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SCIENCE

Blazing Trails in Brain Science

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Profiles in Science

By **BENEDICT CAREY**

BETHESDA, Md. — The police arrived at the house just after breakfast, dressed in full riot gear, and set up a perimeter at the front and back. Not long after, animal rights marchers began filling the street: scores of people, young and old, yelling accusations of murder and abuse, invoking Hitler, as neighbors stepped out onto their porches and stared.

It was 1997, in Decatur, Ga. The demonstrators had clashed with the police that week, at the Yerkes National Primate Research Center at nearby Emory University, but this time, they were paying a personal call — on the house of the center's director, inside with his wife and two teenage children.

“I think it affected the three of them more than it did me, honestly,” said Dr. Thomas R. Insel, shaking his head at the memory. “But the university insisted on moving all of us to a safe place for a few days, to an ‘undisclosed location.’

“I’ll say this. I learned that if you’re going to take a stand, you’re going to make some people really angry — so you’d better believe in what you’re doing, and believe it completely.”

For the past 11 years, Dr. Insel, a 62-year-old brain scientist, has run an equally contentious but far more influential outfit: the National Institute of Mental Health, the world’s leading backer of behavioral health research.

The job comes with risk as well as power. Patient groups and scientists continually question the agency’s priorities, and politicians occasionally snipe at its decisions. Two previous directors resigned in the wake of inflammatory statements (one on marijuana laws, one comparing urban neighborhoods to jungles), and another stepped down after repeatedly objecting to White House decisions.

Dr. Insel has not merely survived; he is the longest-serving director since Dr. Robert H. Felix, the agency’s founder, retired almost a half-century ago. His tenure stretches over three presidencies and, more important, coincides with a top-down overhaul in the substance and direction of behavioral science.

The extent of this remodeling is not widely understood outside scientific circles nor universally appreciated within them. But in recent months, its author has begun to reveal his instincts publicly, in blog posts and speeches. Last summer, he questioned whether people with schizophrenia should remain indefinitely on antipsychotic medications — a shot at accepted medical wisdom.

A few months earlier, he had called out psychiatry’s diagnostic encyclopedia, the D.S.M.-5, as “not scientifically

valid," weeks before a new edition was released. Psychiatrists were not happy, and they told him so. Days later, he issued a statement saying that the manual was the best "currently available," if imperfect.

For anyone with a psychiatric diagnosis, or a family member with one, Dr. Insel's long, twisting career and the convictions it has fostered provide a guided tour through behavior science: where it has been, where it's going and why.

The story is neither predictable nor probable, at least by the standards of Washington officialdom. It is less a tale of perseverance than one of restless curiosity — of ascending the trail by straying off it, repeatedly and without approval.

The Young Doctor

The first time he walked away was from premedical studies.

Dr. H. Herman Insel, an eye surgeon in Dayton, Ohio, and his wife, Ruth, a social worker, were determined that all four of their boys get a medical education, and the first three went fairly smoothly. The last one out of the house, the Eagle Scout who collected insects and snakes and filled the basement with aquariums, was ahead of the program, if anything.

At the age of 15, Tom Insel had entered the prestigious six-year B.A.-M.D. program at Boston University. But two years in, the boy wanted out. He decided it was time to step off the treadmill and see the world.

"My father didn't want me going anywhere, and I was too young to be drafted for Vietnam," Dr. Insel said in a recent interview at his office here. "I told him, 'O.K., so how about I go to Hanoi? They could use some help there.' "

The two reached a compromise, and the son spent six months backpacking around the world, stopping to work in a tuberculosis clinic in Hong Kong and at a mission hospital in Bihar, India. The experiences brought him full circle, back to medicine and to Boston, where he completed the M.D. program in 1974. “I was sure I was going to be a doctor of global health or tropical medicine in some underdeveloped country,” he said.

Instead, he found an untamed world closer to home: psychiatry, which in the 1970s was ruled by a cabal of Freudian theorists and lacked a scientific infrastructure. After a graduate course at Stanford, followed by an internship and residency in psychiatry, he landed a position in the mental health institute’s in-house research branch, known as the intramural program.

There he embarked on another kind of walkabout, this time studying the effect of an early antidepressant drug in people with obsessive-compulsive disorder. In a series of studies, he and a senior colleague, Dr. Dennis Murphy, showed that the drug soothed people’s symptoms within weeks, much faster than standard psychotherapy.

