Newsweek

Sins of the Grandfathers

What happens in Vegas could affect your offspring. How early-life experiences could cause permanent changes in sperm and eggs.

by Sharon Begley (/authors/sharon-begley.html) **October 30, 2010**

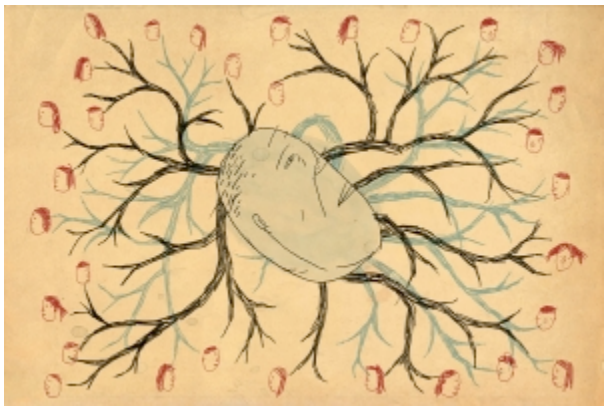

Illustration by Brian Rea

Michael Skinner has just uttered an astounding sentence, but by now he is so used to slaying scientific dogma that his listener has to interrupt and ask if he realizes what he just said. Which was this: “We just published a paper last month confirming epigenetic changes in sperm which are carried forward transgenerationally. This confirms that these changes can become permanently programmed.”

OK, so it’s not bumper-sticker-ready. But if Skinner, a molecular biologist at Washington State University, were as proficient with soundbites as he is with mass spectrometry, he might have explained it this way: the life experiences of grandparents and even great-grandparents alter their eggs and sperm (http://www.newsweek.com/blogs/techtonic-shifts/2010/06/21/dating-site-creates-online-sperm-and-egg-bank.html) so indelibly that the change is passed on to their children, grandchildren, and beyond. It’s called transgenerational epigenetic inheritance: the phenomenon in which something in the environment alters the health not only of the individual exposed to it, but also of that individual’s descendants.

Gallery: The Evolution of Birth Control

The Evolution of Birth Control (/photo/2009/10/28/the-history-of-birth-control.html)

The astounding part of Skinner's statement is that this altered inheritance does not occur the way generations of biologists have been taught. Instead of changing the DNA sequences (http://www.newsweek.com/2010/08/06/dna-dilemma-day-five-time-to-decide.html) that make up the genes that ancestors pass down to descendants—the A's, T's, C's, and G's that spell out the genetic code—something more subtle occurs in epigenetic inheritance. A life experience—in Skinner's study, exposing rats to a fungicide called vinclozolin—alters the on-off switches that control DNA in sperm or eggs (http://www.newsweek.com/2010/05/18/dna-as-crystal-ball-buyer-beware.html) . Biologists have long known about the switches, which are clusters of atoms called methyl groups. The cluster can silence a gene it attaches to; when the cluster is removed, the gene is active again. (This silencing is why the DNA for, say, insulin is turned off in brain cells but active in pancreas cells.) But biologists believed that when sperm and eggs grew up, as it were, and created an embryo, the tags were reset, nature's way of scrubbing the sins (http://www.newsweek.com/2010/01/13/controlling-your-genes.html) of the fathers and mothers before they could afflict the next generation.

Skinner's discovery that not all those marks are erased, but are instead permanently modified (at least as far out as he bred his rats: four generations), has challenged a decades-old tenet of reproductive biology … which, when it's brought to his attention, he acknowledges with an *Oh, right*: "The 'permanently' does astonish me," he concedes. "I guess it's why we got such pushback from the medical community."

Skinner's findings are far from anomalous. For one thing, they're not confined to rats or to the fungicide he fed them. Other labs, too, are finding that experiences—everything from a lab animal being exposed to a toxic chemical to a person smoking, being malnourished in childhood, or overeating—leaves an imprint on eggs or sperm, an imprint so tenacious that it affects not only those individuals' children but their grandchildren as well.

