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ADDICTED

WHY DO PEOPLE GET HOOKED? MOUNTING EVIDENCE POINTS TO A POWERFUL BRAIN CHEMICAL CALLED DOPAMINE

BY J. MADELEINE NASH

Imagine you are taking a slug of whiskey. a puff of a cigarette. A toke of marijuana. A snort of cocaine. A shot of heroin. Put aside whether these drugs are legal or illegal. Concentrate, for now, on the chemistry. The moment you take that slug, that puff, that toke, that snort, that shot, trillions of potent molecules surge through your bloodstream and into your brain. Once there, they set off a cascade of chemical and electrical events, a kind of neurological chain reaction that ricochets around the skull and rearranges the interior reality of the mind.

Given the complexity of these events--and the inner workings of the mind in general--it's not surprising that scientists have struggled mightily to make sense of the mechanisms of addiction. Why do certain substances have the power to make us feel so good (at least at first)? Why do some people fall so easily into the thrall of alcohol, cocaine, nicotine and other addictive substances, while others can, literally, take them or leave them?

The answer, many scientists are convinced, may be simpler than anyone has dared imagine. What ties all these mood-altering drugs together, they say, is a remarkable ability to elevate levels of a common substance in the brain called dopamine. In fact, so overwhelming has evidence of the link between dopamine and drugs of abuse become that the distinction (pushed primarily by the tobacco industry and its supporters) between substances that are addictive and those that are merely habit-forming has very nearly been swept away.

The Liggett Group, smallest of the U.S.'s Big Five cigarette makers, broke ranks in March and conceded not only that tobacco is addictive but also that the company has known it all along. While RJR Nabisco and the others continue to battle in

the courts--insisting that smokers are not hooked, just exercising free choice--their denials ring increasingly hollow in the face of the growing weight of evidence. Over the past year, several scientific groups have made the case that in dopamine-rich areas of the brain, nicotine behaves remarkably like cocaine. And late last week a federal judge ruled for the first time that the Food and Drug Administration has the right to regulate tobacco as a drug and cigarettes as drug-delivery devices.

Now, a team of researchers led by psychiatrist Dr. Nora Volkow of the Brookhaven National Laboratory in New York has published the strongest evidence to date that the surge of dopamine in addicts' brains is what triggers a cocaine high. In last week's edition of the journal *Nature* they described how powerful brain-imaging technology can be used to track the rise of dopamine and link it to feelings of euphoria.

Like serotonin (the brain chemical affected by such antidepressants as Prozac), dopamine is a neurotransmitter--a molecule that ferries messages from one neuron within the brain to another. Serotonin is associated with feelings of sadness and well-being, dopamine with pleasure and elation. Dopamine can be elevated by a hug, a kiss, a word of praise or a winning poker hand--as well as by the potent pleasures that come from drugs.

The idea that a single chemical could be associated with everything from snorting cocaine and smoking tobacco to getting good grades and enjoying sex has electrified scientists and changed the way they look at a wide range of dependencies, chemical and otherwise. Dopamine, they now believe, is not just a chemical that transmits pleasure signals but may, in fact, be the master molecule of addiction.

This is not to say dopamine is the only chemical involved or that the deranged thought processes that mark chronic drug abuse are due to dopamine alone. The brain is subtler than that. Drugs modulate the activity of a variety of brain chemicals, each of which intersects with many others. "Drugs are like sledgehammers," observes Dr. Eric Nestler of the Yale University School of Medicine. "They profoundly alter many pathways."

Nevertheless, the realization that dopamine may be a common end point of all those pathways represents a signal advance. Provocative, controversial, unquestionably incomplete, the dopamine hypothesis provides a basic framework for understanding how a genetically encoded trait--such as a tendency to produce too little dopamine--might intersect with environmental influences to create a serious behavioral disorder. Therapists have long known of patients who, in addition to having psychological problems, abuse drugs as well. Could their drug problems be linked to some inborn quirk? Might an inability to absorb enough dopamine, with its pleasure-giving properties, cause them to seek gratification in drugs?

Such speculation is controversial, for it suggests that broad swaths of the population may be genetically predisposed to drug abuse. What is not controversial is that the social cost of drug abuse, whatever its cause, is enormous. Cigarettes contribute to the death toll from cancer and heart disease. Alcohol is the leading cause of domestic violence and highway deaths. The needles used to inject heroin and cocaine are spreading aids. Directly or indirectly, addiction to drugs, cigarettes and alcohol is thought to account for a third of all hospital admissions, a quarter of all deaths and a majority of serious crimes. In the U.S. alone the combined medical and social costs of drug abuse are believed to exceed \$240 billion.

