

What Addicts Need

Addiction isn't a weakness; it's an illness. Now vaccines and other new drugs may change the way we treat it.

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Annie Fuller knew she was in trouble a year ago, when in the space of a few hours she managed to drink a male co-worker more than twice her size under the table. Of course, she'd been practicing for a quarter of her life by then; at 47, she was pouring a pint of bourbon, a 12-pack of beer and a couple of bottles of wine into her 115-pound body each day. She had come to prefer alcohol to food, sex or the company of friends and loved ones. Her marriage had ended; she had virtually stopped leaving the house, except to work and to drink. Fuller had tried and failed enough times over the years to know that she would not be able to sober up on her own. The last time she'd stopped drinking her body went into violent seizures, a common and terrifying symptom of alcohol withdrawal. But the single mother and mortgage-company VP refused to sign into rehab. "I live in a small town," she says. "And when you go to a hospital for something like that, everybody knows about it." So when a family doctor told her about Vivitrol, a monthly injection that prevents patients from drinking alcohol by obliterating its ability to intoxicate, Fuller agreed. She took a sabbatical from work, sent her 15-year-old daughter to stay with relatives and hunkered down to weather the painful, frightening blizzard of detoxification in the comfort of her own living room.

What does it mean to be an addict? For a long time the answer was that someone like Fuller "lacked willpower," a tautology that is pretty much useless as a guide to treatment. In the current jargon of the recovery movement, addiction to alcohol, drugs or nicotine is a "bio-psycho-social-spiritual disorder," a phrase that seems to have been invented by the treatment industry to emphasize how complex the problem is and how much more funding it deserves. But the word itself comes from the Latin *addictus*, a debtor who was indentured to work off what he owed; someone addicted to alcohol or drugs is powerless over his or her fate in the same way—except debtors-as-addicts can never fully balance the books. It had been years since the pleasure of drinking outweighed the pain it caused Fuller. Looked at that way, the "social" and "spiritual" aspects of her problem seem insignificant compared with the contribution of biology. If you weigh advances in neuroscience over the last few decades against social and spiritual progress, it's clear which field is more likely to produce the next breakthrough in treatments.

While the roots of addiction remain a dark tangle of factors—most experts agree that addicts trying to quit will always need psychological support—the old white-knuckle wisdom that addicts simply lack resolve passed out of fashion decades ago. The American Medical Association recognized addiction as a disease back in 1956. But only now are we beginning to see treatments that target the underlying biochemistry of that disease.

The emerging paradigm views addiction as a chronic, relapsing brain disorder to be managed with all the tools at medicine's disposal. The addict's brain is malfunctioning, as surely as the pancreas in someone with diabetes. In both cases, "lifestyle choices" may be contributing factors, but no one regards that as a reason to withhold insulin from a diabetic. "We are making unprecedented advances in understanding the biology of addiction," says David Rosenblum, a public-health professor and addiction expert at Boston University. "And that is finally starting to push the thinking from 'moral failing' to 'legitimate illness'."

In laboratories run and funded by the National Institute on Drug Abuse

(NIDA), fMRI and PET scans are forcing that infuriating organ, the addicted brain, to yield up its secrets. Geneticists have found the first few (of what is likely to be many) gene variants that predispose people to addiction, helping explain why only about one person in 10 who tries an addictive drug actually becomes hooked on it. Neuroscientists are mapping the intricate network of triggers and feedback loops that are set in motion by the taste—or, for that matter, the sight or thought—of a beer or a cigarette; they have learned to identify the signal that an alcoholic is about to pour a drink even before he's aware of it himself, and trace the impulse back to its origins in the primitive midbrain. And they are learning to interrupt and control these processes at numerous points along the way. Among more than 200 compounds being developed or tested by NIDA are ones that block the intoxicating effects of drugs, including vaccines that train the body's own immune system to bar them from the brain. Other compounds have the amazing ability to intervene in the cortex in the last milliseconds before the impulse to reach for a glass translates into action. To the extent that "willpower" is a meaningful concept at all, the era of willpower-in-a-pill may be just over the horizon. "The future is clear," says Nora Volkow, the director of NIDA. "In 10 years we will be treating addiction as a disease, and that means with medicine."

Volkow's vision of the future, however, is being greeted warily by big pharmaceutical companies, reluctant to develop products that would associate their brands with drug addicts. It is also facing resistance from some elements in the addiction-treatment community, who are wedded to the 12-Step model pioneered by Alcoholics Anonymous in 1935. Twelve-Step programs traditionally discourage members from using any psychoactive substances, on the ground that addicts will simply trade one dependency for another. That rationale has some unfortunate history on its side; both opium and cocaine were first introduced to the United States as cures for alcoholism in the late 1800s. More recently there is the example of methadone, the synthetic heroin that turned out to be addictive in its own right, and Antabuse, a drug that makes you throw up when you drink alcohol—which suffers from the shortcoming that an alcoholic planning a binge can just skip his dose.

