

“Why did you ever try narcotics?” William Burroughs writes in *Junky*, his classic tale of descent into the hell of drug addiction. “Why did you continue using it long enough to become an addict?” To Burroughs, the answer is simple, if not mundane: “You become a narcotics addict because you do not have strong motivations in any other direction. Junk wins by default. I tried it as a matter of curiosity. I drifted along taking shots when I could score. I ended up hooked.”

To scientists, drug addiction is considerably more complex. For half a century, they have searched for the biological mechanisms that lead to addiction—the cascade of chemical and electrical phenomena that starts with an injection or a snort or a puff or a sip and ends with abuse and addiction. Why, they’ve asked, have addictive drugs been constant companions to the human condition, used by the Sumerians in Mesopotamia, the ancient Egyptians, the Greeks of Homer’s era and the Romans of Virgil’s? Why are almost 2 million Americans today using crack cocaine and more than 200,000 hooked on heroin?

These biologists have learned about the nature of human desires and the biochemical and genetic basis of pleasure. And they have come upon at least one simple fact of life and neuroanatomy: substances that have the power to make us feel good, that evoke a strong sensation of physical pleasure, seem to share remarkable similarities once they hit the brain. Indeed, their most profound effects take place in a few specific brain regions—known as “reward” or “pleasure” centers—and involve their capacity to boost the levels of a single brain chemical, dopamine. Research is revealing that addiction is not evidence of human weakness or lack of willpower but rather a disease in which these reward centers become dysfunctional through some combination of genes and environment. The research is also generating a host of new clues and potential targets that might be employed someday to cure or treat the affliction.

If there is a single villain in the neuro-anatomical world of drug addiction, says

Marc Caron, an HHMI investigator at Duke University, it may be evolution. “Survival of the species,” he says, is what brought about a reward system in the brain that reinforces healthy behavior with a sense of pleasure. Prehistorically, those behaviors involved food and procreation of the species. If something felt good, you were more likely to do it again. Over the centuries, however, mankind has become adept at locating or manufacturing substances that hijack these reward systems, putting pursuit of the particular substance ahead of all else.

James Olds, a psychologist at the California Institute of Technology, first identified and mapped the reward centers of the brain. At McGill University in the 1950s, Olds showed that he could induce a sensation of pleasure in a rat by placing an electrode in its brain and applying a mild electric stimulus. The intensity of the pleasure seemed to depend on the precise position of the electrode. Drawing on the work of the legendary Harvard psychologist B.F. Skinner, Olds developed a system in which rats could administer their own stimuli by pushing a lever, and they would do so as many as 6,000 times an hour if the electrode was placed to their liking. He measured how frequently and monomaniacally the rats pressed the lever for their cerebral buzz when the electrode was

