were also differences in the activity of genes associated with motor activity and anxiety. There seems to be a window of opportunity for the microbiota to influence behavior patterns: Colonizing germfree mice with normal mouse microbes negated these differences in young, but not older, mice, they reported.

Some work suggests that gut microbes influence behavior through the vagus nerve, which connects the brain with the digestive system, but Pettersson and others suspect a role for blood-borne bacterial products as well. These products, which make up 10% or more of the metabolites in blood, may extend the reach of the gut microbiota throughout the body.

That realization may mean that prenatal development in mammals isn't as free from microbial influence as everyone has thought. In mammals, the developing fetus is virtually bacteria-free; hence, researchers have focused on finding a role for bacteria in development after birth. Yet blood-borne metabolites from a mother's gut germs could exert an effect on a growing fetus. "That was one of the assumptions, that pregnancy did not involve microbes," Gilbert says. "But it probably does."

As such assumptions are overturned, researchers are addressing new issues. What is the molecular dialogue that enables the microbial world to influence development? How did that dialogue evolve and how often is it a friendly one? "The big questions are now exposed," says Michael Hadfield, a developmental biologist at the University of Hawaii, Manoa. "After all the years we tended to ignore the bacteria, most people who are studying development should be looking for where the bacteria are and what roles they are playing."

–ELIZABETH PENNISI

How Does Fetal Environment Influence Later Health?

Parents pore over their newborn's face, drinking in the fuzz of her eyebrows, the shape of the chin, searching for themselves in her smile. But they're not thinking about what they can't see, and what ultimately matters more: the heft of her heart, the hormones churning from the liver, all those invisible features that influence her health into adulthood.

While their baby's biology of course reflects a mingling of the mother's and father's DNA, there's more to her than that. In a peculiar way, all newborns are "an expression of the mother," in the words of David Barker, a physician and epidemiologist at the University of Southampton in the United Kingdom. He believes that people are shaped, inside and out, by the maternal environment that sustained them before they were born.

In the late 1980s, Barker scrutinized thousands of birth and death certificates of people from Hertfordshire, U.K., and concluded that those whose birth weight fell on the low end of normal were much more likely to die of heart disease as adults. Since then, Barker has promulgated his theory that maternal environment controls a baby's destiny in more ways than we yet understand.

These days, there's broad agreement that the fetal world, the most rapid period of human growth and development, shapes one's risk of future disease, although how much influence it has remains uncertain. A key missing link is in the mechanism. What switches in the fetus, or the placenta that nourishes it, are flipped by a mother's diet or stress levels? In other words, how does fetal environment mold development?

Those exploring this fundamental mystery have at least one intriguing discovery to follow up. No matter what the stressor on the fetus, studies of people and animals suggest that the output is similar: a higher risk of type 2 diabetes, obesity, heart disease, insulin resistance, and high blood pressure. In rodents, "anything that could be a nutritional stressor seems to have the same effect," says Simon Langley-Evans of the University of Nottingham in the United Kingdom, suggesting that the fetus is implementing a universal response to stress, perhaps to ensure its survival.

The early focus of the field that Barker spawned was on birth weight, a crude reflection of a fetus's surroundings: Smaller babies tended to reflect poorly nourished or highly stressed mothers. But what a mother eats when she's pregnant is only a small part of the fetal environment, Barker notes. "The mother's body is the product of her lifetime nutrition," he says—and even her own mother's nutrition, too, because most or all of her eggs are formed before birth.

Scientists are now striving for greater sophistication in exploring the black box of the womb. Animal studies have found that without good nutrient flow across the placenta, the offspring responds "by building its organs on the cheap," says Kent Thornburg, a cardiac physiologist at Oregon Health & Science University in Portland. Hearts have fewer muscle cells. Kidneys have fewer nephrons for filtering urine. There's less skeletal muscle in limbs and fewer insulin-producing cells in the pancreas.

Peeling back the layers, scientists are also finding differences in DNA patterns in the offspring, depending on whether their mothers were properly fed or malnourished. One long-running effort examines men and women who developed in utero during the Dutch Hunger Winter of 1944 to 1945, when the Germans cut off food and fuel shipments to part of the Netherlands. A birthday soon

Prebirth world. The fetal environment correlates with health later on, but researchers are still disentangling exactly how one connects to the other.

CREDIT: CAROLINA BIOLOGICAL SUPPLY CO./VISUALS UNLIMITED INC.

