alpha lactalbumin protein into a havoc-wreaking form.

Svanborg dubbed the acidified form of the protein HAMLET, for human alpha-lactalbumin made lethal to tumors.

Cancer cells take up far more HAMLET than healthy cells do. The huge quantities of unfolded proteins destroy the cancer cells.

Svanborg found that HAMLET killed 40 kinds of tumor cells in lab dishes. She has also studied the reactive compound in rats with human-cancer cells implanted in their brains. She used an invasive cancer called glioblastoma that usually kills people in less than a year. She injected HAMLET directly into the tumors of some of the rats, while others received injections of alpha-lactalbumin that hadn't been activated by acid.

After 7 weeks, the rats getting inactive protein bore tumors seven times, on average, as large as the tumors in the HAMLET-treated rats, the researchers reported in 2004.

Svanborg has also found that HAMLET reduces warts in people. Warts and tumors share the property of growing without respect to normal controls. HAMLET reduced the volume of more than 95 percent of the warts to which it was applied, whereas only 20 percent of warts treated with a placebo decreased in size.

Svanborg is currently concluding human trials of HAMLET for bladder cancer. She says that her results "look very good," and that the treatment produced no side effects. Pharmaceutical companies are now developing the activated protein for clinical use.

Hanson, the first scientist to isolate immune antibodies from breast milk, says that HAMLET is "quite a discovery," especially since it seems to be effective against so many kinds of cancer. He cautions, though, that "the crucial thing will be the clinical studies."

Whether or not breast milk turns out to be the source of a potent cancer therapy, its remarkable properties have led to a new view of its role. "My thinking on milk has changed totally," says Newburg. "I used to think of it as the best source of nutrients. Now, it's looking like milk is really designed to be protective."

Soon, that protection may extend to the rest of us.

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