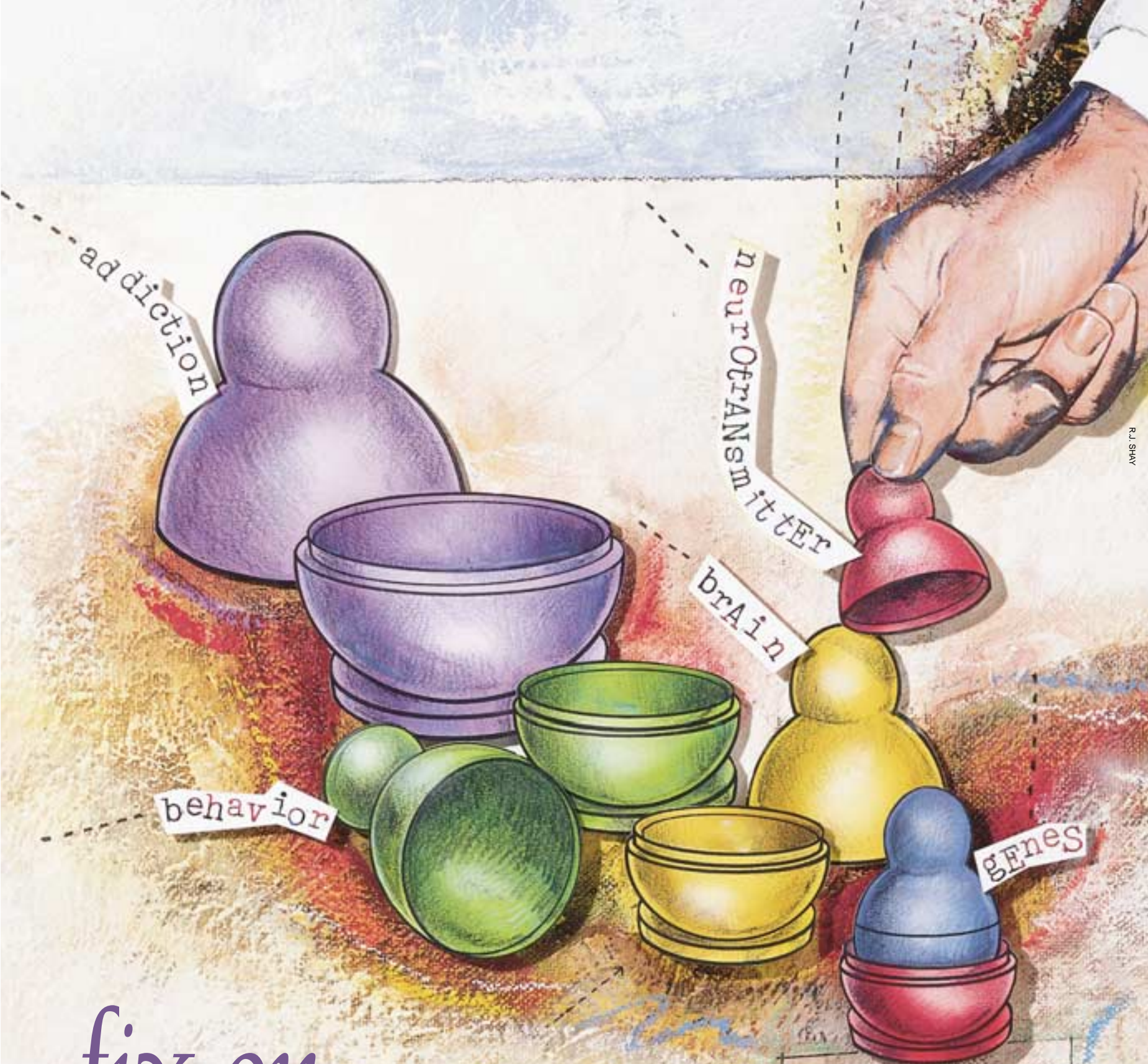
neurons and reinforcement loops runs from the prefrontal cortex through the lateral hypothalamus to a small but potent bundle of neurons known as the nucleus accumbens. It ends at the ventral tegmental area, atop the brain stem.

While Olds was at work with electrical stimulation, psychologists and pharmacologists were using similar systems to characterize the pharmacology and phenomenology of drug abuse. In their laboratories, rats and monkeys pushed levers to get intravenous amphetamines, cocaine or opiates. These researchers wanted to know which brain chemicals these drugs affected, so they simultaneously gave the animals other drugs to interfere with some of the brain chemicals to see what would happen. In particular, the researchers suspected that a class of neurotransmitters known as catecholamines—which includes norepinephrine, dopamine and serotonin—might be involved. Sure enough, “what we found was that selective blockade of the dopamine system made it so rats wouldn’t work for cocaine or amphetamines anymore,” says National Institute of Drug Abuse psychologist Roy Wise, who pioneered research in this area in the 1960s and 1970s. “And blocking the dopamine system made animals lose interest in the electrical brain stimulation as well.”

science's by Gary Taubes GROWING

placed in different positions. What he found were hotspots of pleasure sprinkled throughout the brain but one common neural pathway that rats would happily die for. Known as the medial forebrain bundle, this highway of pleasure-inducing

By the late 1980s, researchers had demonstrated that activation of this dopamine system in the reward pathways of the nucleus accumbens is the common denominator in all drugs of abuse—whether “downers” such as heroin, mor-



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phine and alcohol, or “uppers” such as cocaine and amphetamines. As Caron describes it, the drugs are simply “hijacking” the evolutionary mechanism that rewards beneficial behaviors by making the organism feel good. “Because we did not evolve to just use drugs,” he says, “things like eating and any other kind of pleasure, whether sex or eating chocolate, will create the same changes in the dopamine system that many of these drugs do. But the drugs produce changes in the dopamine system that are much, much greater than what natural behaviors would ever do.” Drug abuse becomes a search for chemical equilibrium in the brain, a homeostatic regulation mechanism to keep dopamine levels higher than could be attained through normal activity.