The results had the opposite effect on many old-school psychiatrists. “Obsessive-compulsive neurosis,” as it was known then, was a specialty of Freudian analysts, and here was some upstart barely out of school saying he’d discovered a better, faster form of treatment.

He wasn’t yet 30 years old. “I don’t think it helped that I still looked like I was 17,” Dr. Insel said.

The pendulum has swung so far toward drug therapy in recent years that it is hard to recapture how disruptive those 1980s studies were. Dr. Insel’s work and that of many others, testing the effect of new medications, would turn the field away from long-term talking cures and increasingly toward medication and short-term behavior therapies rooted in the same kind of randomized, controlled trials conducted in other fields of medicine. (Today, psychiatrists

often treat O.C.D. with short-term cognitive therapy, complemented by antidepressant medication.)

Any young investigator at the forefront of such a shift was bound to feel a professional updraft, and Dr. Insel was soon fielding offers from universities trying to build a psychiatric research department.

At an age when most young scientists are scrambling for a foothold, a mentor and a viable project, his path was all but set. He and his wife, Deborah, a writer, had two young children and every reason to grab for longer-term stability.

Instead, they passed. Again, Dr. Insel abandoned course in midstride, taking a year's sabbatical to study basic neuroscience.

"I just wanted to try something else," he said. "I got bored, that's really what it was."

The Biology of Love

He also lost his job.

In 1985, returning to the mental health institute after his year away, he began studying tiny mouselike rodents called voles in an effort to understand the biology of attachment. This project was a long way from O.C.D., and to many others in the field, it seemed like the brain-science equivalent of backpacking to Hanoi.

"No one told me at the time that it was pointless to try to reduce a complex social behavior like pair bonding to neural biology, so I didn't know any better," Dr. Insel said. "I just assumed we could do it and started looking for the best model."

He settled on voles for a good reason. One species, the prairie vole, is monogamous; it forms long-term pair bonds after mating. Another, the montane vole, is polygamous; it mates and moves on. The two species are closely related, so the difference in their behavior might be rooted in some discrete neural process that could be isolated, Dr. Insel argued.

In a series of studies in the late 1980s and early 1990s, his team showed just that: Injections of a protein called vasopressin induced monogamous bonding in male prairie voles even when the animals didn't mate. Likewise, blocking the action of the protein prevented the post-mating bond that usually formed. Injections of the hormone oxytocin prompted similar bonding instincts in female prairie voles.

In a paper published in the journal Nature in 1993, Dr. Insel's group reported that vasopressin is "both necessary and sufficient for selective aggression and partner preference formation, two critical features of pair bonding in the monogamous prairie vole."

The paper was widely reported, and again put the mental health institute in the vanguard of a new area of research. But the agency was changing emphasis, phasing out its research into social behaviors. Dr. Michael Brownstein, the scientific director at the time, politely instructed his young research star to find another project — or another job. (The two are now good friends.)

He chose Door No. 2, and it took all of three months. Emory University was looking to replace the director of the Yerkes primate center, who was about to retire, and Dr. Insel was at the top of their list. He had already run a lab, as chief of the neurobiology division of the mental health institute, and his work with voles would diversify Yerkes's portfolio, which then was focused on studying H.I.V. in primates.

He packed up his family and his voles, and moved south. “Acclaimed Researcher to Head Yerkes Center,” read the headline in The Atlanta Journal-Constitution on Aug. 20, 1994, the day the hiring was announced. “All I know is I had to go out and buy my first tie,” is how Dr. Insel tells it.

He quickly expanded rodent research at the center and also deepened his own work on the biology of attachment, with the help of an Emory postdoctoral student, Larry Young, who has since extended the research on his own. The work with voles effectively scotched the assumption that a complex behavior could not be reduced to brain biology. Oxytocin and vasopressin are now a focus of intense interest as possible modulators of social behaviors in other species, though the effects of such proteins are still a matter of debate.

His necktie came in handy at Yerkes. Between the march on his home in Decatur and other crises, the “psychiatrist who became a bench scientist,” as he has described himself, took on yet another role: He became a public official.

He was comfortable in front of audiences, relaxed with the news media, and willing to see at-home protests as part of the job, nothing to lose sleep over. The precociousness was long gone. By 2000, he had some well-tailored suits to go with his ties, a commanding view over his field, and some strong beliefs about how to improve its infrastructure.

All of which made him “the natural choice” for the mental health institute’s director, in the words of Dr. Elias Zerhouni, then director of National Institutes of Health who hired him for the job in 2002, citing his “ability to communicate a compelling vision for mental health research, his outstanding scientific record, and his proven leadership skills.”