Addictive drugs like cocaine and heroin flood the brain with the neurotransmitter dopamine, a chemical that induces a sensation of pleasure and trains the subconscious to remember everything that preceded that sensation. Together with alcohol, nicotine and amphetamines, these make up the five drugs generally considered the hardest to give up; right now, some 22 million Americans are hooked on at least one of these substances. While each causes a distinct form of intoxication and a different range of side effects and health problems, all five hijack the same pathway, deep within the brain. It's the pathway that conditions us to eat, have sex, form emotional attachments and carry out the other activities essential to our species' survival. But the agents of addiction are far more powerful than any of those natural highs. Just one dose of cocaine, for example, can release two to 10 times the amount of dopamine produced by your favorite meal, person, song or sight. Take a drug like that consistently enough, and your brain and body will come to depend on it—first for euphoria, then for normalcy. Eventually, the pursuit and consumption of drugs will become as instinctive as the pursuit and consumption of food—only far more urgent and destructive.

People vary in their innate sensitivity to dopamine, which may partly explain why addiction runs in families. A gene that codes for a dopamine receptor designated D2 (one of at least five dopamine receptors that have been identified so far) comes in several different versions, and each produces a different concentration of receptors. People with fewer receptors may receive less stimulation from their naturally occurring dopamine, and therefore be more inclined to seek an artificial high from drugs. Unfortunately, tinkering directly with the dopamine system to control addiction hasn't worked out very well. Dopamine is crucial to voluntary movement and interfering with it can cause symptoms resembling Parkinson's.

So far, other neurotransmitters that play a role in addiction have been easier to tackle. Gamma-aminobutyric acid, or GABA, exerts an inhibitory effect on neurons, telling the body to stop instead of go. Addicts' brains are deficient in GABA, so researchers are investigating a drug called Vigabatrin, which stimulates its production. In December, the pill cleared its first double-blind, placebo-controlled trial; 30 percent of patients who took Vigabatrin stayed off cocaine during the nine-week study, compared with just 5 percent in a control group. "It's the best

efficacy signal that we've seen in any clinical trial for cocaine treatment," says Frank Vocci, director of the pharmacotherapies division at NIDA. "And it's worked on what many have written off as an intractable population—hard-core, long-term cocaine addicts." A drug called Camparal, which is already on the market as a treatment for alcoholism, works on yet another brain chemical, glutamate. While the early stages of addiction are driven by pleasure-seeking—hence the importance of dopamine—the motive eventually shifts to avoiding the pain of withdrawal; at that point, drug-seeking behavior is fueled by glutamate. By suppressing this neurotransmitter, Camparal has the potential to reduce cravings and help prevent relapses during recovery. Researchers think these drugs hold enormous promise. "The treatment of depression was revolutionized by medications that manipulate serotonin concentrations," says Alan Leshner, former head of NIDA, referring to Prozac and its cousins. "Drugs that act on GABA and glutamate could do the same thing for addiction."

If you're trying to quit drinking, you are advised not to hang out in bars, and if you're trying to kick cigarettes, you probably should avoid French movies from the 1950s. One reason addictions are so hard to break is that the pleasure of taking the drug becomes associated with all the situations and activities around it, which then become cues for a relapse. Researchers at the University of Pennsylvania found that showing cocaine addicts pictures of drugs or crack pipes for just 33 milliseconds—below the threshold of conscious awareness—was enough to trigger cravings. Beverly Dyess, 58, learned this last year when, after six months of sobriety—her longest stretch in 15 years—she went into a supermarket and discovered that her favorite brand of Scotch was on sale. She was seeing a therapist daily, but "as soon as I saw the label, everything else went out the window," she says. For the next two months she rode a roller coaster of frenzied drinking and crushing guilt. Some days she would get up early enough to get drunk and then sober up in time for her evening counseling session. Other days she would run to the store, buy a bottle of whisky and then, her resolve mysteriously stiffened, pour it down the sink when she got home. By suppressing the surge of glutamate that directed her to the Scotch aisle in the first place, Camparal helped ease the pain of withdrawal and allowed the counseling and behavioral therapy to work. "I still do the talk therapy," she says. "But Camparal really helps, because everything is still a cue for drinking."

Of course, you can't protect yourself against every encounter with a bottle, or, in some environments, heroin, cocaine or amphetamines. So researchers are working on ways to break the association that was Dyess's downfall. A drug called D-cycloserine, or DCS, has the remarkable effect of helping to erase learned fear responses. The classic example, in animals, is the association of a particular place with an electric shock. If you stop giving the shock, the animal eventually "unlearns" the response and is no longer afraid; DCS makes this happen faster. It has been successfully tested in people as a treatment for acrophobia (fear of heights). Now researchers want to see if it can be used to wipe out the association between visual or social cues and the impulse to relapse into addiction. So far, it's been tested only on cocaine, but if it works there it might work for other addictions as well.

