



# THE FATHER FACTOR

Could becoming a father after age 40 raise the risks that your children will have a mental illness? **By Paul Raeburn**

**W**hen my wife, Elizabeth, was pregnant, she had a routine ultrasound exam, and I was astonished by the images. The baby's ears, his tiny lips, the lenses of his eyes and even the feathery, fluttering valves in his heart were as crisp and clear as the muscles and tendons in a Leonardo da Vinci drawing. Months before he was born, we were already squabbling about whom he looked like. Mostly, though, we were relieved; everything seemed to be fine.

Elizabeth was 40, and we knew about all the things that can go wrong in the children of older mothers. We worried about Down syndrome, which is more common in the offspring of older women. Elizabeth had the tests to rule out Down syndrome and a few other genetic abnormalities. That was no guarantee the baby would be okay, but the results were reassuring to us.

The day after Henry was born, while we were still bleary-eyed from a late-night cesarean delivery, we caught part of a report on the hospital television about an increased risk of autism in the children of older fathers. Until then, all we'd thought about was Elizabeth's age—not mine. We'd had no idea that my age could be an important factor in our baby's health.

When we got home, I looked up the study. Researchers had analyzed medical records in Israel, where all young men and most women must report to the draft board for mandatory medical, intelligence and psychiatric screening. They found that children born to fathers 40 or older had nearly a sixfold increase in the risk of autism as compared with kids whose fathers were younger than 30. Children of fathers older than 50—that includes me—had a ninefold risk of autism.

The researchers said that advanced paternal age, as they call it, has also been linked to an increased risk of birth defects, cleft lip and palate, water on the brain, dwarfism, miscarriage and “decreased intellectual capacity.”

What was most frightening to me, as someone with mental illness in the family, is that older fatherhood was also associated with an increased risk of schizophrenia. The risk rises for fathers with each passing year. The child of a 40-year-old father has a 2 percent chance of having schizophrenia—double the risk of a child whose father is younger than 30. A 40-year-old man's risk of having a child with schizophrenia is the same as a 40-year-old woman's risk of having a child with Down syndrome.

We wouldn't know for two years or so whether Henry had

autism. And because schizophrenia does not usually appear until the early 20s, we had decades to wait before we would know if Henry was affected.

### Advancing Years

Data collected by the National Center for Health Statistics, part of the Centers for Disease Control and Prevention, show that in the U.S. the number of births to men aged 40 to 49 nearly tripled between 1980 and 2004, rising from 120,702 to 328,465. Much of that jump is the result of an increase in the overall population. But there has been a shift over the past generation toward more older fathers beyond what can be accounted for by the growth in population. Birth rates for men in their 40s (a number that takes population growth into account) have risen by up to 40 percent since 1980—whereas birth rates for men younger than 30 have fallen by as much as 21 percent.

The idea that a father's age could affect the health of his children was first hinted at a century ago by an unusually perceptive and industrious doctor in private practice in Stuttgart, Germany. Wilhelm Weinberg was a loner who devoted much of his time to caring for the poor, including delivering 3,500 babies during a 40-year career. He also managed to publish 160 scientific papers without the benefit of colleagues, students or grants. His papers, written in German, did not attract much

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attention initially; most geneticists spoke English. It was not until years later that some of Weinberg's papers were recognized as landmarks.

One of these was a 1912 study noting that a form of dwarfism called achondroplasia was more common among the last-born children in families than among the first-born. Weinberg didn't know why that was so, but he speculated that it might be related to the age of the parents, who were obviously older when their last children were born. Weinberg's prescient observation was confirmed decades later when research showed that he was half right: the risk of dwarfism rose with the father's age but not the mother's.

Since then, about 20 inherited ailments have been linked to paternal age, including progeria, the disorder of rapid aging, and Marfan syndrome, a disorder marked by very long arms, legs, fingers and toes, as well as life-threatening heart defects. More recent studies have linked fathers' age to prostate and other cancers in their children. And in September 2008 researchers linked older fathers to an increased risk of bipolar disorder in their children.

### Eggs vs. Sperm

Dolores Malaspina, a professor of psychiatry at the New York University Langone Medical Center, was in college when her sister, Eileen, who was two years younger, began behaving in ways the family couldn't explain. At first, Malaspina recalls, Eileen seemed like she was going through the usual problems of adolescence. Eileen's behavior became harder to overlook, however, and she was soon diagnosed with schizophrenia.

It was the early 1970s, when many psychiatrists believed schizophrenia was caused by a dominant, overpowering mother who rejected her child. Further, Eileen's doctors said, there was no treatment. The damage done by a schizophrenia-inducing mother was irreparable.