The Path Ahead

In one way, it was a homecoming, a return to Washington and to the National Institute of Mental Health, where he'd made a name for himself. In a more consequential sense, however, Dr. Insel's arrival as director signaled yet another departure, this one far larger than just about anyone could have anticipated. Dr. Insel has sharply shifted the agency's focus — to basic neuroscience and genetics, at the expense of the very type of behavioral research he himself had once done. That change has generated a mix of optimism and outrage.

"I met Tom when he came in, and my expectations were low," said Dr. E. Fuller Torrey, of the Stanley Medical Research Institute, a nonprofit supporting research in schizophrenia and bipolar disorder, and a longtime critic of the mental health institute. "He was a bench scientist, and I frankly doubted that he had the political skills to be an effective director or had a strong commitment to serious mental illness.

"I was wrong on both counts. I think he's the best director we've had."

Others strongly disagree. "Instead of being an institute of mental health, he has made it almost exclusively a brain research institute," Dr. Allen Frances, an emeritus professor of psychiatry at Duke and the author of the book "Saving Normal," wrote in an email. "N.I.M.H. is betting the house on the long shot that neuroscience will come up with answers to help people with serious mental illness." He added, "It does little or no psychosocial or health services research that might relieve the current suffering of patients."

Dr. Insel says the agency does in fact support some psychosocial research — testing new services for people with schizophrenia, for instance — but does not deny that its primary mission is biological. Still, he has generally been spared such sharp public criticism, perhaps because many have confused a reflexively earnest good nature with an

easily compromising one.

“He’s been able to use the bully pulpit without being a bully, without being offensive,” said Dr. Steven E. Hyman of the Broad Institute at M.I.T. and Harvard. Dr. Hyman was Dr. Insel’s predecessor as director of the mental health institute; the two share most scientific instincts and speak regularly.

“It’s not something I was particularly good at,” he went on. “They kept giving me media training, and it never stuck.”

That open-minded nature can mask two stubborn convictions. One is that the previous generation of biological research in psychiatry has been largely a disappointment, both in advancing basic science and in improving lives.

Yes, the revolution in pharmacology (in which he played a role) gave doctors more drugs to use, allowing millions of people to reduce their symptoms. Yet the overall impact of this drug revolution on public health has been mixed, and decades of research on the drugs’ mechanisms — on serotonin, for example, the target of antidepressant drugs like Prozac — has taught scientists nothing about the causes of mental illness.

The same is true of most research using “animal models,” in which scientists try to create psychiatric problems in animals and study them.

“We’ve had this huge increase in the use of all interventions, a 250 percent increase in use of antipsychotics, without any change in the morbidity or mortality in people with mental disorders; it hasn’t budged,” Dr. Insel said. “If that were the case for cancer, there’d be an outcry for more research, money and new priorities.”

In a blog post in August, he questioned the wisdom of long-term drug treatment for people with schizophrenia,

writing, “We need to ask whether in the long term some individuals with a history of psychosis may do better off medication.” The post became an overnight sensation among patient advocates who had been making the same case for decades.

His second stubborn conviction is that the only way to build a real psychiatric science is from first principles — from genes and brain biology, as opposed to identifying symptom clusters. Some of the mental health institute’s largest outlays under Dr. Insel have been to support projects that, biologically speaking, are like mapping the ocean floor.

One is the Psychiatric Genomics Consortium, a far-flung group of top research centers that share data and analysis, based at the lab of Dr. Patrick F. Sullivan at the University of North Carolina. The other is the Human Connectome Project, a $40 million, five-year program to build a baseline database for brain structure and activity using M.R.I. imaging.

In April, when in a blog post Dr. Insel wrote that the D.S.M.-5, was “at best a dictionary” and lacked scientific validity, he wasn’t exaggerating for effect. He had to qualify his comments because he doesn’t yet have a replacement. But he is determined to remake psychiatric diagnosis entirely and has set up an alternative framework for doing so, called the Research Domain Criteria — RDoC, for short — to be built from the ground up, on genetic findings.

“My philosophy is really based on humility,” he said. “I don’t think we know enough to fix either diagnostics or therapeutics. The future of psychiatry is clinical neuroscience, based on a much deeper understanding of the brain.”

That future may feel too far away for many patients, as well as many scientists. But this is one path Dr. Insel is not likely to wander from, no matter who disapproves.

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