Neuroscientists don't talk about "willpower," which is a philosophical concept, but they are starting to get a handle on the parts of the brain involved in self-control, the ability to impose a rational calculus on behavior. They distinguish three kinds of self-control, and, unsurprisingly, addicts score poorly on all of them, although it isn't clear whether taking drugs is the cause or consequence of this deficiency, and which of the three types plays the biggest role in addiction has yet to be determined. These are:

- Delayed discounting, the willingness to put off present gratification in the interest of a bigger long-term reward. Addicts always take the immediate reward.
- Reflection impulsivity, a measure of how much information is required to make a decision. Addicts typically act without processing all the available information.
- Intentional action, the ability to consciously stop a behavior that has become automatic.

To measure this, NIDA researchers had addicts watch a screen and push one of two buttons, according to whether a light has flashed on the

left or right side—except when the light was accompanied by a tone. After several rounds, pushing the button becomes an automatic response that has to be overridden consciously, and addicts were much less able to do this than non-addicts. As scientists have known since the 1980s, the neurons that control movement are activated even before a person is aware of the intention. Now researchers have identified the part of the brain—the fronto-medial cortex—that is activated when someone stops himself from executing such automatic behaviors. This is as close as we have got to finding the seat of willpower in the brain. Put an addict in an fMRI machine, and you can observe reduced activity in the fronto-medial cortex. But a drug called Provigil, which is ordinarily used to treat narcolepsy, stimulates that part of the brain and is now being tested as a treatment for amphetamine addiction. "The idea that we can restore 'self-control' or 'free will' with medication is a very, very exciting one," says Vocci of NIDA. "It could be paradigm shifting. But we need more studies to see how consistently that impacts recovery."

That is a useful caution; these drugs are new and their mechanisms are still only partially understood. The brain has a way of resisting attempts to tinker with its chemistry. The discovery in 1960 that Parkinsonism was caused by a deficiency of dopamine quickly led to the use of synthetic dopamine precursors, such as L-dopa, which relieved the symptoms at first, but were not the long-term cure patients had hoped for.

A more straightforward approach to treating, or preventing, addiction is to block the action of the drug directly. If it doesn't feel good, the thinking goes, you won't do it. Naltrexone, a pill that has been around for a decade, works that way against alcohol, but an addict intent on getting high can just skip his dose. The solution to that problem is Vivitrol, a longer-lasting, injectable form of Naltrexone, which came on the market in 2006. Vivitrol, the drug Annie Fuller took, does not enhance self-control or stop the craving for liquor, but it does block liquor's effects. The day Fuller got her shot, her leg swelled to twice its normal size. The swelling subsided a day or two later, but the next few weeks were a torment of sweating, shaking, vomiting and tears—side effects that came from both Vivitrol and alcohol withdrawal. At times she couldn't walk and needed help to use the bathroom. The only thing that kept her from drinking was the knowledge that she could not get drunk. "The shot just took the relapse option off the table," she says. She got the same injection every month for the rest of the year, suffering a little less each time, and she is now off the medication and sober.

Vaccines that would arm the immune system against addictive drugs and prevent them from making the user high are, potentially, the ultimate weapons against addiction. A cocaine vaccine is poised to enter its first large-scale clinical trial in humans this year, and vaccines against nicotine, heroin and methamphetamine are also in development. In theory, these addiction vaccines work the same way as the traditional vaccines used to treat infectious diseases like measles and meningitis. But instead of targeting bacteria and viruses, the new vaccines zero in on addictive chemicals. Each of the proposed vaccines consists of drug molecules that have been attached to proteins from bacteria; it's the bacterial protein that sets off the immune reaction. Once a person has been vaccinated, the next time the drug is ingested, antibodies will latch onto it and prevent it from crossing from the bloodstream into the brain. Nabi Biopharmaceuticals, a small biotech company in Maryland, has engineered a nicotine vaccine that is in late-stage clinical trials. Earlier studies showed that it was twice as effective as a placebo in helping people quit smoking. The cocaine vaccine, developed by Thomas Kosten of Baylor College of Medicine, could be on the market as early as 2010. It would have to be given three or four times a year, but presumably not for life, says Kosten. While the vaccine is being studied in people who are already addicted to cocaine, it could eventually be used on others. "You could vaccinate high-risk teens until they matured to an age of better decision-making," Kosten says. He acknowledges the obvious civil-liberties issues this raises. "Lawyers certainly want to argue with us on the ethics of it," he says, "but parent groups and pediatricians have been receptive to the idea."

