Alan I. Green, M.D.: "Glee" club

By Jennifer Durgin

Dr. Alan Green wasn't sure he'd ever get better. He had been gravely ill for several years, and there was no end in sight. As he lay bedridden, Green, now chair of the Department of Psychiatry at Dartmouth, remembers pledging to himself that if he did get well, he was going to pursue a career in research.

Green was a psychiatry resident at the Massachusetts Mental Health Center in Boston in 1974, when he suddenly became ill with a systemic cytomegalovirus (CMV) infection. Most CMV infections lie dormant and never cause problems; in fact, the Centers for Disease Control and Prevention estimates that 50% to 80% of adults are infected with CMV by the age of 40.

But for reasons unknown to Green or his doctors, CMV wreaked havoc in his body—causing high fevers, an enlarged spleen and liver, and anemia. For five years, he was so ill that he could do little more than read and write. Finally, slowly, he started getting better; even so, it took a year and a half before he had recovered sufficient physical strength that he was able to get back to completing his residency.

Green already had some impressive research accomplishments under his belt before he got sick. His interest in doing research had been sparked in San Francisco in 1966. During the summer after his first year of medical school at Johns Hopkins, he shadowed staff at the Langley Porter Psychiatric Institute, affiliated with the University of California at San Francisco. Many of the patients there were being treated for psychiatric problems as a result of using amphetamines, LSD, and other illegal drugs. Before seeing these patients, "I didn't realize that medication could change your personality," Green recalls. "I thought this was fascinating."

Once back at Hopkins, Green worked in a lab that studied chemicals in the brain called neurotransmitters, which amphetamines and other drugs affect. Green got hooked on the research and worked in the lab for the next three years. After medical school and a year of internship at Beth Israel Hospital, he took a research position at the National Institute of Mental Health, studying how morphine affects the brain. Then, in 1971, President Nixon's drug czar, Dr. Jerome Jaffe, recruited Green as his personal assistant.

It wasn't long before Jaffe had promoted Green to be the director of biomedical research within Nixon's Special Action Office for Drug Abuse Prevention. A primary focus of the office was to develop a treatment for heroin addiction, a major problem among soldiers serving in Vietnam. Green worked with private companies to develop various narcotic antagonists, and one of these drugs, naltrexone, eventually made it to market and is now used to treat alcoholism, too.

When Green returned to Boston to start his psychiatry residency at the Harvard-affiliated Massachusetts Mental Health Center (MMHC), it seemed as though he was on the fast track to an ambitious career as a physician-researcher. And then he got sick.

For six and a half years, his life was on hold. Now, when Green talks about that time, it's as if it were just another milepost in the course of his life. Such an experience might have stymied, or at least dampened, the ambition of many people, but not Green.

"That man loves his work," says Dr. Mary Brunette, an associate professor of psychiatry at Dartmouth and medical director for the New Hampshire Bureau of Behavioral Health. Brunette recalls one of the first times she met Green. He was sitting in front of a computer and "giggling with glee about the results of his study," she says. He called her over and said, "Look at these data!"

Green's energy and passion for research have served him well. Once he was able to return to MMHC to finish his residency, his career took off again. He spent the next 20 years there, in various clinical, research, and leadership roles. He built up MMHC's Commonwealth Research Center, whose mission is "to stimulate research on the biological basis of psychosis and the optimal treatment for severe mental illness." And he fell in love with a line of research that has led to some key discoveries about schizophrenia and what's known as the brain reward circuitry.

Grew up: South Norwalk, Conn.

Education: Columbia College '65 (A.B. in history), Johns Hopkins University School of Medicine '69 (M.D.)

Training: Beth Israel Hospital, Boston, Mass.; Massachusetts Mental Health Center

Earliest jobs: Counting cars for a traffic survey, lifeguarding, and selling encyclopedias

Little-known fact: Helped set up a Head Start program in Mississippi in 1965

Family: Wife Franny Cohen, a trial lawyer in Boston, and 14-year-old twins, Isobel and Henry, both students at Milton (Mass.) Academy

Musical interests: Plays the piano and guitar

What he did while he was bedridden: Listened to baseball games; wrote a novel about a scientist who gets sick; and read a lot, including novels by Charles Dickens and William Makepeace Thackeray and books "about people . . . confined against their will," such as Thomas Mann's *Magic Mountain*

"That man loves his work," says a colleague, who recalls Green "giggling with glee" about some study data.

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MARK WASHBURN

Green has seen both ups and downs in his life. Now recognized internationally for his research on schizophrenia, he spent five years in the 1970s so ill he was bedridden.

