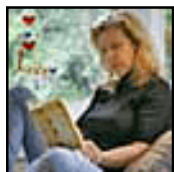


Riddle of addiction lures researchers

Complex network of brain mechanisms underlies cravings

Carl T. Hall, Chronicle Science Writer

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After 14 years of continuous sobriety, Lydia Yaffe knows she has much to be thankful for -- a career, two children, good health. She also knows the alcoholism and cocaine addiction that once threatened everything are still threats, hardwired into her brain.

"The disease is me," she said.

So Yaffe, 44, a San Francisco real estate agent, still attends Alcoholics Anonymous meetings, still works her 12-step recovery program, still maintains strict abstinence.

In the recovery world -- a world that received fresh attention Monday when San Francisco Mayor Gavin Newsom revealed that he had decided to seek "professional assistance" to help him stop drinking alcohol -- the idea of finding a permanent cure for addiction is considered laughable, if not a dangerous deception that sets up the addict for relapse.

It also sets up a question: After 30 years of scientific research into the root causes of addiction, what's really changed?

The research has yet to erase the stigma of drug dependency, and medications that target the brain pathways of addiction are typically not effective, at least not for long.

For most people, treatment still relies on AA and other forms of group support and psychosocial counseling.

"Advances in treatments based upon science are just beginning to take off," said Dr. Lori Karan, a

research physician at UCSF who specializes in drug dependence. "The research has been advancing quickly, but to get to the point where the neuroscience is used in the clinic, that's where it's a more complicated process."

Most experts agree that medications alone will never work. Addiction may be a brain disease, but it plays out in a social setting, and often requires a thorough reworking of attitudes, lifestyle and relationships to vanquish.

Dr. David Pating, head of addiction medicine for Kaiser Permanente's Chemical Dependency Recovery Program in San Francisco, put it this way: "I can get you undrunk, but there's no pill I can give you that will keep you undrunk for the rest of your life."

Even if a permanent cure seems remote, researchers are making progress understanding the complicated mesh of brain circuits that underlie addiction. They have not given up on the idea of finding ways to tweak the circuits to relieve cravings and reduce the odds of relapse -- at least long enough to help some people make progress in counseling or group therapy programs.

The latest research in nicotine dependence implicates a neglected part of the brain known as the insular cortex. It's a region long associated with "gut feelings" -- a connection point between the body and the brain's control circuitry -- now thought to be an important seat of cravings. By pinpointing the source of cravings, researchers suspect it might be possible to tamp them down, or at least improve how cravings are monitored during treatment.

Studies in fruit flies have found new reasons to explain why some people's brain cells can soak up more alcohol than others. Having a low "sensitivity" to alcohol may seem to be a good thing, but, in fact, studies have shown it adds to the risk of alcoholism.

In other studies, scientists have shown how genetic factors may help explain problems with impulse control. In effect, the addiction-prone brain may have a built-in biological preference for immediate over-delayed reward.

On Friday, some of the nation's top addiction researchers will review the latest such findings during the annual meeting of the American Association for the Advancement of Science in San Francisco. One of the main themes is expected to be how brain-imaging studies are finding links between

addiction and obesity.

Research that focuses on genetics and the workings of the brain dovetails with a broad change in addiction treatment that no longer emphasizes 28-day stays in residential detox programs and all-or-nothing expectations. The new "medical model" portrays addiction as a chronic condition that demands long-term care, usually in outpatient clinics, with individualized approaches that attend both to the biological needs and social aspects of a patient's life.

Some 40 experimental drugs are in development for alcoholism and other forms of addiction, and researchers are finding a wealth of addiction-related genes and brain circuits to target next. But it's unclear which new tools will work for which people, and how all the genetic signals combine with someone's upbringing to produce an addict.

So no one expects the brain research to bring a revolution to addiction clinics anytime soon.

"We can't just operate on the side of technology. We have to operate within people's lives," Kaiser's Pating said. "It's more than just a brain disease. You've got to put a glass to your mouth before you become an alcoholic."

Dr. Nora Volkow, director of the National Institute on Drug Abuse and one of the participants in Friday's seminar, focuses on the role of dopamine, one of the most important signaling molecules in the brain's reward circuits.

Different drugs of abuse work in different ways on the brain, but all seem to converge on the dopamine circuitry. Eventually, chronic use of a drug shifts the circuits so that the user doesn't feel "normal" without the drug onboard.

"Nothing else is enough," said Rita Goldstein, a scientist and colleague of Volkow's at Brookhaven National Laboratory in New York. "Anything but the drug is not as salient or valuable or important. Everything else just recedes to the background ... and you don't really have an alternative."

The result is a brain hardwired for out-of-control cravings. "Every behavior, every emotion has underlying neurobiological underpinnings, including cravings for drugs," Goldstein said. "If you look with sensitive enough tools, you will see something measurable. Craving and the desire for drugs, and

the highs produced by the drugs, are associated with brain changes."

These changes alter decision-making pathways. Whatever the substance, if it's something that can change the way a person feels, it can alter biologically ancient structures deep in the brain and how they are controlled -- or not -- by conscious thought.

Since the 1970s, researchers have found these changes through genetic studies, animal models of addiction and new brain imaging technologies. But it's proved to be a hard sell.

