PETER MENZEL/SPL

Ingredients in breast milk can help to establish a healthy community of microorganisms in the infant gut.

MICROBIOTA

Baby thrivers

Is a person's future health shaped by microorganisms encountered early in life?

BY SARAH DEWEERDT

Within a few weeks of being born, a baby is host to a community of billions of bacteria, viruses and fungi — most of which are found in the gut — that can shape many aspects of health. How that community, or microbiota, assembles is a matter of debate: some researchers have begun to question the dogma that the womb is a sterile environment. Yet it's clear that birth sets off a radical transformation of the infant gut.

"It's an incredible ecological event," says Phillip Tarr, a paediatric gastroenterologist at Washington University in St. Louis, Missouri. Colonization of the gut begins in earnest when a baby encounters microorganisms from its mother's vagina during birth. As the baby suckles at the breast, it picks up more microbes from its mother's skin. It also consumes microbes from its mother's gut that have infiltrated her breast milk.

Later, microbes are picked up from adoring visitors or a lick from the family dog, as well as what Nicholas Embleton, a neonatologist at Newcastle University, UK, refers to as "living in a normal, dirty home environment". By the age of two or three, the composition of a child's gut microbiota is very similar to that of an adult's.

Should the assembly process be derailed, the consequences can be deadly. A considerably altered microbiota has been linked to a form of gut inflammation that is a leading cause of death in infants who are born prematurely. Less extreme changes to the microbiota in otherwise healthy babies might have long-term consequences for health, perhaps playing a part in conditions such as asthma and diabetes.

Researchers are looking for ways to rebalance the microbiota in premature infants. And some are wondering whether it might be possible to reshape the microbial community of the healthy infant gut to help prevent chronic diseases in adulthood.

EARLY PERILS

Premature infants are especially vulnerable to disruption of the microbiota. Many are delivered by caesarean section, and therefore do not come into contact with the microbes that live in the birth canal. Such babies are also often given courses of powerful antibiotics and housed in sterile plastic incubators where they have minimal contact with human skin. Given that these interventions separate babies from their environment, it's not surprising that the gut microbiota of premature infants is markedly different from that of babies born at full term. It tends to have a lower proportion of microbes that are beneficial to gut health, such as *Bifidobacterium* and *Lactobacillus*, as well as a greater abundance of disease-causing bacteria and a lower diversity of bacteria in general. And the bacterial community is often chaotic, with dramatic shifts in composition over a matter of days.

The abnormal gut microbiota of premature infants is thought to have a role in their vulnerability to necrotizing enterocolitis, a severe form of gut inflammation that strikes suddenly in the first few weeks of life and can cause permanent damage to the intestine. Although full-term babies can develop the condition, at least three-quarters of cases occur in infants born prematurely. In the past two decades, as doctors have learnt to manage the respiratory problems of premature infants more effectively, necrotizing enterocolitis has become a main threat to such babies.

The cause of necrotizing enterocolitis isn't a particular microbe, but rather a dysfunction of the gut microbiota as a whole. As well as its role in digestion, the gut is an immune organ, says Barbara Warner, a neonatologist at Washington University in St. Louis. Early interactions of the gut with microbes are therefore powerful shapers of a child's immune system.

Necrotizing enterocolitis could be the consequence of this process going awry — perhaps representing "the baby's immune system struggling to work out what's the right thing to do", Embleton says. "Probably, this disease we see

is a sort of exaggerated inflammatory condition challenging a very immature and naive gut immune system."

Treatment for the condition "is very, very crude and basic", Embleton adds. Some babies with necrotizing enterocolitis can be treated with antibiotics and a temporary switch to intravenous feeding to give the intestine time to heal. More-severe cases require surgery to remove the damaged portion of intestine. The loss of a large part of the intestine can lead to lifelong difficulties with feeding or absorbing nutrients. About one-quarter of babies who develop the condition will die.

But now, researchers are looking to the gut microbiota for ways to stop the condition taking hold. Some are searching for clues that could help to predict the development of necrotizing enterocolitis, enabling earlier medical intervention. For example, an overgrowth of bacteria from the phylum Proteobacteria can precede the condition. But these microbes are also found in healthy infants, so it's not always clear when to sound the alarm. And such changes in microbiota composition might not be the true cause of the illness.

FORTIFIED MILK

Breast milk might hold a solution. Since the 1990s, several studies have shown that breastfed babies are less vulnerable to necrotizing enterocolitis than are those fed with formula milk. A subsequent flurry of research into the relationship between breast milk and gut microbes found that breast milk contains ingredients that promote the establishment of a healthy gut microbiota.

One example is short chains of sugar molecules known as human-milk oligosaccharides. "They're the second-most-abundant carbohydrate source in human milk after lactose, but they're not for nutrition of the babies," says Victoria Niklas, a neonatologist at the University of California, Los Angeles. Instead, these oligosaccharides provide food for helpful microbes such as *Bifidobacterium*. They also coat the lining of the gut and bind to pathogenic bacteria, making it more difficult for disease-causing microbes to invade.

