New Head of Drug Institute Is Wired for Action

The director of the National Institute on Drug Abuse settles into the job with images of addicted brains in mind

BETHESDA, MARYLAND—Nora Volkow knows precisely what makes her happy. "I love music. I love the high of running. I love intellectual concepts." An afternoon nap, a few glasses of wine, and a sedative are not on the list. "I don't like to be too relaxed or too calm. It's aversive for me."

Such preferences, Volkow believes, are hardwired into the parts of our brains involved in pleasure and reward. And they help explain why some people become addicted to drugs and others don't. For 20 years, Volkow, a psychiatrist born in Mexico, has used brain-imaging techniques to study addictive behaviors, finding common threads among an addict's craving for cocaine and an obese person's desire for food. Now these findings are guiding her as she takes the helm of the National Institute on Drug Abuse (NIDA), the $962 million agency of the National Institutes of Health (NIH) that leads the nation's research on addiction.

Volkow is a dynamo who churned out papers—more than 275, at last count—and built a top brain-imaging research group at Brookhaven National Laboratory on Long Island before coming to NIH. "You really have to be in the field to appreciate how productive she's been," says psychiatrist Charles O'Brien of the University of Pennsylvania in Philadelphia. Colleagues also praise Volkow's people skills and her charm. "It is a major coup that we now have her as the head of NIDA," says neuroscientist Hans Breiter of Massachusetts General Hospital in Boston.

After 2 months at NIDA, Volkow met with *Science* last week in her office, where African statues and Mexican painted cows brighten bookshelves and abstract paintings wait to be hung. She is still adjusting to the new job. Its many demands mean that her time is now broken into "30-minute chunks" instead of hours. But she says that using NIDA's resources to bring addiction research to the public is "very rewarding."

Volkow, 47, is the great-granddaughter of exiled Russian revolutionary Leon Trotsky, who found asylum in Mexico and was assassinated there in 1940. She grew up in Trotsky's house in Mexico City, although the main rooms were only for studying because her father wanted to keep "everything as it was." It eventually became a museum. At the medical school of the National Autonomous University of Mexico, she did her first animal experiment, showing that a water-deprived monkey would push a lever far more insistently for a sip of water than it would for drugs. One weekend, she broke down and gave the despondent animal water. She says she realized then that because she is so compelled to help any living thing "in distress," she cannot work directly with animals.

While in medical school, Volkow read an article in *Scientific American* on early positron emission tomography (PET) scan brain-imaging experiments at Brookhaven. The notion that PET could peer into the living brain "blew my mind," she says. En route to a Ph.D. program at the Massachusetts Institute of Technology in Cambridge, she "got diverted" by 6 months of research at New York University (NYU), which had a joint program with the Brookhaven imaging group. Fascinated by the work, she opted for a residency in psychiatry at NYU instead.

Mind reader. Nora Volkow's pioneering work on using brain imaging to study addiction made her a natural choice to guide NIDA.

In those early days of PET, Volkow used the technique to probe the brain activity patterns of schizophrenia. In the later stage of the disease, when patients are no longer hallucinogenic but instead apathetic, activity is reduced in the orbitofrontal cortex, the part of the brain just above the eyes. Her team suggested that the neuroleptic drugs given to patients led to this erosion of activity by blocking signaling of dopamine, the neurotransmitter that triggers feelings of motivation and pleasure.

Next Volkow turned to another kind of patient: people addicted to cocaine. As an assistant professor at the University of Texas, Austin, in 1985, she saw tiny hemorrhages where the blood supply was cut off in the brains of these addicts, indicating that the drug was triggering strokes. "This was a shock. Most people believed that cocaine was a safe drug," she says.

Volkow quickly moved on to a new line of inquiry, looking for commonalties among addictions, whether to drugs, alcohol, or even food. By then she was back at Brookhaven, where her team found that addicts have fewer dopamine receptors in their brain and that these decreases are linked to less activity in the orbitofrontal cortex than in normal people. This reduced activity may help explain why addicts turn to dopamine-simulating substances to achieve a sense of well-being. And obese people have fewer dopamine receptors as well (*Science*, 2 November 2001, p. 980). Although heavy drug use erodes dopamine receptors, some people are probably primed to become addicts because they start with lower levels, Volkow says. This research has helped shape a consensus articulated by Volkow's predecessor as NIDA director, Alan Leshner—now CEO of the American Association for the Advancement of Science and executive publisher of *Science*—that addiction is a brain disease.

Now the question in Volkow's mind is: If many addictions involve a lack of dopamine receptors, why don't all addicts crave the same thing? She and Brookhaven co-worker Gene-Jack Wang have found a few clues. Obese people have higher-than-normal activity in parts of the brain that process the taste and feel of food. Alcoholics, they've found, hate being given a stimulant, just as people addicted to stimulants can't stand drugs that slow them down.

Volkow has produced this work with a Brookhaven team that she and chemist Joanna Fowler built into "one of the best PET centers in the country for studies of addiction and other psychiatric disorders," says Eric Nestler of the University of Texas Southwestern Medical Center in Dallas. She also moved up the management ladder there, despite obstacles; at one point, she says, her all-male peers recommended against her chairing the medical de-

CREDIT: RICK KOZAK

partment at Brookhaven. Four years ago, she was named associate director for life sciences, one of the four science divisions at the lab.

Her leadership in addiction research, both clinical and basic, made her an obvious choice for the NIDA directorship, she and others say. But taking the job was "by far the hardest decision I've ever made in my life," because it meant devoting less time to her research, she says.

