

Like one in 100 Americans, David Peterson has schizophrenia. Why so many? One physician-scientist has devoted her career to finding the answer—and improving the lives of her patients.

Grasping Reality

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> Patient:
DAVID PETERSON

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16





When

David Peterson was 26 years old, he looked in the mirror in the middle of the night and saw the Devil staring back at him. In terror, he told himself not to think anything bad, but in the next instant a thought jumped into his mind: “I’m going to kill somebody.” He ordered himself not to think anything worse, and immediately imagined killing his family. “I thought, ‘Are you crazy?’” he recalls. “You’re in the house, and there are knives in the kitchen. How does a person know they’re not going to pick one up and run into a bedroom and kill their whole family?” So he hatched a plan: “If I go near the knives, I’ll kill myself before I go upstairs.”

Peterson had attended the Pratt Institute in Brooklyn, seeking a degree in industrial design. But before he could pursue a career, he was diagnosed with schizophrenia. At the hospital he was taken to, he did attempt suicide. “I went into the bathroom, and someone had left a plastic razor on the sink,” he says. “I put it on the ground, I stepped on it with my heel, and I took out the razor blade. I locked the door, slit open my wrists, and put them under the hot water. I lost so much blood I was unconscious. The next thing I remember was sitting on the end of a doctor’s table, and he was stitching up my wrists, saying something really charming like, ‘Hey, Dave buddy, you’re back with us.’”

In truth, though, Peterson was not really back. After this episode of mental illness—his third since the age of 18—he spent 14 months in locked wards, shuttling between hospitals, and the next 20 years taking Haldol, an antipsychotic medication on which he felt barely any better. He would kick his leg compulsively—a side effect of the drug—until his tendons ached and calluses grew on his heel. Every time he closed his eyes, he saw fireworks. “You get this incredible uncomfortable feeling,” he explains. “It’s like hitting yourself on your head with a hammer so you don’t think of your illness. You’re living a nightmare, and every second of it seems like an eternity.”

Today David Peterson is 50, a dapper, handsome man with curly salt-and-pepper hair who speaks calmly and deliberately, smiles easily, and even jokes about

his past suffering. Four years ago he was placed under the care of Dolores Malaspina, M.D., M.P.H., the Anita Steckler and Joseph Steckler Professor of Psychiatry and Chairwoman of Psychiatry.

She tapered him off the medication that had tormented him for two decades and prescribed an antidepressant, as well as a range of newer antipsychotics and anti-anxiety drugs. “A couple of weeks after I met her,” recalls Peterson, “I was starting to feel 50 percent better.” Within another two months, he had begun to feel 95 percent well, and remains so to this day. An artist whose riotously colored paintings and drawings have been exhibited widely, Peterson lives independently, designs his own chairs, studies sculpture, plays tennis, and works out with a trainer regularly.

Peterson’s dramatic progress after years of torment is not entirely typical of people with schizophrenia, however. For one thing, he’s financially stable, which enables him to deal with daily stresses that others with the disease might find overwhelming. But the fact that Peterson credits his resounding improvement to Dr. Malaspina is hardly a surprise. An effervescent woman with a radiant smile and an air of spirited optimism, she has devoted her life to understanding and treating schizophrenia, caring for hundreds of patients over the course of her career. She herself encountered the disease early on: her only sister, Eileen, who had yearned to become a doctor, was diagnosed in 1971 with schizo-affective disorder—a mix of mania, depression, and psychosis—

during her senior year in high school and never made it to medical school. Although Eileen did, eventually, graduate from college and marry at the age of 46, it was Dolores who became a doctor. She applied to study medicine with the sole goal of becoming a psychiatrist to help people with schizophrenia. Dr. Malaspina, who came to NYU in 2006 after 22 years of teaching and research at Columbia University and the New York State Psychiatric Institute, has not confined her career to treating patients; she has also published more than 150 research papers on the genetics and epidemiology of the disease, as well as its environmental triggers.