For nearly a quarter-century the U.S. has been waging a war on drugs, with little apparent success. As scientists learn more about how dopamine works (and how drugs work on it), the evidence suggests that we may be fighting the wrong battle. Americans tend to think of drug addiction as a failure of character. But this stereotype is beginning to give way to the recognition that drug dependence has a clear biological basis. "Addiction," declares Brookhaven's Volkow, "is a disorder of the brain no different from other forms of mental illness."

That new insight may be the dopamine hypothesis' most important contribution in the fight against drugs. It completes the loop between the mechanism of addiction and programs for treatment. And it raises hope for more effective therapies. Abstinence, if maintained, not only halts the physical and psychological damage wrought by drugs but in large measure also reverses it.

Genes and social forces may conspire to turn people into addicts but do not doom them to remain so. Consider the case of Rafael Rios, who grew up in a housing project in New York City's drug-infested South Bronx. For 18 years, until he turned 31, Rios, whose father died of alcoholism, led a double life. He graduated from Harvard Law School and joined a prestigious Chicago law firm. Yet all the while he was secretly visiting a shooting gallery once a day. His favored concoction: heroin spiked with a jolt of cocaine. Ten years ago, Rios succeeded in kicking his habit--for good, he hopes. He is now executive director of A Safe Haven, a Chicago-based chain of residential facilities for recovering addicts.

How central is dopamine's role in this familiar morality play? Scientists are still trying to sort that out. It is no accident, they say, that people are attracted to drugs. The major drugs of abuse, whether depressants like heroin or stimulants like cocaine, mimic the structure of neurotransmitters, the most mind-bending chemicals nature has ever concocted. Neurotransmitters underlie every thought and emotion, memory and learning; they carry the signals between all the nerve cells, or neurons, in the brain. Among some 50 neurotransmitters discovered to date, a good half a dozen, including dopamine, are known to play a role in addiction.

The neurons that produce this molecular messenger are surprisingly rare. Clustered in loose knots buried deep in the brain, they number a few tens of

thousands of nerve cells out of an estimated total of 100 billion. But through long, wire-like projections known as axons, these cells influence neurological activity in many regions, including the nucleus accumbens, the primitive structure that is one of the brain's key pleasure centers. At a purely chemical level, every experience humans find enjoyable--whether listening to music, embracing a lover or savoring chocolate--amounts to little more than an explosion of dopamine in the nucleus accumbens, as exhilarating and ephemeral as a firecracker.

Dopamine, like most biologically important molecules, must be kept within strict bounds. Too little dopamine in certain areas of the brain triggers the tremors and paralysis of Parkinson's disease. Too much causes the hallucinations and bizarre thoughts of schizophrenia. A breakthrough in addiction research came in 1975, when psychologists Roy Wise and Robert Yokel at Concordia University in Montreal reported on the remarkable behavior of some drug-addicted rats. One day the animals were placidly dispensing cocaine and amphetamines to themselves by pressing a lever attached to their cages. The next they were angrily banging at the lever like someone trying to summon a stalled elevator. The reason? The scientists had injected the rats with a drug that blocked the action of dopamine.

In the years since, evidence linking dopamine to drugs has mounted. Amphetamines stimulate dopamine-producing cells to pump out more of the chemical. Cocaine keeps dopamine levels high by inhibiting the activity of a transporter molecule that would ordinarily ferry dopamine back into the cells that produce it. Nicotine, heroin and alcohol trigger a complex chemical cascade that raises dopamine levels. And a still unknown chemical in cigarette smoke, a group led by Brookhaven chemist Joanna Fowler reported last year, may extend the activity of dopamine by blocking a mopping-up enzyme, called MAO B, that would otherwise destroy it.

The evidence that Volkow and her colleagues present in the current issue of *Nature* suggests that dopamine is directly responsible for the exhilarating rush that reinforces the desire to take drugs, at least in cocaine addicts. In all, 17 users participated in the study, says Volkow, and they experienced a high whose intensity was directly related to how extensively cocaine tied up available binding sites on the molecules that transport dopamine around the brain. To produce any high at all, she and her colleagues found, cocaine had to occupy at least 47% of these sites; the "best" results occurred when it took over 60% to 80% of the sites, effectively preventing the transporters from latching onto dopamine and spiriting it out of circulation.

Scientists believe the dopamine system arose very early in the course of animal evolution because it reinforces behaviors so essential to survival. "If it were not for the fact that sex is pleasurable," observes Charles Schuster of Wayne State University in Detroit, "we would not engage in it." Unfortunately, some of the activities humans are neurochemically tuned to find agreeable--eating foods rich in fat and sugar, for instance--have backfired in modern society. Just as a surfeit

of food and a dearth of exercise have conspired to turn heart disease and diabetes into major health problems, so the easy availability of addictive chemicals has played a devious trick. Addicts do not crave heroin or cocaine or alcohol or nicotine per se but want the rush of dopamine that these drugs produce.

