

The Womb. Your Mother. Yourself.

Cancer. Heart disease. Obesity. Depression. Scientists can now trace adult health to the nine months before birth

BY ANNIE MURPHY PAUL

WHAT MAKES US THE WAY we are? Why are some people predisposed to be anxious, overweight or asthmatic? How is it that some of us are prone to heart attacks, diabetes or high blood pressure?

There's a list of conventional answers to these questions. We are the way we are because it's in our genes: the DNA we inherited at conception. We turn out the way we do because of our childhood experiences: how we were treated and what we took in, especially during those crucial first three years. Or our health and well-being stem from the lifestyle choices we make as adults: what kind of diet we consume, how much exercise we get.

But there's another powerful source of influence you may not have considered: your life as a fetus. The kind and quantity of nutrition you received in the womb; the pollutants, drugs and infections you were exposed to during gestation; your mother's health, stress level and state of mind while she was pregnant with you—all these factors shaped you as a baby and a child and continue to affect you to this day.

This is the provocative contention of a field known as fetal origins, whose pioneers assert that the nine months of gestation constitute the most consequential period of our lives, permanently influencing the

wiring of the brain and the functioning of organs such as the heart, liver and pancreas. The conditions we encounter in utero, they claim, shape our susceptibility to disease, our appetite and metabolism, our intelligence and temperament. In the literature on the subject, which has exploded over the past 10 years, you can find references to the fetal origins of cancer, cardiovascular disease, allergies, asthma, hypertension, diabetes, obesity, mental illness—even of conditions associated with old age like arthritis, osteoporosis and cognitive decline.

The notion of prenatal influence may conjure up frivolous attempts to enrich the fetus: playing Mozart to a pregnant belly and the like. In reality, the shaping and molding that goes on in utero is far more visceral and consequential than that. Much of what a pregnant woman encounters in her daily life—the air she breathes, the food and drink she consumes, the chemicals she's exposed to, even the emotions she feels—is shared in some fashion with her fetus. The fetus incorporates these offerings into its own body, makes them part of its flesh and blood.

Often it does something more: it treats these maternal contributions as information, biological postcards from the world outside. What a fetus is absorbing in utero is not Mozart's *Magic Flute* but the answers to questions much more critical to its

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survival: Will it be born into a world of abundance or scarcity? Will it be safe and protected, or will it face constant dangers and threats? Will it live a long, fruitful life or a short, harried one?

Research on fetal origins—also called the developmental origins of health and disease—is prompting a revolutionary shift in thinking about where human qualities come from and when they begin to develop. It's turning pregnancy into a scientific frontier: the National Institutes of Health embarked last year on a multidecade study that will examine its subjects before they're born. It's also altering the perspective of thinkers outside of biology. The Nobel Prize-winning economist Amartya Sen, for example, co-authored a paper about the importance of fetal origins to a population's health and productivity: poor prenatal experience, he writes, "sows the seeds of ailments that afflict adults." And it makes the womb a promising target for prevention, raising hopes of conquering public-health scourges like obesity and heart disease through interventions before birth.

The Origins of Fetal Origins

TWO DECADES AGO, A BRITISH PHYSICIAN named David Barker noticed an odd correlation on a map: the poorest regions of England and Wales were the ones with the highest rates of heart disease. Why would this be, he wondered, when heart disease was supposed to be a condition of affluence—of sedentary lifestyles and rich food? He decided to investigate, and after comparing the adult health of some 15,000 individuals with their birth weight, he discovered an unexpected link between small birth size—often an indication of poor

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prenatal nutrition—and heart disease in middle age. Faced with an inadequate food supply, Barker conjectured, the fetus diverts nutrients to its most important organ, the brain, while skimping on other parts of its body—a debt that comes due decades later in the form of a weakened heart.