"The pharmaceutical industry overall is not very interested at all in developing drugs for addiction," Volkow said.

A few medications have been on the market for years, including some that make it virtually impossible for a person to drink or use drugs -- unless the person stops taking the medication, as someone with an addiction is often prone to do. So the latest idea is to design an anti-craving medication to get around the compliance problem.

A slow-release form of a drug called naltrexone, which blocks opiate receptors and is thought to reduce the high of some drugs, thereby reducing craving, hit the market last summer. It's sold under the trade name Vivitrol. Once-monthly injections are given in a doctor's office.

"It was the missing link I needed," said Chrys Parmentar, a 45-year-old recovering alcoholic in St. Louis. "I found my craving levels had gone down immensely."

Clinical studies suggested the injections, along with standard counseling or group therapy, can reduce the number of "heavy drinking days," defined as a day with five or more drinks for men, four or more drinks for women.

But overall results have "not been glamorous," Pating said.

In a six-month clinical trial published last year, alcoholics on Vivitrol dropped from 19 "heavy drinking days" a month to about three. But those getting placebo injections in the same counseling programs also cut back, from 19 heavy drinking days to six. Women appeared to do better than men with talk therapy alone, and for them the drug appeared to hold no clear benefit, for reasons not yet

understood.

Researchers insist that addiction should be considered in much the same way as heart disease or diabetes -- chronic relapsing conditions that may be controlled but rarely cured, in which medications may help, but more often than not also require lifestyle changes and constant vigilance.

The difference is that being labeled a drug addict or alcoholic carries a special stigma not shared by diabetics and heart patients.

Percy Menzies, head of Parmentar's St. Louis treatment clinic, said this is one reason the disease model of addiction has been remarkably slow to gain traction in treatment circles.

"This is almost the last holdout we have, where people believe the problem is largely self-afflicted," he said. "This is one of the few diseases where the very nature of it is you are going to relapse, you are going to have multiple failures, and yet it's always the patient who is blamed."

Dr. Peter Banys, head of the addiction treatment program at the San Francisco Veterans Affairs Medical Center, said addiction needs to be considered a disease of many subtypes, similar to leukemia, each linked to a different set of genes or environmental factors. Some people may be hardwired thrill-seekers, he said, while others may fall prey because of depression or "cognitive processing" disorders. Each subtype might respond to a different medication or counseling approach.

"You've got to be thinking about it as multiple disorders that look the same but are not," Banys said. "They're not genetically the same. We already know that there are at least six different chromosomal locations heavily implicated, and many more are turning up."

It may take a long time for the research to catch up with the complexity of the problem. Even now, however, treatments are available that can make a difference.

Brain research offers "forgiveness, but not excuses," Banys said.

"We can honorably say to patients, 'It's not your fault you became an alcoholic. Your genetics caught up with you. Maybe your brain likes it better than my brain. But while you're not to blame for getting it, you may be to blame for not doing something about it. Because it's a disease, we can do something

about. People do get into recovery.' "

Correcting a neurochemical imbalance could be a first step. But in true recovery, Banys said, "what's really recovered is intimacy."

"Addiction diminishes your capacity for ordinary human intimacy," he said. "You devote such a great part of your life to a relationship with inanimate substances - liquids and powders. We attribute human qualities to these inanimate chemicals."

That's why the typical active addiction nearly always ends up wrecking human relationships.

Don't expect any pill, or even monthly injections, will be enough to fix those.

"We harm our marriages, we harm our children, we lie, we don't keep our commitments, we don't show up at soccer games. We harm the living nexus of the people we love and who love us," Banys said. "So in recovery, what I think is recovered is the capacity to return to the living world, the world of children and wives and employers and friends, and the world in which your word means something when you promise your kid you will go to the soccer game."

That type of recovery, he said, takes something like participation in AA or various lesser-known alternatives to achieve. Medications clearly have a place, at least for some people who can't get sober.

"But in the long run, there's no way around it: You have to do that hard recovery work," Banys said.

For Lydia Yaffe, recovery means attending two or three Alcoholics Anonymous meetings every week. She keeps working and reworking the AA 12 steps, only one of which, the first step, has anything directly to do with stopping use of a substance.

The other steps have to do with such matters as developing a clear sense of one's faults, accepting the idea that willpower alone won't be enough, establishing a spiritual connection to a higher power, making amends to those one has harmed and ultimately, the final step, being of service to others.

Yaffe said she has no choice.

"Some people talk about how they were binge drinkers. Others say they were daily drinkers. Well, I

was a daily binge drinker," she said.

She steers clear of alcohol nowadays, but said the underlying syndrome, her "obsessive behavior," is always ready to cause trouble if she lets down her guard.

"That's why I have to continue to go to meetings, to deal with my behavior and learn how to deal with my defects in my behavior, and learn how to control them.

"I hate it, but at the same time I think I'm fortunate to have tools maybe normal people don't have," she said. "Because of this disease, I am forced to work on myself -- which I guess is a blessing in disguise."

By this reckoning, once an alcoholic, always an alcoholic. But Yaffe and the addiction experts agree on one fundamental point: Even if there's no magic cure, there may be such a thing as a grateful recovering alcoholic.

<http://sfgate.com/cgi-bin/article.cgi?f=/c/a/2007/02/11/ADDICTION.TMP>

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