Schizophrenia is a surprisingly common mental illness—about one in every 100 people will be diagnosed with it over the course of their lives—and yet it is also one of the most commonly misunderstood. Much of this confusion can be traced back to its name. Eugene Bleuler, the Swiss psychiatrist who coined the term schizophrenia in 1908, drew it from the Greek words *schizo*, meaning “split,” and *phrenos*, meaning “mind.” That in turn has led to the widespread misconception that people with schizophrenia suffer from “split personality.” In fact, Bleuler himself believed that the basic symptoms of the disease included disordered thinking and fragmentation of personality. As the National Institute of Mental Health now defines it, schizophrenia destroys “the inner unity of the mind” and “weakens the will and drive that constitute our essential character.”

In some ways Bleuler was far in advance



of his time: he believed schizophrenia to be a group of diseases, a view widely held today. “Schizophrenia is a syndrome,” explains Dr. Malaspina, “a collection of several different diseases, with many different types of broad symptoms.” These typically fall into three categories: positive symptoms, which include hallucinations and delusions; negative symptoms, which may involve social withdrawal, self-neglect, and loss of motivation or the ability to feel pleasure; and cognitive deficits, which may undermine memory and attention.

It has been known for some time that schizophrenia tends to run in families: the risk of developing the disease rises from 1 percent to 6 percent in first-degree relatives of patients, and to 40 percent in identical twins of affected people. In the spring of 2001 Dr. Malaspina gained widespread attention from peers and the public when she published a groundbreaking study in the *Archives of General Psychiatry* showing that children of older fathers were up to three times as likely to suffer from schizophrenia as those born to younger men. In effect, her results bolstered a growing awareness of the Male Biological Clock. The older men are, goes the theory, the likelier they are to father children with genetic disorders. At

first, her findings were met with disbelief. After all, it is commonly assumed that genetic diseases are more frequent in the offspring of older women.

Dr. Malaspina’s quest to decipher the disease did lead her to a parent — only this time, it was the father. She has managed to solve a riddle that has long surrounded schizophrenia: How does so disabling a disease manage to persist when its victims rarely reproduce. In 2000 she began analyzing an archive, the Jerusalem Perinatal Study, that had recorded parental ages and demographic data on all residents born in one area of Jerusalem between 1964 and 1976, and had linked that data to a national registry of psychiatric illness maintained by the State of Israel since 1950.

From this analysis, she learned that the risk of developing the disease tripled in children whose fathers were over the age of 45 when their children were born, as compared with children whose fathers were younger than 25 at their children’s birth. One in every 121 children born to men in their 20’s had developed schizophrenia by age 34; by contrast, one in 46 children born to men aged 45 or over developed the disease. Advanced paternal age seems to account for one-quarter of

all cases of schizophrenia; no such effect could be seen in children of older mothers.

One initial skeptic was Dr. Ezra Susser, a psychiatrist and epidemiologist at Columbia who co-authored the study. It was he who first alerted Dr. Malaspina to the Jerusalem Perinatal Study and put her in touch with one of its founders, epidemiologist Dr. Susan Harlap. “When Dolores wanted to study the relation of father’s age to schizophrenia, I wasn’t so keen,” Dr. Susser recalls. “Then I came around.” Other explanations had been put forward, he says—for example, that men with a predisposition to schizophrenia tend to marry and have children later. “In the end, none of the alternative explanations are that convincing,” says Dr. Susser, in part because Dr. Malaspina’s original study has now been replicated multiple times in different settings and societies. These cases arise spontaneously—that is, they appear in people with no family history of the disease, suggesting that each new instance of the disease may be the result of a new change or mutation in a gene.

In fact, it had been known for some time that certain rare genetic diseases are likelier to occur in children with older fathers. However, this was the first time the effect had been seen for schizophrenia, a disease



Paintings by David Peterson

Shortly after emerging from his maelstrom of mental illness in 2005, David Peterson began to celebrate his recovery by painting. He has produced nearly 100 works of art, some of which he has sold to private collectors. The self-portrait at left was inspired by a photo taken when he was 18, one month before he was diagnosed with schizophrenia.