The revolution these new drugs promise will have a huge impact on the addiction-treatment industry (or, as it prefers to think of itself, the "recovery movement"), which runs the gamut from locked psychiatric wards in big-city hospitals to spallike mansions in the Malibu Hills of California. And the reaction there is guarded; the people who run them have seen panaceas come and go over the years, and the same addicts return with the same problems. They also, of course, have a large

investment in their own programs, which typically rely on intensive therapy and counseling based on the 12-Step model. "We need four or five more years to see how [Vivitrol] does," says staff psychiatrist Garrett O'Connor at the Betty Ford Center, in Rancho Mirage, Calif. "And we need to be very cautious, because a failed treatment will set a person back." The Ford Center and the Hazelden Foundation, in Minnesota, use drugs sparingly, and mostly just in the first days or weeks of recovery, the "detox" phase. "Hazelden will never turn its back on pharmaceutical solutions, but a pill all by itself is not the cure," says William Moyers, Hazelden's vice president of external affairs. "We're afraid that people are seeking a medical route that says treatment is the end, not the beginning." As for Alcoholics Anonymous and its imitators, they mostly do not forbid members to use medication but there are strong institutional biases against it. "I'm not judging others, but for myself, using something like Vivitrol or Campral feels like a crutch," says one longtime AA member, who, following the organization's practice, asked not to be named. "It's not true sobriety."

The competing view is that of Lisa Torres, a New York lawyer who has been in recovery from heroin addiction for nearly 20 years, and continues to take methadone, which she regards as medication for a chronic condition, analogous to blood-pressure or cholesterol-lowering drugs. "It's a paradox that some of addicts' biggest advocates have been the most resistant to new treatments," she says. "But a lot of them come to the field after recovering from their own addictions, and they can be very stubborn about what works and what doesn't." More pointedly, she adds, "some people feel recovery from addiction should not be easy or convenient."

So for this new paradigm to take hold, a lot of long-held prejudices will have to change. Doctors (and insurance companies) will have to get used to the idea of medicating their addicted patients, rather than handing them a brochure for AA, which a study published in 2005 in *The New England Journal of Medicine* found was the most common form of "treatment" offered. "If you have hypertension and it flares up, you go to a specialist," says psychologist Thomas McLellan of the University of Pennsylvania. "The specialist doesn't discharge you to a church basement. If he did, we would call it malpractice." Addicts, he adds, are by no means unique in their propensity to relapse. In a study comparing alcoholics and drug addicts to patients with diabetes, asthma and hypertension, McLellan found nearly identical rates of noncompliance and relapse; between 30 and 40 percent of each group failed to follow even half their doctors' guidelines.

Where doctors go, drug companies are likely to follow. Most of the research on addiction treatments has been done by NIDA (total 2007 budget: \$994 million) or small pharmaceutical companies. "I have been imploring the bigger companies to work on this," says Volkow. "Their scientists get it, but the business people are tough to persuade." Companies with billion-dollar stakes in selling drugs for osteoporosis or cholesterol don't want their names on a product used by heroin addicts, says Leshner. Even the relatively unknown Nabi, according to CEO Raafat Fahim, decided to focus on a vaccine for nicotine "because it's not illicit and it's not something you can overdose on" (and afterward sue the company that made the drug that didn't stop you from taking it). But Steven Paul, the head of research for Eli Lilly, believes the landscape is changing. There used to be a stigma attached to depression, too, he says, but the development of Prozac put an end to that. "Anything that has a large unmet need," says Paul, "is ultimately going to succeed commercially."

And addicts may need to change their thinking, too. For nearly 75 years, that thinking has been dominated by the principles laid down by Bill W., the founder of Alcoholics Anonymous. The amount of good AA has done in the world is incalculable; most people reading this article probably can think of someone they know who owes his or her life to it. Some readers themselves have surely benefited. But in 1935 AA was, essentially, the only legitimate option. There were "cures" of various sorts, including gold chloride injections, but there was virtually no modern neuroscience or psychopharmacology. Many people are now living in society with mental illnesses like schizophrenia and bipolar disorder that would have required institutionalization back then. Addicts, like the rest of the public, need to recognize the fact that we are entering a new era in addiction treatment. Viewing her condition as a chronic, recurring disease that could be treated was precisely what Dyess needed to return to sobriety. "In the past, when I would relapse," she says, "the thinking from 12-Step

or from family was that I had failed. Now I know that if it happens, it happens, and I can pick myself up and move on, instead of assuming it's all over so I might as well keep drinking." The 12 Steps begin with a confession of powerlessness over addiction. But there's hope that science may some day help put that power within the reach of anyone who needs it. And then who would choose not to grasp it, and begin the long war for sobriety—a war without end, but one worth the fighting.

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