When he presented his findings to colleagues, he was greeted with hoots and jeers. "Heart disease was supposed to be all about genetics or adult lifestyle factors," says Barker, now 72 and a professor at the University of Southampton in England and at Oregon Health and Science University. "People scoffed at the idea that it could have anything to do with intrauterine experience." Barker persisted, however, amassing evidence of the connection between birth weight and heart disease in many thousands of individuals. For years the idea was known as the Barker hypothesis.

In time his idea began to win converts. Janet Rich-Edwards, an epidemiologist at Brigham and Women's Hospital in Boston, deliberately set out to disprove the Barker hypothesis. "I was convinced that your current risk factors determine your odds of developing disease," says Rich-Edwards, "not something that happened when you were a fetus." But, she adds, "there's nothing like your own data to change your mind." Rich-Edwards analyzed findings from the Nurses' Health Study, a long-running investigation of more than 120,000 RNs. Even when she took account of the nurses' adult lifestyles and socioeconomic status, the relationship between low birth weight and cardiovascular-disease risk remained robust. "Similar studies have been conducted at least two dozen times since then," she notes. "It's one of the most solidly replicated findings in the field of public health."

As a journalist who covers science, I was intrigued when I first heard about fetal

origins. But two years ago, when I began to delve more deeply into the field, I had a more personal motivation: I was newly pregnant. If it was true that my actions over the next nine months would affect my offspring for the rest of his life, I needed to know more.

Of course, no woman who is pregnant today can escape hearing the message that what she does affects her fetus. She hears it at doctor's appointments, sees it in the morning newspaper and in the pregnancy guidebooks: Do eat this, don't drink that, always be vigilant—but never stressed. Expectant mothers could be forgiven for feeling that pregnancy is nothing but a nine-month slog, full of guilt and devoid of pleasure, and this research threatened to add to the burden.

But as I began applying what I learned to my own pregnancy, I developed a very different perspective on fetal origins. The scientists I met weren't full of dire warnings but of the excitement of discovery—and the hope that their discoveries would make a positive difference. We're used to hearing about all the things that can go wrong during pregnancy, but as these researchers are finding out, it's frequently the intrauterine environment that makes things go right in later life.

The Power to Change Behavior

TAKE, FOR EXAMPLE, THE PROSPECT OF maintaining a healthy weight. Americans are heavier than ever, and their weight gain begins ever earlier in life. Could it be that a tendency for obesity is being programmed in the womb? A pair of studies conducted by researchers at Harvard Medical School suggest that may be the case: the greater a woman's weight gain during pregnancy, one study found, the higher the risk that her child would be overweight by age 3. The second study indicated that this relationship persists into the offspring's adolescence.



Compared with the teenagers of women who had moderate weight gain during pregnancy, those of women who had excessive weight gain were more likely to be obese.

Of course, children could share eating habits or a genetic predisposition to obesity with their mothers; how can we know the prenatal environment is to blame? Researchers have compared children born to obese mothers with their siblings born after the mothers have had successful antiobesity surgery. The later-born children inherited similar genes as their older siblings, and (research shows) practice similar eating habits, but they experienced different intrauterine environments. In a 2006 study published in the journal *Pediatrics*, researchers found that the children gestated by women post-surgery were 52% less likely to be obese than siblings born to the same mother when she was still heavy. A second study by the same group, published in 2009, found that children born after their mothers lost weight had lower birth weights and were three times less likely to become severely obese than their older brothers and sisters.

"The bodies of the children who were conceived after their mothers had weight-loss surgery process fats and carbohydrates in a healthier way than do the bodies of their brothers and sisters who were conceived at a time when their mothers were still overweight," says John Kral, a professor of surgery and medicine at SUNY Downstate

FETAL LINKS

Heart Disease

Individuals weighing less at birth have a higher risk of heart disease later in life than those of normal birth weight, perhaps in part because an undernourished fetus diverts nutrients to the brain, giving short shrift to the developing heart.

Obesity

Mothers who gain excessive weight during pregnancy tend to have heavier toddlers; the link may be more than genetic. Kids conceived after a mother's successful weight-loss surgery were 52% less likely to be obese than siblings born while she was overweight.