< Antique Coffee Pot



< The Trail



< Young Teddy Roosevelt

that researchers now believe may be caused by a mutation in any one of many genes. The increase in genetic mutations in the offspring of older fathers can be traced back to a deceptively simple cause: the older a man is, the more times his sperm cell precursors, called spermatogonia, have divided. By the time he is 40, each spermatogonium has divided approximately 660 times, or about 23 times a year after puberty. The more times they divide, the greater the chance that a harmful mutation will occur when DNA is copied.

Dr. Malaspina's finding of an association between older paternal age and schizophrenia in offspring is a reflection of her determination to explore every possible cause for spontaneous cases, including environmental factors such as head injury. "Dolores has always thought rather imaginatively," says Columbia's Vice Chairman of Education, Dr. Ronald Rieder, who supervised Dr. Malaspina during her days as a resident. "It was a field which was highly competitive and there were a number of people who quickly dismissed her findings, saying it's unlikely to be true. But then there were numerous replications. She's the first person I know of who in a scientifically rigorous way said that older fathers convey a risk for schizophrenia."

But Dr. Malaspina wasn't content to rest with this one result. The more she could learn about how the disease arises and affects its victims, she reasoned, the better her chances of treating it—and preventing further brain damage. She views schizophrenia as akin to any other adult-onset chronic illness, like heart disease, hypertension, or kidney disease. "A lot of people don't think of it that way, so they'll let someone continue to be psychotic or tolerate the symptoms," she says. "But just like other chronic deteriorating diseases, early and thorough treatment is very important." Learning about the underlying biology of the disease could also

enable doctors to offer the right medication—perhaps, in the future, one tailored to a specific form of schizophrenia. "For schizophrenia, our medicines are still at the surface level," laments Dr. Malaspina. "We can get rid of the psychosis, but the primary problem is deeper in the brain."

When Dr. Malaspina began to look at how the spontaneous form of schizophrenia was expressed in the affected children of older fathers, she found that they all had a specific profile, or phenotype, of the illness: they typically fell prey to the scourge at about age 20; they were often educated; men and women were affected with equal severity; and nearly all of them suffered from auditory, not visual, hallucinations. When off medication, they experienced serious psychoses—false beliefs, delusions, hallu-

cinations—but these symptoms responded well to drugs. There were also differences in brain function: neuroimaging studies showed that sporadic paternal-age-related cases had reduced blood flow in the frontal area of the brain, as compared with patients with a family history of the disease. People with the inherited form — as opposed to the sporadic form that arises in children of older fathers — tend to have abnormal blood flow and function on the left side of the brain, which includes the language circuits.

Contrary to popular myth, people with schizophrenia are not all tortured souls; with the right medication and cognitive-behavioral therapy to enhance social skills, people with the illness can often lead productive, independent lives. "To truly recover is still something exceptional," Dr. Malaspina says. "But it's important to note that the lives of people who are helped are really transformed. Even if you can't make someone perfectly well, people can be dramatically better." Dr. Malaspina also stresses that the vast majority of people with schizophrenia are not violent; in fact, they are likelier than others to be the victims of assault because they tend to be passive and withdrawn.

A key element in the treatment of the disease—and in particular, those cases linked to advanced paternal age—is a better understanding of its genetics and how environmental factors, such as severe stress, head injury, or exposure to toxic chemicals, could influence its onset or course. So Dr. Malaspina has conducted a series of landmark studies in both humans and mice that examines both of these effects. In research published in 2001 in the *American Journal of Psychiatry*, for example, she showed that people with schizophrenia were likelier to have suffered a traumatic head injury than those with other mental illnesses, such as bipolar disorder.

