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# A Scientist's Final Quest Is to Find New Schizophrenia Drugs. Will He Live to See Them?

Edward Scolnick led the development of dozens of medicines while at Merck; his current mission pits him against time and the mental illness of millions, including his son

By *Amy Dockser Marcus* [Follow](#) | *Photographs by Alyssa Schukar for WSJ*

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Dr. Edward Scolnick figures he needs five, maybe 10 more years to solve one of the brain's greatest mysteries.

Scolnick, 84 years old, has spent most of the past two decades working to understand and find better ways to treat schizophrenia and bipolar disorder, mental illnesses suffered by tens of millions of people, including his son.

"I know I can crack it," said Scolnick, a noted drug developer who spent his career plumbing the building blocks of DNA for new treatments.

Long before his latest quest, Scolnick spent 22 years at Merck, mostly as head of the drug giant's laboratory research. He led development of more than two dozen medicines, including the first approved statin to lower cholesterol, an osteoporosis treatment and an anti-HIV therapy.

He also was the company's chief scientist during the development and rollout of Merck's pain reliever Vioxx in 1999. Researchers in a published study later estimated that tens of thousands of people died from heart attacks after taking the drug before Merck pulled it off the market in 2004. The company paid \$4.85 billion to settle lawsuits with people who claimed they were injured by the drug.

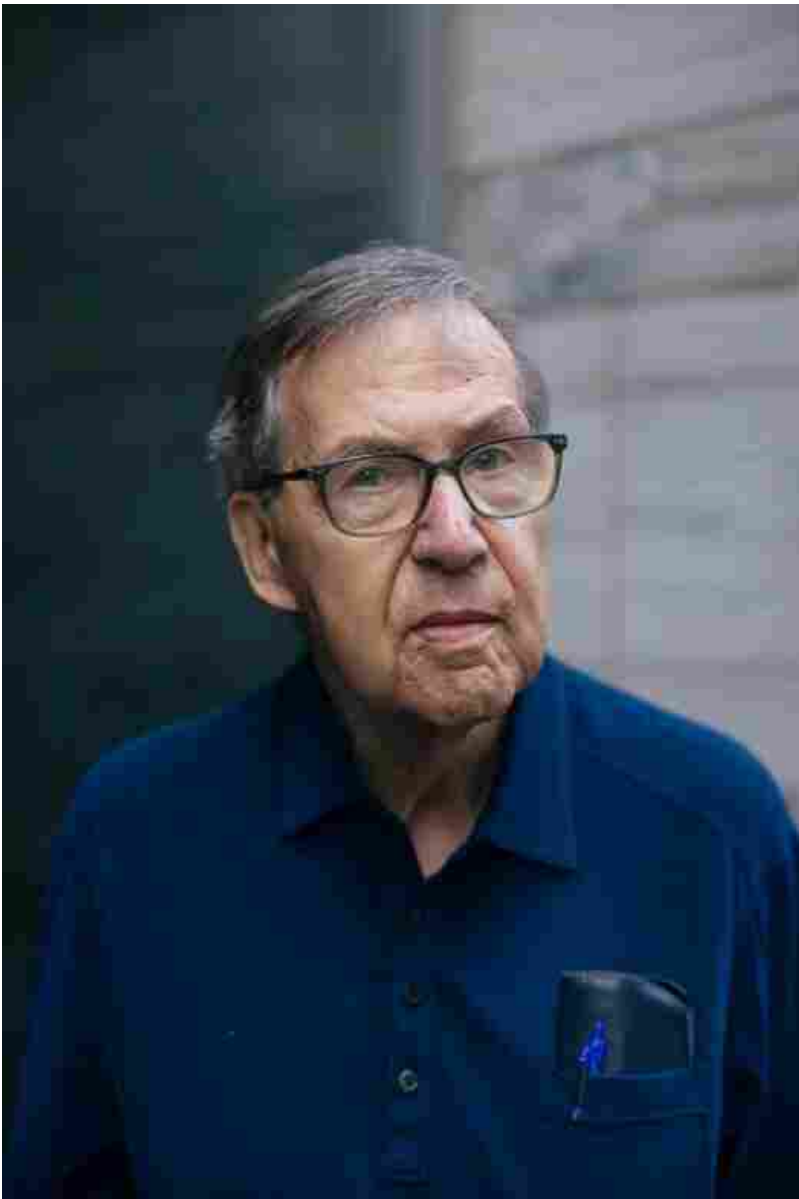
Scolnick stepped down as head of Merck's research lab in 2002. He told friends he wanted to spend the rest of his working life searching for better psychiatric treatment. Scolnick believed advances in genetic technologies would lead to the unraveling of even conditions as complex

as schizophrenia, which brings hallucinations and delusions, and bipolar disorder, which causes extreme mood swings.