Diabetes

A diabetic mother's high blood sugar may disrupt the metabolism of a fetus, predisposing it to diabetes, as suggested by research on the Pima Indians, plagued by the world's highest rate of Type 2 diabetes.

Medical Center in New York and a co-author of both papers. Their metabolisms were, in effect, made normal by their prenatal experience—perhaps through a process known as epigenetic modification, in which environmental influences affect the behavior of genes without altering DNA. It may be that the intrauterine environment is even more important than genes or shared eating habits in passing on a propensity for obesity, Kral says. If that's so, helping women maintain a healthy weight before and during pregnancy may be the best hope for stopping obesity before it starts.

The science of fetal origins also offers hope to people who believe that heredity has doomed their families to disease—people like the Pima Indians of the Gila River Reservation in Arizona, who have the highest rate of Type 2 diabetes in the world. There is little doubt that the high incidence of diabetes among the Pimas, and among Native Americans in general, has a significant genetic component. But new research from a study that has followed a large group of Pima Indians since 1965 points to an additional influence: prenatal experience. During pregnancy, a diabetic woman's high blood sugar appears to disrupt the developing metabolism of the fetus, predisposing it to diabetes and obesity.

Exposure to maternal diabetes in utero accounts for most of the increase in Type 2 diabetes among Pima children over the past 30 years, says Dana Dabelea, associate professor of epidemiology at the University of Colorado at Denver and an investigator on the study, and it may well be a factor in the alarming rise of the disease nationally. But it also opens a door to intervention. "If we could intensively control diabetic women's blood sugar during pregnancy," Dabelea says, "we could really bring down the number of children who go on to develop diabetes."

What's more, an understanding of the role of gestational factors in disease can change individual behavior, notes Daniel Benyshek, a medical anthropologist at the University of Nevada at Las Vegas, who has interviewed members of Arizona's Native American tribes. He finds that those who believe diabetes is their genetic destiny tend to hold fatalistic attitudes about the illness. When Benyshek shared findings about the fetal origins of diabetes with tribe members, however, he noticed a different reaction. "The idea that some simple changes made during pregnancy could reduce the

offspring's risk for diabetes fosters a much more hopeful and engaged response," he says. "Young women in particular are enthusiastic about the idea of intervening in pregnancy to break the cycle of diabetes. They say, 'I tried dieting, I tried exercising, and I couldn't keep it up. But I could do it for nine months if it meant that my baby would have a better chance at a healthy life.'"

The Impact of Air

THE CHANCE OF A HEALTHIER LIFE IS what Frederica Perera is trying to give children in some of New York City's struggling neighborhoods. Perera, the director of the Center for Children's Environmental Health at Columbia University, became interested in the effects of pollution on fetuses more than 30 years ago, when she was conducting research on environmental exposures and cancer in adults. "I was looking for control subjects to compare to the adults in my study, individuals who would be completely untouched by pollution," she says. She hit on the idea of using babies just out of the womb as her controls, but when she received the results from samples of umbilical-cord blood and placental tissue she'd sent to a laboratory to be analyzed, she was sure there had been a mistake. "I was shocked," she says. "These samples I thought would be pristine already had evidence of contamination."

Since then, research by Perera and others has tied exposure to traffic-related air pollution during pregnancy to a host of adverse birth outcomes, including premature delivery, low birth weight and heart malformations. One of Perera's most striking studies got under way in 1998, when more than 500 pregnant women fanned out across upper Manhattan and the South Bronx wearing identical black backpacks, which they wore every waking moment for two days. Inside each backpack was an air monitor continuously measuring levels of polycyclic aromatic hydrocarbons, or PAHs, a type of pollutant that comes from vehicle exhaust and is also present in the fumes released by cigarettes and factory smokestacks.