She found further evidence of paternal-age-related mental illness in a study of autism published in the *Archives of General Psychiatry* in 2006 in collaboration with psychiatrist Avi Reichenberg of Mount Sinai School of Medicine. An analysis of a large group of Israeli men showed that children of men 40 years old or older were nearly six times as likely to suffer from autism spectrum disorder—a chronic condition characterized by social dysfunction, language abnormalities, and repetitive patterns of behavior—as those born to men younger than 30. As with schizo-

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phrenia, Dr. Malaspina was determined to understand exactly how genetic mechanisms could lead to increases in mental impairment. “I would say that I learned early on to persevere,” she says. “It’s my style to think outside the box.”

The most obvious explanation for the raised risk of schizophrenia in children of older fathers, she reasoned, is a copying error during spermatogenesis, leading to a mutation in a gene controlling brain development. There is another possible explanation, though: faulty imprinting of a paternally expressed gene. It is known that some genes code only for proteins if inherited from the mother, and others are turned on only if inherited from the father; if a gene is expressed on a chromosome that comes from the mother, the gene on a paternal chromosome must be silenced, and vice versa. Environmental factors such as stress can influence this process, as rat studies have shown. Remarkably, Dr. Malaspina has found that similar stress factors could also influence the onset of schizophrenia in humans. In a recent study of Israeli women pregnant during the June 1967 Six-Day War—the conflict that pitted Israel against the combined forces of Egypt, Jordan, and Syria—she found that children who were

in their second month of fetal development during this period of extreme stress were twice as likely to develop schizophrenia in adulthood as were matched controls. For girls, the risk was fourfold. A similar increase in schizophrenia was seen among children born during the May 1940 German invasion of the Netherlands. “We think that the severe stressor has left a footprint, if you will, on whatever stage of brain development was going on at that time,” says Dr. Malaspina.

Dr. Malaspina’s great hope is that she will be able to translate her research in epidemiology and genetics into clinical intervention, especially for young people experiencing initial signs of schizophrenia, since it is thought that ongoing psychotic attacks can lead to further brain damage. “It has become very clear that the quality of treatment early in the course of the disease is what determines the long-term outcome,” she says. “So if you miss this opportunity for early intervention, people may do more poorly the rest of their lives.” In a 2005 study Dr. Malaspina and her colleagues at the New York State Psychiatric Institute found that adolescents with early-onset psychosis had a diminished ability to smell odors, an impairment typical of adults with the illness, too. The deficit may be related to a loss of social functioning, since, as Dr. Malaspina explains, “It’s really through the sense of smell that most mammals build social relationships; the olfactory brain is really the social brain.” Identifying a loss of ability to smell in adolescents exhibiting early warning signs of schizophrenia could aid diagnosis.

Together with Dr. Mary-Claire King at the University of Washington School of Medicine, who has done pioneering research on the genetics of breast and ovarian cancer, Dr. Malaspina is also embarking on a comprehensive analysis of the genetic mechanisms that underlie paternal-age-related schizophrenia. After taking blood samples from participants in the Jerusalem Perinatal Study, they will analyze their DNA for evidence of new mutations or suspicious alterations in gene expression. Again, her goal is to find better treatments for the disease itself—perhaps, in the future, by developing a blood test to detect a specific paternal-age-related sub-type or even medicines tailored to that phenotype. “Many times when a new medication is found, they’ll do a study of a large group of patients, and they’ll find not a significant effect,” Dr. Malaspina says. “But often a sub-group of people had a very robust effect.”

These days, such research consumes a significant chunk of her time. Yet Dr. Malaspina enthusiastically continues to mentor younger doctors and to see patients such as David Peterson. He himself admits that intermittent paranoia and some lingering anxieties prevent him from feeling 100 percent well. “I know now that there is something wrong with my mind,” he says. Yet, as Dr. Malaspina adds, “He’s someone who’s really had a wonderful resolution of his psychotic and mood symptoms. But he’s worked really hard to be well.” Helping people like David Peterson is one of the things that motivates Dr. Malaspina most. “People don’t realize that in psychiatry,” she says, “you actually save lives.” ●

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 primary problem is