At the same time Eileen was deteriorating, Malaspina earned a master's in zoology and took a job at a drug company, where she drifted into research on substances that could alter brain chemistry. She was in the job for a while before she made the connection with her sister. "I was looking at molecules in the lab that might be related to psychosis," she says. "My sister had very bad psychosis." Researchers were then beginning to establish a biological basis for schizophrenia that would ultimately demolish the so-called schizophrenogenic-mother theory. Malaspina quit her job, went to medical school, became a psychiatrist and focused her research on schizophrenia.

While schizophrenia was being recast as a biological illness, most researchers still looked to mothers as the cause of

#### FAST FACTS Older Fathers

**1»** It is widely recognized that a 40-year-old woman has an increased risk of bearing a child with Down syndrome. What is not known is that a 40-year-old man has the same risk of fathering a child with schizophrenia—and even higher odds of his offspring having autism. The risk of bipolar disorder appears to rise as well.

**2»** In the past couple of decades, the number of older fathers has increased. Birth rates for men older than 40 have jumped as much as 40 percent since 1980.

**3»** The mechanisms behind the higher risks are still being investigated, although scientists have several hypotheses that could someday lead to better therapies or possibly even cures for these mental illnesses.

the illness. A woman's eggs age as she does, and it seemed reasonable to conclude that they deteriorate over the years, giving rise to increased problems in her offspring. Sperm are freshly manufactured all the time.

That's not quite the way biology works, however. Because sperm are being continuously manufactured, genetic copying is going on constantly. Geneticists think it is that incessant copying and recopying that gives rise to the genetic errors that cause dwarfism, Marfan syndrome and the other inherited ailments. Malaspina decided to explore whether genetic errors in sperm might be at least partly responsible for schizophrenia. It was an unfashionable line of research. Nobody worried about fathers because everybody assumed mothers were the source of most problems in children. But Malaspina and others were beginning to think about it differently.

### Schizophrenia and Autism

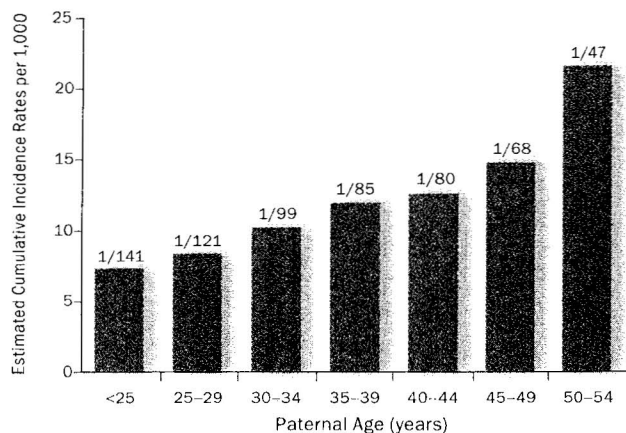
Later, while doing her residency at Columbia University, Malaspina learned about a unique research opportunity in Israel. During the 1960s and 1970s, all births in and around Jerusalem were recorded in conjunction with information on the infants' families, including the ages of the parents. And all those children received a battery of medical tests as young adults, a requirement of Israel's military draft. Because the records cover an entire population, the data are free from the biases that might creep in if researchers looked at, say, only people who graduated from college or only those who went to see a doctor.

Malaspina used the Israeli group to look first at the risk of schizophrenia in children of older fathers—and then at the risk of autism. Then she correlated birth and family information on some 90,000 children with information on which of them had developed schizophrenia as recorded on their military physicals. In 2001 Malaspina and her colleagues reported that paternal age was strongly linked to the risk of schizophrenia, as she had suspected.

It was the first large-scale study to link sporadic cases of

### A Rising Risk

The rate of offspring estimated to have an onset of schizophrenia by age 34 grows with paternal age.



When a large study linked schizophrenia to paternal age, some researchers wondered if the root cause, rather than age, was that men who had waited had the makings of the disease themselves.

schizophrenia to fathers' age, and few researchers believed it. "We were absolutely convinced it was real, but other people didn't think it was," Malaspina says. "Everybody thought men who waited to have children must be different." That is, maybe these older fathers had some of the makings of schizophrenia themselves—not enough for the disease to be recognized but enough that it took them a little longer to get settled, married and have children.

Other groups tried to repeat the study using different populations. In all these studies, researchers took a close look at whether there was something about the older fathers—unrelated to age—that increased the risk of schizophrenia in their children. When they did, the link with age became even clearer. "That result has been replicated at least seven times," says Robert K. Heinsen, chief of the schizophrenia research program at the National Institute of Mental Health (which has funded some of Malaspina's work). "We're talking about samples from Scandinavia, cohorts in the United States, Japan.

### (The Author)

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