Dopamine, however, is more than just a feel-good molecule. It also exercises extraordinary power over learning and memory. Think of dopamine, suggests P. Read Montague of the Center for Theoretical Neuroscience at Houston's Baylor College of Medicine, as the proverbial carrot, a reward the brain doles out to networks of neurons for making survival-enhancing choices. And while the details of how this system works are not yet understood, Montague and his colleagues at the Salk Institute in San Diego, California, and M.I.T. have proposed a model that seems quite plausible. Each time the outcome of an action is better than expected, they predicted, dopamine-releasing neurons should increase the rate at which they fire. When an outcome is worse, they should decrease it. And if the outcome is as expected, the firing rate need not change at all.

As a test of his model, Montague created a computer program that simulated the nectar-gathering activity of bees. Programmed with a dopamine-like reward system and set loose on a field of virtual "flowers," some of which were dependably sweet and some of which were either very sweet or not sweet at all, the virtual bees chose the reliably sweet flowers 85% of the time. In laboratory experiments real bees behave just like their virtual counterparts. What does this have to do with drug abuse? Possibly quite a lot, says Montague. The theory is that dopamine-enhancing chemicals fool the brain into thinking drugs are as beneficial as nectar to the bee, thus hijacking a natural reward system that dates back millions of years.

The degree to which learning and memory sustain the addictive process is only now being appreciated. Each time a neurotransmitter like dopamine floods a synapse, scientists believe, circuits that trigger thoughts and motivate actions are etched onto the brain. Indeed, the neurochemistry supporting addiction is so powerful that the people, objects and places associated with drug taking are also imprinted on the brain. Stimulated by food, sex or the smell of tobacco, former smokers can no more control the urge to light up than Pavlov's dogs could stop their urge to salivate. For months Rafael Rios lived in fear of catching a glimpse of bare arms--his own or someone else's. Whenever he did, he remembers, he would be seized by a nearly unbearable urge to find a drug-filled syringe.

Indeed, the brain has many devious tricks for ensuring that the irrational act of taking drugs, deemed "good" because it enhances dopamine, will be repeated. pet-scan images taken by Volkow and her colleagues reveal that the absorption of a cocaine-like chemical by neurons is profoundly reduced in cocaine addicts in contrast to normal subjects. One explanation: the addicts' neurons, assaulted by abnormally high levels of dopamine, have responded defensively and reduced the number of sites (or receptors) to which dopamine can bind. In the absence of

drugs, these nerve cells probably experience a dopamine deficit, Volkow speculates, so while addicts begin by taking drugs to feel high, they end up taking them in order not to feel low.

PET-SCAN images of the brains of recovering cocaine addicts reveal other striking changes, including a dramatically impaired ability to process glucose, the primary energy source for working neurons. Moreover, this impairment--which persists for up to 100 days after withdrawal--is greatest in the prefrontal cortex, a dopamine-rich area of the brain that controls impulsive and irrational behavior. Addicts, in fact, display many of the symptoms shown by patients who have suffered strokes or injuries to the prefrontal cortex. Damage to this region, University of Iowa neurologist Antonio Damasio and his colleagues have demonstrated, destroys the emotional compass that controls behaviors the patient knows are unacceptable.

Anyone who doubts that genes influence behavior should see the mice in Marc Caron's lab. These tireless rodents race around their cages for hours on end. They lose weight because they rarely stop to eat, and then they drop from exhaustion because they are unable to sleep.

Why? The mice, says Caron, a biochemist at Duke University's Howard Hughes Medical Institute laboratory, are high on dopamine. They lack the genetic mechanism that sponges up this powerful stuff and spirits it away. Result: there is so much dopamine banging around in the poor creatures' synapses that the mice, though drug-free, act as if they were strung out on cocaine.

For years scientists have suspected that genes play a critical role in determining who will become addicted to drugs and who will not. But not until now have they had molecular tools powerful enough to go after the prime suspects. Caron's mice are just the most recent example. By knocking out a single gene--the so-called dopamine-transporter gene--Caron and his colleagues may have created a strain of mice so satiated with dopamine that they are oblivious to the allure of cocaine, and possibly alcohol and heroin as well. "What's exciting about our mice," says Caron, "is that they should allow us to test the hypothesis that all these drugs funnel through the dopamine system."

Several dopamine genes have already been tentatively, and controversially, linked to alcoholism and drug abuse. Inherited variations in these genes modify the efficiency with which nerve cells process dopamine, or so the speculation goes. Thus, some scientists conjecture, a dopamine-transporter gene that is superefficient, clearing dopamine from the synapses too rapidly, could predispose some people to a form of alcoholism characterized by violent and impulsive behavior. In essence, they would be mirror images of Caron's mice. Instead of being drenched in dopamine, their synapses would be dopamine-poor.

