

## **SHARED VISION: THREE LIVES CONVERGE TO REVITALIZE MENTAL HEALTH RESEARCH**

As the director of the National Institute of Mental Health (NIMH) from 1996 to 2001, Steven Hyman, a distinguished neuroscientist and psychiatrist, had a front-row seat to one of the most exciting scientific events in recent history.

In 2001, a consortium of scientists published the first draft of the human genome. Hyman knew this had enormous potential to move the field of psychiatry from its decades-long impasse. Already, scientists were trying to find the genetic roots of schizophrenia, bipolar disorder, and other devastating mental illnesses. But progress was painstakingly slow, and as Hyman prepared to leave his NIMH post, he despaired over whether researchers would map out the biological basis of psychiatric disorders in his lifetime.

“We still weren’t making substantive progress,” said Hyman, who now heads the Stanley Center for Psychiatric Research at the Broad Institute of MIT and Harvard. “We needed a new approach if we were serious about finding the genetic roots of these disorders.”

The stakes were — and still are — enormous. Hundreds of millions of people worldwide suffer from psychiatric disorders, and the tolls on individuals, families, and societies are staggering. Yet therapies have virtually remained the same over the past five decades.

Little did Hyman know then that in a few years’ time, the picture would change dramatically thanks to the combined efforts of two other men — philanthropist Ted Stanley and Edward Scolnick, a scientist highly esteemed for his work on cancer genes in the 1970s and his leadership in the pharmaceutical industry. They, too, were also frustrated with the state of things — and they were determined to make a difference.

### **A VISIONARY PHILANTHROPIST**

In the early 1980s, Ted Stanley, who had built a multimillion-dollar business, and his late wife Vada received devastating news that would ignite their passion for the cause of mental health research. Their only child Jonathan was stricken with severe bipolar disorder while in college.

The first few years were difficult, but Jonathan overcame his illness with the help of lithium, a landmark drug first used to treat patients with mental illnesses in 1949. Now a successful attorney, Jonathan is also actively involved in the Treatment Advocacy Center, where he is a founding board member, and the National Alliance on Mental Illness.

While lithium transformed their son’s life, other patients who suffer from mental illness have not been as fortunate. Inspired to help others, Ted and Vada Stanley founded the Stanley Medical Research Institute in 1989 to find treatments that would be as effective for others as lithium had been for their son.

Over the next 15 years, SMRI became one of the largest non-governmental sources of funding for psychiatric research in the United States. But one of the Stanley’s most generous gifts to the psychiatric research community was yet to come.

### **A VISIONARY SCIENTIST**

In the early 2000s, as the plans for what would become the Broad Institute of MIT and Harvard began taking shape, Scolnick was weighing a career change. Scolnick had had a stellar career, first in cancer research in the 1970s and then as one of the most respected scientists in the pharmaceutical industry. As president of Merck Research Laboratories, Scolnick led the development of the first drugs to effectively combat HIV; the first drugs to effectively treat high cholesterol, statins; the first vaccine against cervical cancer; and many other breakthroughs.

Instead of retiring, Scolnick took on a new challenge. In 2004, he joined the Broad Institute to tackle mental illness because he had a deep personal interest in the field. Early in his career, Scolnick had helped launch a revolution in cancer research based on the discovery of the first cancer genes. He wanted to set psychiatric research on the same path.

Scolnick believed that in order to succeed, his program needed to be of a size and scale never before seen in psychiatry. But Scolnick knew he would need a philanthropic partner to make this vision possible.

“We wanted to launch an unprecedented genetics program,” said Scolnick. “Early studies of schizophrenia and bipolar disorder didn’t offer any conclusive genetic evidence. But there were convincing clues that we would ultimately succeed with increased sample size and strategic utilization of genetic sequencing technology.”

Armed with encouraging preliminary data generated by Broad scientists, Scolnick presented the Stanleys with his vision of tackling the genetic basis of psychiatric disorders in a systematic, sustained way — a risky proposal as other researchers had for decades failed to reach this goal.

Scolnick told the Stanleys, “If you want to get at the molecular pathogenesis of these disorders, you’ve got to crack the genetics. That’s what has held this field back for so long.” Scolnick argued for the importance of critical mass — and asked them to contribute \$2 million to launch a program at the Broad Institute.

