

Dad's Hidden Influence

By Tina Hesman Saey
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A father's legacy to a child's health may start before conception and last generations

Pregnant women know the drill. Don't drink. Don't smoke. Don't eat too much fish. Take vitamins. Mothers have long shouldered the responsibility, and the blame, for their children's health. Fathers don't usually face the same scrutiny. How a man lives, where he works, or how old he is when his children are conceived doesn't affect their long-term health, scientists used to think. But growing evidence suggests that a father's age and his exposure to chemicals can leave a medical legacy that lasts generations.

Animal studies demonstrate that drugs, alcohol, radiation, pesticides, solvents, and other chemicals can lead to effects that are handed from father to son. Human studies are less clear, but some show that fathers play a role in fetal development and the health of their children.

Teenage dads face increased risk that their babies will be born prematurely, have low birth weight, or die at birth or shortly afterward, a new study in *Human Reproduction* shows.

Babies of firefighters, painters, woodworkers, janitors, and men exposed to solvents and other chemicals in the workplace are more likely to be miscarried, stillborn, or to develop cancer later in life, according to a review in the February *Basic & Clinical Pharmacology & Toxicology*.

Fathers who smoke or are exposed at work to chemicals called polycyclic aromatic hydrocarbons put their children at risk of developing brain tumors. And, older fathers are more likely to have children with autism, schizophrenia, and Down syndrome and to have daughters who go on to develop breast cancer. Though some of these observations are decades old, attitudes lag even further behind, says Cynthia Daniels, a political scientist at Rutgers University–New Brunswick in New Jersey. Dads aren't held accountable if something goes wrong during fetal development. Since men make new sperm every 74 days, people used to reason, the genetic slate is wiped clean every couple of months. And even if a man makes defective sperm, the "all-or-nothing" view of reproduction holds that damaged sperm don't fertilize eggs. No harm. No foul.

So no one bothers to remind men to protect themselves against environmental toxins. There are no images of "crack dads" and "crack babies" in the media like those of women who harm developing fetuses with drug and alcohol use, Daniels said in February at a meeting of the American Association for the Advancement of Science held in Boston.

Men can produce sperm throughout life, but that doesn't mean their cells are forever young.

"Every cell in the body ages," says Fisch. "Every cell. The older you get, the more chance of an abnormality. The same thing goes for sperm." Men younger than 20 and older than 30 make more abnormal sperm than men in their 20s.

These damaged sperm could create an unhealthy embryo or pass on damage that could lead to birth defects or illness in offspring.

Studies demonstrate that older men are at increased risk of passing on genetic abnormalities. It's a matter of math. The cells that produce sperm continue to divide throughout a man's lifetime. Each year after puberty, a man's sperm-producing cells replicate about 23 times. Every time the cells divide is another chance for error. As a result, the sperm produced by a 40-year-old man have gone through about 610 rounds of replication. That's 610 chances of introducing a mutation in the DNA, or improperly divvying up genetic material.

Parents over age 40 are six times more likely to have children with Down syndrome than 25-year-old parents, Fisch and colleagues showed in a 2003 study in the *Journal of Urology*. An extra copy of chromosome 21 causes Down syndrome. This extra chromosome is just as likely to come from dad as mom in the older couples.

Older dads also have a higher risk of fathering children with rare mutations that cause dwarfism or a premature aging disease called Hutchinson-Gilford progeria syndrome. But sometimes aging fathers pass along traits that can't be traced to only a single mutation. Fathers 40 and older have an increased chance that their children will develop complex disorders such as autism or schizophrenia. There is growing evidence that those disorders are caused by defects in many genes and the way genes are turned off and on. Scientists don't yet understand the changes that age induces in sperm-making germ cells, and environmental exposure presents an even bigger mystery.

People come in contact with a plethora of chemicals every day. But it is no easy task to sort out exactly which ones, or which combinations, cause inheritable problems. The effects chemicals and radiation may have on offspring don't always follow predictable patterns either.

And when researchers do find a clear link between a father's lifestyle and his children's health, it's not always clear what the data mean.

"What we can say is that we identified a group of fathers with adverse outcomes for their fetuses, but we don't have an idea of the mechanism," says Shi Wu Wen of the University of Ottawa in Canada and one of the lead authors of the study showing that babies of teenage fathers have a greater risk of birth problems. Wen and his colleagues examined birth records for more than 2.6 million babies born between 1995 and 2000 to married, first-time, 20-something mothers in the United States. Looking at the husbands' ages, the team found that babies of teenage fathers, but not middle-age men, had an elevated risk of still birth, low birth weight, and other birth problems. The study was **published online Feb. 6 in *Human Reproduction***.

In recent decades, scientists have discovered that chemical modifications to DNA and proteins can change the way genes are packaged and regulated without changing the genes themselves. Such modifications are known as epigenetic changes.

Male mice exposed to cocaine, for example, pass memory problems on to their pups, a 2006 study in *Neurotoxicology and Teratology* shows. The male mice inhaled cocaine in long daily sessions akin to crack binges. When they mated with females never given coke, they had pups that had trouble learning and remembering where to find food in simple mazes. The problem was especially severe for female offspring. The researchers couldn't find any obvious DNA damage in coke-smoking males' sperm, but did find altered levels of two enzymes involved in the methylation of DNA in sperm-producing tissue in the father mice. The result suggests that epigenetic changes may be responsible for the offspring's behavior problems.

Matthew Anway can prove that male rats exposed to a fungicide in the womb can pass tumors and diseases of the prostate and kidney down for at least three generations. The rats could provide the first model for how prostate disease is inherited, he says. But only male rats could pass along the defects. The exposed rats bequeathed their fungicide legacy to their sons, grandsons, and great-grandsons even though none of the later generations were exposed to the chemical.

Exposed animals decrease production of enzymes that methylate DNA, Anway says. But he hasn't yet found consistent changes in the methylation patterns in exposed rats. It's not clear whether Anway's results have any implication for human health. The rats were exposed to extremely high doses of fungicide through the completely unnatural route of injection.

What's important is that the male shares experiences with descendants for years to come. Further research could give new insights, Anway says, into how alterations in early development could lead to adult disease in humans.