Discoveries in the years since show he was on the right track.

In 2021, Scolnick learned that a group of scientists analyzing DNA from thousands of people with schizophrenia had found mutations in 10 genes that substantially increased the risk of developing the illness. They estimated that a mutation on a single gene, called *Setd1a*, raised the risk 20-fold.

“It got my blood boiling,” Scolnick said. He began pursuing an emerging class of treatments called LSD1 inhibitors, hoping to develop a new drug. Scolnick enlisted Dr. Hugh Young Rienhoff Jr., who recently developed an LSD1 inhibitor to treat blood disorders.



Edward Scolnick, former director of the Stanley Center for Psychiatric Research at the Broad Institute.

Scolnick hopes the work will lead to the first approved drug to help with cognitive symptoms—such as trouble paying attention and making plans—for people with schizophrenia. Cognitive decline from disease robs people of the ability to hold jobs and manage daily lives.

Rienhoff anticipates testing a new drug for safety as early as next year, first in animals. He said he saw Scolnick's passion about fielding a breakthrough treatment but didn't fully understand why until Scolnick shared about his son's lifelong struggles with mental illness.

Jason Scolnick, 54, said his doctor has been regularly fine-tuning his medications for bipolar disorder over the years to minimize their debilitating side effects. Using the drugs currently prescribed for schizophrenia or bipolar disorder is like undergoing chemotherapy, he said.

“There’s no guarantee it will work and it makes you feel terrible, but the cancer will feel worse or kill you.”

There remains a long road ahead for any new medicine. It takes more than a decade, on average, to get a drug from the research lab through government approvals to patients.

Ed Scolnick tries to make the most of his days. In May, he walked stiffly to the podium at a meeting of scientists to report on how he landed on LSD1 inhibitors as an avenue for treatment of schizophrenia.

Phillip Sharp, a Nobel Prize-winning drug developer and professor emeritus at Massachusetts Institute of Technology, was in the audience. Sharp, who has known Scolnick for years, said he was moved that his friend devoted his time and attention to a drug he likely won’t see to fruition.

Rienhoff said Scolnick has asked him to finish the work if he is no longer around.

“This is going to be my last hurrah,” Scolnick said.



A photo of Jason Scolnick as a one-year-old with his father, Edward Scolnick.

## **Blind luck**

More than 60 years ago, doctors by chance stumbled upon drugs that evolved into treatments for mental illness. Medicines relieved symptoms long before researchers knew how mental illness worked. Lithium, for instance, stabilized moods for people with bipolar disorder, and clozapine tamped down hallucinations and delusions from schizophrenia.

Scientists have since learned that psychiatric disorders can result from interactions among hundreds of genes, in still-unsolved combinations believed to vary by individuals and within families. To find the gene mutations that carry a higher risk, researchers would have to first compare the DNA of people with mental illness to those without the disease.

After leaving Merck, Scolnick was hired in 2004 by the Broad Institute of MIT and Harvard to lead research on psychiatric disorders. He fostered ties with Ted Stanley, a memorabilia entrepreneur whose son also suffered with mental illness. In 2007, Stanley gave \$100 million to launch the Stanley Center for Psychiatric Research at the Broad, headed by Scolnick for five years.

In the summer of 2017, the Broad organized an international consortium to harness resources and the latest gene technology that ended up analyzing DNA from more than 24,000 people with schizophrenia and more than 97,000 people without. Sifting for useful clues in reams of data would take years more.

Scolnick retired as chief scientist at the Stanley Center in 2020 for health reasons. He played competitive bridge and awoke early to swim laps. Scolnick visited the Broad for scientific meetings and gave talks. He also spoke regularly with one of the chief investigators of the DNA analysis.

In 2021, the investigator told Scolnick about the latest results: the *Setd1a* gene mutation substantially raised the risk of people developing schizophrenia.

Scolnick, inspired by the finding, dug into research papers and learned that Takeda Pharmaceutical had developed and tested an LSD1 inhibitor for Kabuki syndrome, a genetic disorder that can cause intellectual disabilities in children. During a visit to Takeda's lab in Cambridge, Mass., and in follow-up video calls, the company shared data with Scolnick that showed improved cognition in mice given the drug.

Takeda said it dropped the project after concluding it wasn't "a viable therapeutic option." Yet the company's findings convinced Scolnick that a specialized enzyme inhibitor might improve cognitive symptoms without severe side effects.

Developing that kind of drug was too big a job for one man alone, Scolnick said, and too expensive. Such a project might cost hundreds of millions of dollars.

Then chance intervened.



Dr. Morgan Sheng, left, co-director of the Stanley Center for Psychiatric Research, speaking with Scolnick in Cambridge, Mass.