“Put an animal in a cage,” explains Wise, “and let it start pushing a lever to get an injection of heroin or cocaine. The drug will cause dopamine levels to go up two, three, four, even five times normal levels in the nucleus accumbens. The ani-

mal will be satisfied for 5 to 30 minutes, depending on what dose of what drug, and then dopamine falls back down to some trigger point and it presses the lever again and gets another injection.”

Having identified which neurotransmitter was mediating the effect of addictive drugs, and where in the brain this was happening, researchers have spent the past decade dissecting the mechanism and its various interactions with both the drugs and other systems in the brain. Normally, when dopaminergic neurons are given the signal to fire, dopamine is released into the extracellular space. There, in the gap between synapses, it binds to dopamine receptors on downstream cells, thus transmitting messages from neuron to neuron. It’s a communication process controlled as much by the firing signal as by the amount of dopamine available, which in turn depends on the cells’ ability to recapture the dopamine after it has been dispatched. A molecule known as a dopamine transporter has the responsibility of recapturing the dopamine and returning it inside the nerve terminals where it is then repackaged into vesicles for the next firing. “The transporter is often thought of as a pump that pumps neurotransmitters into the cell against their concentration gradients,” says Susan Amara, an HHMI investigator at the Vollum Institute in Oregon.

Addictive drugs can prevent the dopamine transporter from performing this job. Cocaine, for instance, competes directly with dopamine for the binding site on the transporter molecule. Like a passenger unable to board an overcrowded bus, the dopamine is left behind in the extracellular spaces instead of being recaptured and repackaged in the vesicles for further firing. The dopamine hangs around to stimulate receptors downstream, causing the pleasurable rush of cocaine and hyperactivity. Amphetamines, on the other hand, function in a more complex way. They bind to the transporter and are carried by it back into the nerve cell, where they abolish the ability of the vesicles to store dopamine. “Normally the amount of intracellular

dopamine is very low as it is packaged away very rapidly in the vesicles,” says Caron. “When you destroy these vesicles, you drive the dopamine transporter backward, leading to a marked increase in the extracellular concentration of dopamine.” This is why the effects of amphetamines are usually much stronger than those of cocaine.

In the late 1980s, Amara cloned the gene for the norepinephrine transporter. This led other researchers to clone the genes for the transporters of other neurotransmitters. It was a flurry of discovery that “opened up a whole series of experiments you could do,” Amara recalls. “You could now analyze how drugs interact with the transporters, how the transporters function, under what conditions, and how they’re regulated. It was clear it was going to be very informative.”

Since then, Amara and her colleagues have been meticulously picking apart the various mechanisms of transporter function. “These carriers are actually electrically active,” she says. “As they transport dopamine, for instance, they transport ions as well. When these ions are moved across the cell membrane, they generate a measurable current that we can observe in dopaminergic neurons from rat brains as well as in cultured cells expressing the human dopamine transporter.” Not only dopamine but any package the transporter might be carrying—amphetamines, for instance, or even neurotoxin MPP⁺, which destroys dopamine neurons and produces a syndrome resembling Parkinson’s disease—will generate this electrical activity as it is carried by the transporter through the cell membrane.

Amara and her colleagues have also found evidence that cocaine molecules do more at the transporter than interfere with neurotransmitter movement; they also affect the movements of ions through these transporters and block the generation of these electric currents. “In the past,” she says, “we thought cocaine had its effect solely by binding to the carrier and blocking transport of the neurotransmitter. But we found that when we put cocaine on the carrier, it blocks a current that normally goes through the transporter when no dopamine is present. So that may have its own effects in terms of the direct impact of cocaine, one that isn’t involved in the elevation of dopamine lev-



C. BRUCE FORSTER

Susan Amara and her team are studying the dopamine transporters and other molecular players involved in cocaine addiction.