Skinner and his team have gone the furthest in showing how this works. By analyzing the on-off settings of switches on every bit of (http://www.newsweek.com/2010/02/03/who-owns-your-dna.html) sperm DNA, they found that 16 had been altered, turned on when the normal position was off, or off when the normal position was on. Those alterations appeared in the sons of mothers exposed to the fungicide when they were pregnant, in the sons of the sons, and in the sons of the sons' sons. The tags on the sperm DNA did not vanish, as textbooks say. As a result, because some genes that were supposed to be dormant were instead active, and some

genes that were supposed to be active were squelched, the sons and grandsons developed abnormalities in their testes, prostates, and kidneys. The point is not that this fungicide causes these problems in people—humans are exposed to much lower doses—but a proof of principle: by altering sperm in an enduring way, an environmental exposure can leave its mark on at least four subsequent generations.

The environmental exposure doesn't have to be as extreme as chowing down on a fungicide. Scientists at Australia's University of New South Wales fed healthy, svelte, male rats a high-fat diet (43 percent of calories from fat—a typical American diet). Not surprisingly, the rats put on weight and fat, and developed insulin resistance and glucose intolerance—basically, type 2 diabetes, the scientists reported last month in *Nature*. None of that was surprising. What made the scientists take notice was the daughters these rats sired: although their mothers were of normal weight and ate a healthy diet while pregnant, daughters of the high-fat-diet dads developed insulin resistance and glucose resistance as adults—even though they never ate a high-fat diet themselves.

Mothers' diet while pregnant affects their children's health as adults because of how nutrients and toxic compounds pass through the placenta. But fathers have no contact with their daughters except through the sperm that created them. These rat fathers were not genetically diabetic. The conclusion is therefore inescapable: the fathers' high-fat diet altered their sperm in a way that induced adult-onset disease in their daughters. (The next step is to see whether grandchildren develop it, too.) Emma Whitelaw of Queensland Institute of Medical Research, who has found similar transgenerational effects, has called it "a molecular memory of the parent's experience—in this case, diet." Reminiscent of Skinner's finding that sons and grandsons of his fungicide-exposed rats had abnormal on-off switches in their sperm DNA, the Australian team found that 642 genes in the pancreas (which makes insulin) of the daughters of the high-fat-diet fathers had on-off switches in the wrong position. The result raises the intriguing possibility that the childhood-obesity epidemic is at least in part due to alterations in sperm caused by fathers-to-be eating a high-fat diet. After all, while it's fine to blame kids' couch-potato ways and fattening diets, that does not explain why obesity in babies has risen 73 percent since 1980.

Transgenerational effects do not have to be harmful. When 15-day-old female mice frolicked for two weeks in an enriched environment, one filled with exercise wheels, novel objects, and lots of other mice for social stimulation, it strengthened the brain mechanism that underlies memory. That much had been shown many times before: animals raised in an enriched environment remember mazes better. But last year, scientists led by Larry Feig of Rush University Medical Center in Chicago reported in *The Journal of Neuroscience* that the neuronal effect shows up in the mice's offspring—even when those offspring never lived in an enriched environment, and even though those offspring were not so much as a gleam in their mothers' eyes when they lived in the enriched environment. "The idea that qualities acquired from experience can be transmitted to future offspring has long been considered [heresy]," Feig's team wrote. If something similar occurs in humans, how good your memory is during adolescence "can be influenced by environmental stimulation experienced by one's mother during her youth."

One reason that is not so farfetched: transgenerational effects are showing up not only in lab rats but also in people, as if the ghosts of our ancestors haunt our very genes. In 2006 scientists announced the findings of a study in a town in Sweden called Överkalix (chosen

because it keeps excellent birth and death records). If a father began smoking before the age of 11, found Marcus Pembrey of the Institute of Child Health in London, his sons had a greater body-mass index, on average, than did sons of men who took up smoking as adults. In this same population, if a man suffered food shortages as an 8- to 12-year-old child, his sons' sons were more likely to die young; if a woman suffered food shortages as a child, her son's daughters were. Another study in Överkalix found that if a man overate in childhood, his sons' children were four times more likely to develop diabetes and cardiovascular disease, found scientists at Sweden's Umeå University.

Immigrating Can Be Bad for Your Health For some immigrant populations, the United States is more than just "the Land of Opportunity." Moving to America has presented a long history of health challenges for America's immigrants.

At the time these studies were done, it cost about $10,000 per sample to scan DNA for changes in the on-off switches that show this sins-of-the-grandfathers effect. But the cost is dropping fast, says Skinner, making it feasible to see whether life experiences leave indelible marks on the sperm or eggs that give rise to children and grandchildren. Since the answer so far is yes, consider it a warning to hold off on your unhealthy behavior until after you have kids.