She inherits an institute in good shape, observers say; Leshner moved it from an outdated focus on drugs to a molecular approach and also created a clinical network to help move new treatments into practice. Volkow's priorities include expanding research on prevention and treatment, such as the neurobiology of why some young brains are more vulnerable to addiction and social science research on strategies to nudge children and young adults away from drugs.

The just-completed 5-year doubling of NIH's budget has put the field of addiction research in good stead, she says. Slower-growing budgets may put a crimp on new areas, but the key now, Volkow says, is to forge collaborations with other institutions within NIH to bring together researchers interested in brain development, for instance.

Volkow expects to keep her own research going; she will have a lab at the National Institute on Alcohol Abuse and Alcoholism that will collaborate with her Brookhaven team, and she will fly up to Long Island one weekend a month. Colleagues expect her to go at both jobs with her trademark verve. She's a workaholic, she admits, but that's just the way she is—her brain is wired that way.

–JOCELYN KAISER

Neuroscience

Insulin Insults May Spur Alzheimer's Disease

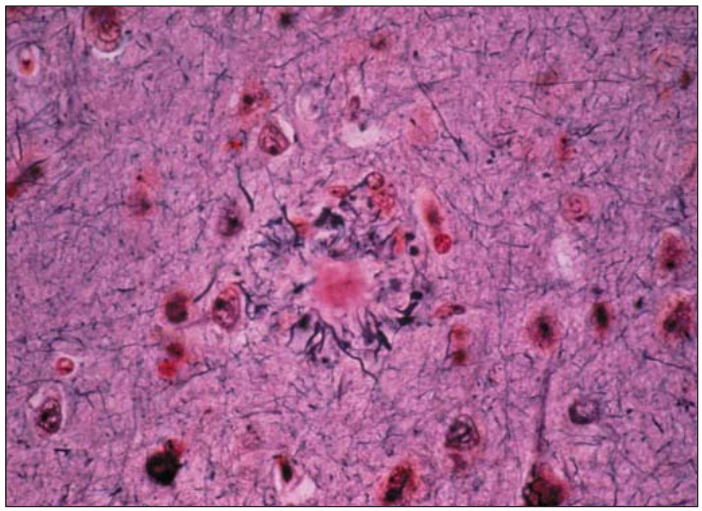
The hormone hogs the attention of an enzyme that would otherwise escort an Alzheimer's protein out of the brain

Neuroscientists in the making could once learn their craft without worrying much about anything below the neck. But those days are over—particularly when it comes to Alzheimer's disease. Over the past few years, evidence has accumulated that pancreatic control of the hormone insulin may play an important role in the genesis of the disease. Excess insulin, some suggest, may help litter the brain with senile plaques.

Two recent lines of research have cast excess insulin in a dark light. One springs from research on the accumulation in the brain of β amyloid, a peptide thought to be the active ingredient in most Alzheimer's disease pathology. Animal experiments suggest that β amyloid is normally cleared from the brain quickly and efficiently. The latest evidence suggests that a dysfunction in the enzymes responsible for that maintenance might result in overaccumulation of β amyloid (*Science*, 25 May 2001, p. 1468).

The second line of research has followed from the realization that insulin, a hormone better known for its role in controlling blood glucose levels and fatty acid storage, also plays a major role in memory and cognition. Over the past decade, neuroscientists have demonstrated that insulin seems to promote neuronal health and that raising insulin levels, in the short term, at least, enhances mental prowess. The flip side of that research has suggested that some dysfunction in insulin signaling contributes to the cognitive deficits apparent in Alzheimer's (*Science*, 24 April 1998, p. 517).

These lines of evidence converge in a small study in the 24 June issue of *Neurology*. Boosting insulin levels in human subjects increases β amyloid in the cerebrospinal fluid, reports a team led by neuroscientist Suzanne Craft of the Veterans Affairs (VA) Puget Sound Medical Center and the University of Washington in Seattle. The study suggests that chronically high insulin levels—known in the lingo as hyperinsulinemia—may cause the accumulation of β amyloid in the brain and, in so doing, play a primary role in the etiology of Alzheimer's.



Gumming up the brain. β amyloid is the active ingredient in senile plaques, a defining characteristic of Alzheimer's disease.

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Insulin appears to boost β amyloid by monopolizing the attention of an enzyme that degrades and clears them both. Research in cell cultures, animals, and now humans suggests that insulin competes with the Alzheimer's protein for insulin-degrading enzyme (IDE), also known as insulysin. The catch is that IDE seems to have a strong preference for insulin over β amyloid. So the more insulin, by this scenario, the less IDE is available to clean up β amyloid, leaving the peptide to clump into plaques. Circumstantial evidence from genetic studies also implicates IDE in Alzheimer's: The gene resides within a region of chromosome 10 that has been linked to an increased risk of the disease.

Abnormally high insulin levels have been associated for decades with heart disease and obesity, says Craft; now they've been implicated in dementia as well. "Insulin has so many beneficial functions. But when insulin is secreted in higher amounts, or when it hangs around for long periods of time, that's when the problems begin to occur."

Double the risk

The first troubling signs that insulin might play some role in Alzheimer's emerged from epidemiological studies revealing that patients with type II diabetes seem to have an increased risk of Alzheimer's disease—although researchers point out that diabetics are likely to suffer from a constellation of problems that might increase the risk of dementia, including heart disease. Type II diabetes is characterized by high levels of insulin circulating in the blood and by insulin resistance—liver and muscle cells, in particular, don't respond well to the hormone and require extra insulin before allowing glucose to enter. One 1997 study from the Mayo