Ted Stanley initially agreed, and after clear initial progress, called Scolnick back with a new proposal: “Let’s do something bigger. How about we give you \$100 million over 10 years?”

“I was humbled by their generosity and commitment to the cause,” said Scolnick. “We believed in this work, and the Stanleys believed in us. Without them, we would have achieved only a fraction of what we’ve been able to accomplish so far.”

The Broad Institute’s Stanley Center for Psychiatric Research launched in 2007, with Scolnick as its founding director. Within the first year, the Broad team and its international collaborators had collected and genetically-analyzed more than 10,000 schizophrenia samples. The following year, with additional support from the Stanleys, the Stanley Center at the Broad Institute launched an effort to collect and sequence bipolar samples as well.

The research team planned to use genotyping methods to rapidly scan the samples for genetic variants commonly found in populations through an approach known as genome-wide association, or GWAS. This approach had been largely unpopular — many scientists (and funders) believed it had been previously tried for psychiatric disorders and failed. (It has, however, been successfully used to unveil new genetic insights into a range of other common diseases, such as type 2 diabetes and Crohn’s disease.)

Critics predicted it was doomed to fail. But Scolnick and the global collaborators knew they were onto something — working together, they tripled the number of samples in their study. Their hunch has paid off: Over the last two years, Broad scientists have helped identify more than 100 regions of the genome and a

number of specific genes that confer risk for schizophrenia, and significant efforts are ramping up in bipolar disorder, autism, and other conditions.

## **A REINVIGORATED LEADER**

The Stanley Center's launch caught the attention of another prominent scientist dedicated to psychiatric research. Harvard University provost and former NIMH director Hyman had been one of the architects of the Broad Institute. And like Stanley and Scolnick, he was also discouraged by the impasse in the understanding and treatment of psychiatric disorders.

"The painful truth was that we were unable to translate insights from basic neuroscience and behavioral science into treatments," said Hyman. "People suffering from these disorders were waiting for progress, and yet we didn't have a single molecular clue what was causing them. At the time, the tools we needed to make real progress didn't exist."

Convinced that genetics could deliver the needed molecular insights, Hyman initiated several collaborative, unbiased genetic studies of these disorders at NIMH. However, the technologies and analytic tools that existed more than a decade ago were no match for the complexity of these disorders.

Prior to accepting the position at Harvard, while serving as NIMH director, Hyman had the opportunity to meet and work with both Scolnick and future Broad Institute director Eric Lander. Scolnick served as a member of Hyman's National Advisory Mental Health Council from 1998 to 2002, and Lander served as a member of the NIMH Genetics Workgroup. Over time, the three had developed a mutual respect and a shared vision for what was needed in the field.

After five years of steering the Stanley Center, Scolnick wanted to get back into the laboratory, where he could focus on translating the emerging genetics into tangible benefits for patients. In early 2012, Scolnick became chief scientist at the Stanley Center, and Hyman was named director.

Under Hyman's leadership, the Stanley Center's network of collaborators has expanded, yielding an even greater number of patient samples and greater strength in neuroscience. The Stanley Center now contributes a large percentage of the genotyping and sequencing data for the Psychiatric Genomics Consortium (PGC) — the largest collaborative genotyping effort in the history of psychiatry, involving more than 80 institutions in 25 countries. As the effort expands, so, too, have the number of regions in the human genome that have been linked to the risk of schizophrenia.

"The data we're providing puts beyond doubt that schizophrenia is a disorder with biological causes. And it completely vindicates Ted Stanley and Ed Scolnick's initial gamble," said Hyman.

Today, the Stanley Center is at the forefront of psychiatric research. In the next three to five years, the goal is to produce a nearly complete catalog of disease-associated genes for schizophrenia and bipolar disorder. Meanwhile, work is well underway to investigate the biological insights gained from these genetic discoveries, and to translate them into new treatments.

A decade ago, these goals seemed implausible. Today, they are within our reach. None of this would have been possible without the remarkable partnership between three men: Ted Stanley, Ed Scolnick, and Steven Hyman.