The monitors revealed that 100% of the women were exposed to PAHs during their pregnancies. After their babies were born, analyses of cord blood from the infants showed that 40% had subtle DNA damage from PAHs—damage that has been linked to increased cancer risk. Further analysis found that those exposed prenatally to high levels of PAHs were more than twice as like-

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ly to be cognitively delayed at age 3, scoring lower on an assessment that predicts performance in school; at age 5, these children scored lower on IQ tests than children who received less exposure to PAHs in the womb.

Investigations like these have prompted scientists to expand their list of populations that are especially vulnerable to pollution. "We used to worry about elderly people and asthma patients," Perera says. "Now we worry about fetuses." And efforts to reduce environmental toxins can make a measurable difference, she says. "Over the years that we've been tracking exposures, New York City buses have switched to cleaner technology, and restrictions have been placed on the idling of diesel buses and trucks," Perera notes. "As a result, we've seen the levels of pollutants in pregnant women's blood coming down, which means their fetuses are encountering fewer of these substances too."

The Sources of Stress

AT THE FARTHEST EDGE OF FETAL-ORIGINS research, scientists are exploring the possibility that intrauterine conditions influence not only our physical health but also our intelligence, temperament, even our sanity. Evidence indicates, for example, that pregnant women subjected to starvation or extreme stress give birth to children with a higher risk of schizophrenia.

Schizophrenia is a complex disorder with many potential causes. But a study based on 30 years of case records from Anhui province in China strongly suggests that prenatal factors can play a role. In the mid-20th century, residents of that region experienced severe malnutrition during the famine that accompanied the Great Leap Forward, Mao Zedong's disastrous modernization campaign. Individuals born to women suffering from the famine were twice as likely to develop schizophrenia as those gestated at other times. Likewise, a study of the

health records of more than 88,000 people born in Jerusalem between 1964 and 1976 found that the offspring of women who were in their second month of pregnancy in June 1967—the time of the Arab-Israeli Six-Day War—were significantly more likely to develop schizophrenia as young adults.

Catherine Monk, an assistant professor of psychiatry at Columbia University, has advanced an even more startling proposal: that a pregnant woman's mental state can shape her offspring's psyche. "Research indicates that even before birth, mothers' moods may affect child development," Monk says. "Can maternal mood be transmitted to the fetus? If so, what is the mode of transmission? And how do such moods affect fetal development? These are new questions to be asking," she says. "We're still figuring out how to get fetuses to answer."

In fact, Monk and her colleagues have gone some way toward putting the fetus on the couch. At her lab, pregnant women who are depressed or anxious and pregnant women with normal moods are hooked up to devices that measure their respiration, heart rate, blood pressure and nervous-system arousal, as well as the movements and heart rate of their fetuses, and then subjected to challenging mental exercises. All of the women show physiological signs of stress in response to the tests, but only the fetuses of depressed or anxious women display disturbances of their own.

"This difference suggests that these fetuses are already more sensitive to stress," Monk says. "Perhaps that's because of a genetic predisposition inherited from the parents. Or it could be because the fetuses' nervous systems are already being shaped by their mothers' emotional states." Women's heart rate and blood pressure, or their levels of stress hormones, could affect the intrauterine milieu over the nine months of gestation, Monk explains, influencing

an individual's first environment and thereby shaping its development.

The differences Monk has found among fetuses appear to persist after birth. And because basic physiological patterns like heart rate are associated with more general differences in temperament, Monk says, "it may be that the roots of temperamental variation go back to the womb."

It could even be the case that a pregnant woman's emotional state influences her offspring's later susceptibility to mental illness. "We know that some people have genetic predispositions to conditions like depression and anxiety," Monk says. "And we know that being raised by a parent with mental illness can increase the risk of mental illness in the offspring. It may be that the intrauterine environment is a third pathway by which mental illness is passed down in families." This kind of research, says Monk, "is pushing back the starting line for when we become who we are."