In January 2023, Scolnick heard a talk by Rienhoff organized by Blackstone, the New York-based investment firm. Scolnick, a senior adviser at Blackstone Life Sciences, wanted to know more about the LSD1 inhibitor Rienhoff developed to treat blood disorders. That same month, Merck completed a \$1.4 billion acquisition of Rienhoff's company, Imago BioSciences.

Scolnick and Rienhoff had sat together at a Blackstone dinner years earlier. During the meal, Scolnick shared stories with his table companions about Merck's development of Crixivan, the anti-HIV drug. "I was hearing a piece of history," Rienhoff said, "not just HIV history."

Scolnick became emotional describing how the drug developers, facing various obstacles, wrestled with whether or not to keep going. He pushed for the study to continue, given the urgency. At the time, AIDS was killing tens of thousands of people a year in the U.S.

"I said to Ed, 'You are thinking like a doctor not a scientist,'" Rienhoff said. "That was the beginning of our relationship."

After Rienhoff's presentation last year, Scolnick learned that Rienhoff was an expert in the enzyme he believed key to a breakthrough drug. In conversations, Scolnick got Rienhoff thinking about using LSD1 inhibitors for schizophrenia and other neuropsychiatric illnesses.

When Scolnick raised the idea of developing a new drug, Rienhoff told him he could make one. Rienhoff founded Aluco BioSciences this year as a first step. To make the leap from hematology, his expertise, to neuropsychiatry, Rienhoff said he has been meeting clinicians and neuroscientists, steeping himself in various theories on the causes of schizophrenia and seeking potential collaborators.

Rienhoff has a team of chemists making and testing compounds at labs in the U.S. and abroad.

“I am optimistic something will come of this,” Rienhoff said. “I can do it, but I wouldn’t have done it if not for Ed. I am, really, doing this in a way for Ed.”

## **‘Before I die’**

Jason Scolnick lives in a light-filled condominium in Watertown, Mass., about a 25-minute drive from his parents. Guitars lean against a wall, and a landscape photo shot by his mother hangs on another. He sometimes watches football games on the big-screen TV with his father. His life now contrasts with years of struggle.

Jason graduated from Harvard University in 1992 and worked as a clerk in the economics department of a biotech firm. Before taking the job, he began to feel paranoid. At work, he couldn’t look colleagues in the eye. Doctors suspected bipolar disorder and prescribed him medications. They left him so tired, he had trouble keeping awake while driving. He missed work, then quit and moved in with his parents in Philadelphia.

Jason’s doctors finally found a drug regimen he could tolerate after two years of trying.

At age 25, Jason returned to Boston to study guitar at Berklee College of Music but dropped out after less than a year. During those months, he said, his paranoia had returned, and he abused alcohol. One night in 1995, Jason said, he took pills, intending to end his life. He woke up hallucinating and called a friend who dialed 911 for an ambulance.



Jason Scolnick practicing guitar at home.

Jason returned to live with his parents in 1996, the same year the Food and Drug Administration approved Merck's anti-HIV drug that his father had helped develop. He tried various medicines over the years, including one drug that landed him in the hospital.

“They call antipsychotics major tranquilizers for good reason,” Jason said. “They clamp down on your head and it’s up to you to suck down large amounts of coffee to deal with how they make you feel. Not just tired, but also cognitively impaired.”

The lack of effective treatments saddened and frustrated his father, who built a career developing drugs for once-intractable conditions.

Jason, who has been sober for more than a decade, is now in his second year of a master’s program at Lesley University, studying to become a clinical mental-health counselor and



music therapist. He credits his psychiatrist for continuing to help calibrate his drugs and therapy.

“There’s nobody I know who can just take medicine and be fine,” Jason said.

His father agreed, to a point.

“It won’t just take some magical drug to fix what people with really severe mental illness have,” Ed Scolnick said.

But as a parent and scientist, he feels certain new treatments will improve lives for many people. “There’s a need for better drugs,” he said, believing he is on the right path. Others also are on the hunt.

Biotech company Oryzon Genomics in Spain is developing LSD1 inhibitors for cancer and other conditions. Columbia University researchers tried Oryzon’s drug in mice and found it reversed cognitive impairments caused by the *Setd1a* genetic mutation connected to schizophrenia. Oryzon is running a small trial in Spain of the LSD1 inhibitor in patients with schizophrenia.

Dr. Joseph Gogos, who led the Columbia research, said it was possible such treatments would be approved for people.

Scolnick is more certain—of both a revolutionary new treatment and his living to witness it.

“Before I die, we will see new medicines, new diagnostics, better outcomes for patients burdened by schizophrenia or bipolar illness,” he said. “I will not be happy to die. But I will die happy that my life helped.”

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