In 2002, Green left MMHC and Harvard to become chair of the Department of Psychiatry at Dartmouth. He decided to take "the opportunity to create something of real greatness," he says. "The ingredients were all here. This is a wonderful department of psychiatry . . . [and] it has this ability to influence the care of people in a whole region. . . . The care in Boston is more Balkanized."

Green points to a sprawling chart showing all the connections that DMS's psychiatry department has with research groups and health-care institutions, both at Dartmouth and throughout the region. Members of the department's faculty care for patients at DHMC, as well as at the VA Medical Center in White River Junction, Vt.; at the state psychiatric hospitals for New Hampshire and Maine; and at West Central Behavioral Health in Lebanon, N.H., an outpatient mental health services clinic. In addition, the department has training and research affiliations with three other VA medical centers—in Maine, New Hampshire, and Massachusetts—as well as research collaborations with numerous institutions throughout the country.

Among the more than 130 faculty in the department are some of the nation's top experts in co-occurring disorders (the combination of a severe mental illness with a substance-abuse disorder); posttraumatic stress disorder; traumatic brain injuries; and sleep disorders. Managing such a diverse and influential department is an all-consuming job, so Green now does his own research "around the edges," as he puts it. "It's been possible for me to have a large administrative job and continue to do research . . . because I have a number of terrific people working with me."

Green's primary research interest has been a drug called clozapine, a highly effective but also highly toxic treatment for schizophrenia. Clozapine was studied in the late 1960s and early 1970s, Green explains, but was taken off the market because of its side effects. Then in the late 1980s, studies showed that clozapine was more effective than any other antipsychotic in treating schizophrenia, and the Food and Drug Administration approved it for use in patients who did not respond to any other drugs.

"I became preoccupied with the idea," says Green. "Why does this drug work? Why is it better than the other ones?" He and his collaborators discovered that clozapine caused the levels of norepinephrine, a neurotransmitter, to skyrocket. "That has sort of puzzled me for the last 15 years," says Green. "I have been trying to understand what does that and how is that related to the effects of clozapine."

A major piece of the clozapine puzzle fell into place as a result of a lab meeting when Green was still at MMHC. He and his colleagues were discussing the fact that half of the patients who wanted to enroll in a trial had to be excluded because of substance abuse. One of the lab technicians raised her hand. "She said to me," Green recalls, "'Alan, have you ever thought about maybe trying to understand why it is that people with schizophrenia have so much substance abuse?" He hadn't. "Maybe we should study those patients," she suggested.

So Green started reading about substance abuse and schizophrenia. He then asked some of the nurses at MMHC if clozapine seemed to affect patients' alcoholism or other addictions. "Well, you know," Green recalls their telling him, "it might be helpful."

One day, he shared some of these budding ideas in a lecture, and not long after that he got a call from a colleague. "We have two patients over here who had been put on clozapine who had longtime, long-standing problems with alcohol [and] who stopped using alcohol," Green recalls the colleague telling him. Soon other providers began sharing similar anecdotes.

That impelled Green to contact Dr. Robert Drake, a psychiatrist at Dartmouth who is acclaimed for his work studying and developing treatments for people who suffer from both severe mental illness and

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addiction. Drake shared with Green some data that he had on patients with schizophrenia who had taken clozapine.

"We looked back and found that, in fact, those who had been put on clozapine had a dramatic decrease in alcohol abuse compared to those who hadn't," observes Green. Those initial findings led him to pursue a whole series of studies about clozapine, which, in turn, helped him to piece together his central theory about schizophrenia and substance abuse.

"Schizophrenia itself," he explains, "is a disorder that is associated with certain brain abnormalities . . . in the area of the brain that, among other things, regulates brain reward circuitry—the [system] that perhaps allows us to appreciate things in the world.

"Drugs of abuse all work through this circuit," Green continues. "Maybe the circuit is faulty in people with schizophrenia . . . and the drugs of abuse may make them transiently better even though, over time, it makes the disease much worse."

For the past several years, Green has been exploring this theory by doing brain-imaging studies. At the same time, he and his lab have been "trying to take clozapine apart," he explains, "take the pharmacologic actions of the drug apart and then add them back together to see if we can create a clozapine-like drug [that] would be safer."

When Green reflects on his career, he chuckles at how his interests have come full circle. It was seeing patients who had experienced bad reactions to illicit drugs that first sparked his interest in the inner workings of the brain. Then, he muses, "I had nothing to do with substance abuse for years. And before you know it, I'm back in the field of substance abuse."

Although his research interests may have followed a circuitous path, his compassion for people with chronic mental illness has been constant—in part because of his own struggle to get well. "I had a chronic illness . . . and I didn't know whether I was going to get better," he recalls.

But fortunately for him—and for those who suffer from schizophrenia and addictions—he did. ■