The dopamine genes known as D2 and D4 might also play a role in drug abuse, for similar reasons. Both these genes, it turns out, contain the blueprints for

assembling what scientists call a receptor, a minuscule bump on the surface of cells to which biologically active molecules are attracted. And just as a finger lights up a room by merely flicking a switch, so dopamine triggers a sequence of chemical reactions each time it binds to one of its five known receptors. Genetic differences that reduce the sensitivity of these receptors or decrease their number could diminish the sensation of pleasure.

The problem is, studies that have purported to find a basis for addiction in variations of the D2 and D4 genes have not held up under scrutiny. Indeed, most scientists think addiction probably involves an intricate dance between environmental influences and multiple genes, some of which may influence dopamine activity only indirectly. This has not stopped some researchers from promoting the provocative theory that many people who become alcoholics and drug addicts suffer from an inherited condition dubbed the reward-deficiency syndrome. Low dopamine levels caused by a particular version of the D2 gene, they say, may link a breathtaking array of aberrant behaviors. Among them: severe alcoholism, pathological gambling, binge eating and attention-deficit hyperactivity disorder.

The more science unmaskes the powerful biology that underlies addiction, the brighter the prospects for treatment become. For instance, the discovery by Fowler and her team that a chemical that inhibits the mopping-up enzyme MAO B may play a role in cigarette addiction has already opened new possibilities for therapy. A number of well-tolerated MAO B-inhibitor drugs developed to treat Parkinson's disease could find a place in the antismoking arsenal. Equally promising, a Yale University team led by Eric Nestler and David Self has found that another type of compound--one that targets the dopamine receptor known as D1--seems to alleviate, at least in rats, the intense craving that accompanies withdrawal from cocaine. One day, suggests Self, a D1 skin patch might help cocaine abusers kick their habit, just as the nicotine patch attenuates the desire to smoke.

Like methadone, the compound that activates D1 appears to be what is known as a partial agonist. Because such medications stimulate some of the same brain pathways as drugs of abuse, they are often addictive in their own right, though less so. And while treating heroin addicts with methadone may seem like a cop-out to people who have never struggled with a drug habit, clinicians say they desperately need more such agents to tide addicts--particularly cocaine addicts--over the first few months of treatment, when the danger of relapse is highest.

Realistically, no one believes better medications alone will solve the drug problem. In fact, one of the most hopeful messages coming out of current research is that the biochemical abnormalities associated with addiction can be reversed through learning. For that reason, all sorts of psychosocial interventions, ranging from psychotherapy to 12-step programs, can and do help. Cognitive therapy, which seeks to supply people with coping skills (exercising after work instead of going to a bar, for instance), appears to hold particular

promise. After just 10 weeks of therapy, before-and-after pet scans suggest, some patients suffering from obsessive-compulsive disorder (which has some similarities with addiction) manage to resculpt not only their behavior but also activity patterns in their brain.

In late 20th century America, where drugs of abuse are being used on an unprecedented scale, the mounting evidence that treatment works could not be more welcome. Until now, policymakers have responded to the drug problem as though it were mostly a criminal matter. Only a third of the \$15 billion the U.S. earmarks for the war on drugs goes to prevention and treatment. "In my view, we've got things upside down," says Dr. David Lewis, director of the Center for Alcohol and Addiction Studies at Brown University School of Medicine. "By relying so heavily on a criminalized approach, we've only added to the stigma of drug abuse and prevented high-quality medical care."

Ironically, the biggest barrier to making such care available is the perception that efforts to treat addiction are wasted. Yet treatment for drug abuse has a failure rate no different from that for other chronic diseases. Close to half of recovering addicts fail to maintain complete abstinence after a year--about the same proportion of patients with diabetes and hypertension who fail to comply with their diet, exercise and medication regimens. What doctors who treat drug abuse should strive for, says Alan Leshner, director of the National Institute on Drug Abuse, is not necessarily a cure but long-term care that controls the progress of the disease and alleviates its worst symptoms. "The occasional relapse is normal," he says, "and just an indication that more treatment is needed."

Rafael Rios has been luckier than many. He kicked his habit in one lengthy struggle that included four months of in-patient treatment at a residential facility and a year of daily outpatient sessions. During that time, Rios checked into 12-step meetings continually, sometimes attending three a day. As those who deal with alcoholics and drug addicts know, such exertions of will power and courage are more common than most people suspect. They are the best reason yet to start treating addiction as the medical and public health crisis it really is.