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els.” Now Amara and her colleagues are trying to put this knowledge to work by finding a molecule that would block the transporter molecule from binding cocaine but leave it free to do its work with the dopamine. Such a molecule, a kind of “cocaine antagonist,” might help ease withdrawal symptoms for addicts.



SCOTT DINGMAN

Marc Caron hopes that growing understanding of the brain pathways involved in addiction may lead to new therapies.

Caron has also been studying the dopamine transporter molecules—with some surprising results. He is a biochemist who has spent a quarter century studying a class of cellular receptors known as G protein-coupled receptors. “They are one of the most important families of molecules that mediate cellular communica-

tion, and they are the receptors that define the specificity of signals,” says Caron. “For example, signal transduction through G protein-coupled receptors is how we perceive light, how we perceive odors, how we perceive tastes, how our heart basically beats and how essentially many of the cells in our body function.” As it turns out, the receptors for catecholamines, and specifically dopamine, are also G protein-coupled receptors, which is why Caron and his colleagues found themselves studying first neurotransmitters and then addiction. After Amara and her colleagues cloned the norepinephrine transporter gene, they followed it up, as did Caron and his colleagues, by cloning the dopamine transporter. Caron has been studying the molecule ever since. His primary tool has been “knockout” mice that are bred without the gene for the dopamine transporter molecule, which makes them unable to produce the transporter. “The absence of the transporter,” says Caron, “created havoc in the brain dopamine system. It changed just about every parameter we ever looked at. The receptors were down-regulated and the storage of dopamine was almost abolished. Yet the small amount of dopamine left in the cell was more active than the big load that was there before.”

Physically, the mice were smaller than average, and they seemed to stay small because they were so hyperactive that they rarely stopped to eat. Indeed, they seemed to show many of the symptoms of attention deficit hyperactivity disorder (ADHD), illustrating just how complicated these systems can be. When Caron and his colleagues gave cocaine or amphetamines to these mice, doing so actually calmed them, mimicking the effect of the stimulant Ritalin on children with ADHD. To Caron, this suggests that cocaine and amphetamines must also interact with the re-uptake of serotonin. In other words, when the dopamine transporter molecule is removed, stimulants may work just like Prozac. “This is a pretty controversial

area,” says Caron, “but we hope that we can start looking at these brain pathways and understand how serotonin interacts with the dopamine system to produce a calming effect.”

After a half century of research, scientists studying drug addiction now find themselves with the neuroanatomical version of nested Russian dolls. The more they learn about how drugs of abuse alter the electrical and chemical circuitry of the brain’s reward centers, the deeper they have to go to understand the ultimate nature of addiction. They now know, for example, that cocaine blocks the transport and re-uptake of dopamine, which in turn activates dopamine receptors, but it’s far less clear what happens next. “Dopamine activating its receptors for longer periods of time will lead to changes in secondary messengers, and that will alter the activity of other neurons, which will fire more or fire less, depending on which they are,” explains Eric Nestler, a neurobiologist and psychiatrist at the University of Texas Southwestern Medical Center. “That has long-term consequences. The neurons adapt to that excessive stimulation through other changes, which in turn means those cells are now different in a stable way. Even without the drug present, they’re different. The neurons are different. The brain is different. The behavior is different. Those are the changes that cause an addictive brain, and they are the changes we have to understand.”

Most researchers are confident, however, that they will eventually nail down these and other details of addiction, at least enough to speed the development of new pharmaceutical treatments. “The process of addiction is as old as mankind,” says Caron, “and there may be mechanisms involved that we haven’t even dreamed of yet. But we now understand an awful lot about what brain pathways are involved in rewards and behavioral manifestation of drug abuse. We still don’t know how to modulate them, we still don’t have any successful therapeutic interventions, but that’s the ultimate goal.”