Back to the Future

TEN YEARS AGO, WHEN MATTHEW GILLMAN, a professor of population medicine at Harvard University, launched Project Viva—a study tracking more than 2,000 Boston-area children since they were fetuses—he knew he wanted to explore the effects of childhood experiences on later health. "But David Barker's research had started me wondering: When do these experiences really begin?" says Gillman. "I came to think they begin before birth, and so my study would have to start there too." Already the project has begun to illuminate the fetal origins of asthma, allergies, obesity and heart disease, as well as the role of gestational factors in brain development.

There are more revelations on the way. This year, the first of 100,000 pregnant women began enrolling in the National Children's Study, a massive, federally funded effort to uncover the developmental roots of health and disease. Researchers are conducting interviews with the women about their behaviors during pregnancy; sampling their hair, blood, saliva and urine; and testing the water and dust in their homes. The women and their children will be followed until the offspring turn 21, and the first results from the study, concerning the causes of premature births and birth defects, are expected in 2012.

Another line of research is developing interventions aimed at preventing disease. David Williams, a principal investigator

THE ROOTS OF MENTAL HEALTH

Schizophrenia

Studies have suggested that women who are pregnant during historical periods of stress or famine give birth to offspring who are more likely than those born in calmer times to develop schizophrenia in young adulthood. Maternal malnutrition may disrupt neural development, contributing to the illness.

Depression

Research has found increased rates of premature delivery and low birth weight among babies born to depressed women. Scientists are also discovering possible links between a mother's mood and a fetus's sensitivity to stress, and perhaps even the temperament it exhibits after birth.



ONGOING RESEARCH

NATIONAL CHILDREN'S STUDY

nationalchildrensstudy.gov
In 2009, pregnant women began enrolling in a study of 100,000 U.S. children from before birth to age 21.

PROJECT VIVA

daccp.org/Viva
For more than a decade, researchers have tracked 2,000 Boston-area kids from the time they were fetuses.

COLUMBIA CENTER FOR CHILDREN'S ENVIRONMENTAL HEALTH

cumc.columbia.edu/dept/malliman/cccch
The research center studies the effects of prenatal exposure to pollutants.

at the Linus Pauling Institute at Oregon State University, is testing the notion that certain substances consumed during pregnancy can provide offspring with lifelong chemoprotection from illness. In Williams' studies, the offspring of mice that ingested a phytochemical derived from cruciferous vegetables like broccoli and cabbage during pregnancy were much less likely to get cancer, even when exposed to a known carcinogen. After they were weaned, the offspring in Williams' experiments never encountered these protective chemicals again, yet their exposure shielded them from cancer well into maturity. He predicts that one day, pregnant women will be prescribed a dietary supplement that will protect their future children from cancer. "It's not science fiction," he says. "I think that's where we're headed."

Knowledge gleaned from fetal-origins research may even benefit those of us whose births are in the past. "I always ask my adult patients what their birth weight was," says Mary-Elizabeth Patti, an assistant professor at Harvard Medical School and a physician-scientist at the university-affiliated Joslin Diabetes Center. "Patients are often surprised at the question—they expect me to ask about their current lifestyle. But we know that low-birth-weight babies become adults with a higher risk of diabetes, so having that information gives me a more complete picture of their case." Patti is researching how data about patients' birth weight could translate into tailored courses of treatment.

These possibilities may seem strange and surprising, but then the notion that we owe anything about our mature selves to our experiences during childhood was once considered preposterous too—before Sigmund Freud first pointed our attention to those formative years. With time and evidence, the idea that our health and well-being are shaped during gestation could also come to seem commonsensical. Perhaps our children, whose first snapshots were taken not in a hospital bassinet but inside a uterus, won't find the idea of fetal origins odd at all.

As for me, the baby in my belly for those nine months is now a sandy-haired toddler named Gus. Where did his particular qualities come from? Will he be strong or sickly, excitable or calm? What will his future hold? These are the questions parents have long pondered about their children. More and more, it looks as if many of the answers will be found in the womb. ■