Another component of breast milk, the protein lactoferrin, has a number of antimicrobial properties. It suppresses the growth of bacteria and can even trigger the death of certain harmful microbes by binding to inflammatory molecules called lipopolysaccharides.

Offering support to mothers of premature infants who wish to breastfeed might therefore help to promote a healthy gut microbiota and prevent necrotizing enterocolitis. A further potential strategy is to supplement the diets of early babies with human-milk oligosaccharides or lactoferrin. Several trials of such supplements have been completed and more are under way. Biotechnology companies are also developing supplements that contain key components of breast milk. (Niklas is chief medical and scientific officer of one such company, Prolacta Bioscience in Duarte, California.)

Another approach to fighting necrotizing enterocolitis is to feed beneficial bacteria, or probiotics, to premature infants. The goal "is to try and mimic what happens in healthy, full-term, breastfed babies", says neonatologist and researcher Keith Barrington at the University of Montreal in Canada.

> ***"It's extremely difficult to engineer microbial populations that will stick and benefit the host."***

In 2011, the neonatal intensive-care unit at Sainte-Justine University Hospital Center, where Barrington works, began to routinely feed probiotics to babies born before 32 weeks' gestation. The infants received a cocktail of four species of *Bifidobacterium* and one of *Lactobacillus*, and the incidence of necrotizing enterocolitis fell by around 50%. More than half of the neonatal intensive-care units in Canada have followed suit in providing probiotics, with similar results. However, it's not a perfect solution. Barrington's team has shown that the probiotic strains are present in stools of the premature babies, which indicates that the microbes are able to grow in the infant gut. But these babies still have fewer beneficial bacteria and more pathogenic bacteria in their gut than do healthy, full-term breastfed babies. Combining probiotics with molecules such as human-milk oligosaccharides or lactoferrin might help to improve the picture, Barrington says. He plans to compare the effects on the gut microbiota of the combination of probiotics and lactoferrin with those of the probiotic treatment alone.

The neonatology community is divided on the role of probiotics in preventing necrotizing enterocolitis. "Half of us think that they're probably a good idea and half think that the case isn't proven yet," says Embleton. "And even if we were to use probiotics, we really don't know which ones we should be using and how much we give," he says.

MICROBIAL IMPACT

As the debate continues, researchers are investigating whether having the correct gut microbes might also be crucial to enabling healthy infants to thrive. For example, children delivered by caesarean section have a different gut microbiota from those born vaginally. Breastfed and formula-fed babies also have distinct microbiotas in their gut. Epidemiological studies suggest that caesarean delivery and formula feeding are associated with an increased risk of obesity and asthma, as well as other conditions, and many researchers think that these effects might be shaped by the gut microbiota. Could the infant gut microbiota therefore hold the key to preventing such conditions in later life?

The links are not straightforward. "These are complex problems and I think, to be honest, the microbiota is just one piece of it," says Warner. However, she adds, the microbiota is an attractive target for intervention because it might be easier to modify than other risk factors for certain conditions.

Some doctors have advocated, for example, that babies born by caesarean section be swabbed with a sample of their mother's vaginal microbiota. But if that microbiota helps to promote a condition such as obesity, the intervention could have a downside. And if the mother harbours disease-causing bacteria, it could even be dangerous.

Few studies have been able to demonstrate the ability of probiotics to make a lasting change to the infant gut microbiota. "It's extremely difficult to engineer microbial populations that will stick and benefit the host," says Tarr. When the probiotics are discontinued, the gut microbiota usually reverts to its previous state with a matter of days.

But there could be progress on that front. In a 2017 study (S. A. Frese *et al. mSphere* **2,** e00501-17; 2017), researchers from the University of California, Davis, and biotechnology company Evolve BioSystems of Davis, California, reported that breastfed infants who were given strain EVC001 of *Bifidobacterium longum infantis* still had the microbes in their guts 30 days after treatment with the probiotic had been stopped. This strain, which was developed as a probiotic supplement to breastmilk for babies by Evolve BioSystems, is extremely efficient at consuming human-milk oligosaccharides, says neonatologist Mark Underwood, who led the study. (Underwood has no financial interest in the company.)

"We thought, maybe we can make a big difference in this [microbial] community by — instead of keeping them on probiotics forever — treating them for a short period of time with probiotics, but then giving these beneficial bacteria a food source that they are uniquely capable of consuming," Underwood says.

The babies seeded with *B. infantis* also had fewer pathogenic bacteria and more beneficial metabolites in their gut than did breastfed babies who did not receive the probiotic. This suggests that the microbiotas of healthy breastfed infants, used as a benchmark for studies in premature babies, are also ripe for improvement.

How far such improvement could go is uncertain. The *B. infantis* study is only a first step, and researchers are unsure about what an ideal neonatal gut microbiota would look like. Yet the growing importance of the microbiota is changing the approach of the doctors who care for the youngest patients. Among the medical specialities, "neonatology has never been at the top of the food chain", Niklas says. "But it has now become abundantly clear that our practices and our interventions really hold the seed of future health." ■

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