Published by AAAS

Under Development

The journey from single cell to mature organism is full of intrigue. Far too much of what we know about development involves what happens when things go awry, says Peter Lawrence of the University of Cambridge in the United Kingdom. "If a mutant gene causes an organism's head to fall off, the conclusion is that the gene's function is to hold the head on," he says. "People have applied this logic, inappropriately, to complex phenomena like the building of an organism." The focus on mutations, he says, has distracted the field from some of the most important questions in development, which require understanding what genes do when they are working as they should. Here are five more mysteries of development. **–GRETCHEN VOGEL**

The shape of things to come. Despite exciting progress reported in this issue (see p. 1183), how cells use genetic instructions to form the shapes that organisms ultimately take is a conundrum. "The shape of your nose? That's all written very precisely somewhere in some form," Lawrence says. "We have no idea where."

Not carbon copies. Although they share the same genome, identical twins are different—sometimes subtly, sometimes dramatically. They show how chance events can influence developing organisms, but many questions remain about just how much of development is due to chance.

Millennial naps. Researchers recently coaxed seeds to sprout after being buried in frozen tundra for thousands of years. How do seeds remain in a state of suspended animation, waiting for the right moment to start putting down roots and pushing up shoots?

Pick your progeny. How do stem cells—which can both replicate themselves and give rise to other cell types—know when to switch from one kind of daughter cell to another?

New parts from old. During evolution, new structures such as turtle shells or bat wings arise through a process that repurposes existing parts. Tracing the genetic changes that lead to new structures as species evolve is a passion of evolutionary developmental biologists; advances in genomics may help solve such mysteries.

after was correlated with more obesity and impaired glucose metabolism in adulthood, along with higher rates of other health issues. In 2008, a group at Columbia University and Leiden University Medical Center added a genetic twist to that well-documented story. They reported that almost 60 years after the famine, those born at the time had different patterns of methylation, a chemical coating of DNA that influences gene expression, in the gene *IGF2* as compared with their siblings who arrived in flusher times. The researchers also found that as adults, men had more differences in methylation than women born at the same time. They are continuing to explore methylation patterns on a genomewide scale among their cohort.

One problem with this work is that no one knows for sure whether the DNA changes occurred in utero in response to the famine, or came about later in life for entirely different reasons. Nor do scientists yet know whether these genetic changes, which are often modest, play a role in disease susceptibility. "It's so damn difficult" to do this research, says Bastiaan T. Heijmans of Leiden University Medical Center, who led these methylation studies of the Dutch Hunger Winter cohort along with his Columbia colleague, Lambert H. Lumey. "There's some quite compelling evidence that indeed this relationship is there" between the fetal environment, the DNA changes, and later health problems. But "it's hard for me to put my finger on" exactly what's going on.

Animal work can help clear up the confusion. And it, too, is identifying striking sex differences in how fetuses react to their surroundings. Ten years ago, Lubo Zhang of Loma Linda University School of Medicine in California began depriving pregnant rats of oxygen, mimicking the effects of a mom-to-be with heart disease, or women whose placentas are poorly formed. Then he studied the hearts of the offspring when they reached adulthood.

The organs, Zhang found, functioned normally. That is, until he induced stress in the animals that mimicked a heart attack. The males lost far more heart muscle tissue than females or than animals whose gestation had been healthy. "They become much more vulnerable to the second hit," he says. "If the heart is not stressed later in life, [the animals] cannot tell the difference."

Over the ensuing years, Zhang traced this effect to dampened expression in a gene called Protein Kinase C epsilon. Protecting fetuses from low oxygen, for example with a compound called N-acetylcysteine, kept this gene's activity up during development and hearts healthy long-term. He hypothesizes that extra estrogen in the placentas of female animals protects them.

Then there are the myriad studies suggesting that pregnant women (or pregnant rodents) who suffer from common infections like the flu or a days-long fever are more likely to have offspring who develop autism or schizophrenia. Here, too, the findings are still tenuous, and researchers are only beginning to address how a woman's immune system battling infection can influence the developing nervous system in her womb.

One underexplored piece of gestation is the placenta. Its morphology varies tremendously—perhaps related to a mother's body composition and diet—and studies have found that the state of the placenta at a baby's birth can predict how the child fares later on. Barker, Thornburg, and others have probed this connection via the Helsinki Birth Cohort Study of more than 20,000 people born in the 1930s and '40s. The hospitals kept detailed measurements of each baby's placentas, and the researchers have linked placental measurements to later adult health, everything from sudden cardiac death to lung cancer to insulin resistance. As with so many fetal environment studies, though, the choreography—the pattern of dance steps that occur between fetus and placenta—is largely unknown.

Solving these mysteries is daunting. "We try to link time points that are so far apart," Heijmans says. "There's no study that goes from preconception to 100 years of age." While "a good part of healthy aging starts in the womb," Heijmans believes, it's just the beginning to a hopefully long life that will mold health and disease.

–JENNIFER COUZIN-FRANKEL

Published by AAAS