ADDICTION FICTION

DOPAMINE MAY NOT BE THE ONLY REASON PEOPLE CAN'T KICK THE HABIT | BY JOE MIKSCH

We're "addicted" to chocolate, jogging, sex, and food because of a rise in the happy-making neurotransmitter dopamine that's associated with pleasurable activity.

Or so the conventional wisdom goes.

Something is satisfying to us. We see the opportunity to do it again, or get some more of it, and our brain releases dopamine. We feel good even anticipating the reward.

Charlie Bradberry's studies of cocaine addiction, however, paint a different picture of real addiction. His work suggests that although dopamine plays a part in keeping people doing cocaine long past the time they find it enjoyable, it may be that many are unable to kick the drug habit because of changes in the brain's decision-making center.

"It's been thought that the only reason these things [like drugs] are enjoyable is because of dopamine," Bradberry says.

"The brain's a much more complicated place."

Particularly the brain of a primate.

Not surprisingly, a human brain is more like that of a monkey than that of a rat. Cocaine alters brain metabolism in humans and monkeys in ways not seen in rats. So Bradberry, a PhD associate professor of psychiatry in the University of Pittsburgh School of Medicine, has abandoned the rodent model often used to study the neurochemical effects of addiction for a primate model.

Vin Mariani combined Bordeaux with cocaine and was a popular tonic in the late 1800s. Although cocaine use has been stigmatized for some time now, neurobiologists are still learning how it and other addictive substances make such a mess of people's lives.

By allowing rhesus monkeys to self-administer cocaine, then monitoring cognitive ability and neurochemistry, Bradberry follows his hunch that cognitive ability—in particular decision making—plays a significant role in addiction and relapse. His work in recent years has confirmed that assumption.

In Bradberry's lab, monkeys were seated in front of a panel of lights indicating when cocaine was available. On that cue, they could choose whether to press a lever that would cause a dose of cocaine to be delivered intravenously. After the monkeys had become sensitized to cocaine, Bradberry examined their brain chemistry, looking for a rise in dopamine levels when the primates were given a visual cue telling them the drug was available. That's the way it worked in rats.

"We were just not able to see any activation of dopamine by environmental cues," he says.

"It was kind of unsettling because you immediately worry about whether you've done something wrong."

But as the results were repeated, Bradberry became convinced they were not evidence of a fluke or error, but were an indication that he should look elsewhere for the internal drive that prompted his monkeys to push that lever.

Since arriving at Pitt from Yale University in 2004, Bradberry has continued to try to divine the source of his monkeys' desire for cocaine. Behavior in primates, he says, is the consequence of the dance between the cerebral cortex—which guides reasoning and control—and regions of the brain that pertain more to urges and appetite.

That led Bradberry to hypothesize that the cortex, the seat of cognition, was a good place to start looking for answers. Measuring cognitive ability in a control group and in cocaine-exposed monkeys confirmed he was looking in the right place. Bradberry found clear-cut cognitive deficits in the cocaine-exposed monkeys long after they'd last taken cocaine. They were slower to adapt to changing rewards and slower to formulate strategies to maximize the number of rewards they earned.

What changed in the brain that made these monkeys less able to make the right decisions? Had they lost the ability to be mentally active enough to remember which choices earned them rewards? Had they merely lost interest in rewards other than cocaine?

In humans, Bradberry says, one can raise the same sort of questions about an addict who is unable to change a pattern of drug abuse despite losing a job, spouse, friends, and family.

If addiction is more than a result of feel-good dopamine, Bradberry says, it's vital to look beyond the dopamine system for explanations.

Perhaps, Bradberry says, a drug could be developed to enhance cognitive ability and, therefore, decision making. Cognitive behavioral therapy might be appropriate, too, he adds.

"You've probably got to do more than just try to regulate an appetitive urge," says Bradberry.

"What's happening when people relapse is that they're making a bad decision." ■

CORBIS

BORN TOO SOON

A STUDENT LEARNS HOW WORK AT THE BENCH MAY SAVE PREEMIES

BY ELAINE VITONE

A boy is born too soon, and his parents wait and worry. He does well on a respirator for three days, then four. His lungs are gaining strength, a reason to exhale.

Then on day five, there's trouble—not in his lungs, where prematurely born infants are commonly known to have problems, but in his gut. His blood pressure falls, his belly swells, and he can't digest food. As he's rushed into surgery, the parents are told he has a terrible disease that's quite common among premature children, but this is the first they've ever heard of it. Inside him, a tiny tangle of intestine is breaking down, turning black, and dying.

This is an imagined story, but it's much like what tens of thousands of young families go through every year in this country. Fifteen percent of all preterm babies, both boys and girls, develop an inflammatory disorder called necrotizing enterocolitis (NEC). Among them, only half survive. If NEC isn't caught early enough, portions of the intestine must be removed. The more the baby loses, the more difficulty absorbing nutrients he'll face throughout his life.

Third-year University of Pittsburgh medical student Chris Rippel says that given the frequency and devastating effect of NEC, it's surprising how few people know about it.

"It seems the only people you'll find outside of the medical community [who know about NEC] are people directly affected by it," he says.

Rippel is on a team that plans to give premature infants a better chance.

He's working with David Hackam, an MD/PhD, assistant professor of surgery, as well as of cell biology and physiology at Pitt, and principal investigator on an ongoing NEC study. Last fall, Rippel received the Phillips Award for his summer-research project on NEC. He's now continuing the same series of experiments for his scholarly research project. (Such multiyear projects are a new curriculum requirement for all Pitt med students.)

Rippel is not the first student to be recognized for work completed under Hackam's guidance. In recent years, Hackam's mentees have won awards from the Pittsburgh Surgical Society, the Eastern-Atlantic Student Research Forum, and the American Medical Association.

The primary cause of NEC is still unknown, but the presence of immune cells called macrophages in the intestines of NEC patients suggests that infection may play some part. It's not clear what kind of infection triggers the immune response, or whether this reaction helps or harms the intestines—it may do both.

Hackam is exploring the idea that NEC may be a result of cells being held incommunicado in the midst of an infection.

"Chris was fascinated by the question," says Hackam.

His lab is focusing on how intestinal cells called enterocytes communicate and what happens if and when they don't.

Throughout the body, certain pathways between cells—channels known as gap junctions—have been shown to act as cellular telephone lines. Cynthia Leaphart, a surgical research fellow in Hackam's lab, was the first to demonstrate the functional significance of the junctions in the intestine. She and Rahul Anand, another surgical research fellow in the lab, worked with Rippel to observe the effects of inflammation on enterocyte communication and to test the hypothesis that the presence of macrophages may be somehow responsible for disconnecting the phone lines.

Rippel found that the hypothesis was correct. As molecules secreted by the macrophage traveled along the cellular party line, the enterocytes stopped communicating with one another.

Next question for Rippel and the Hackam lab: Among the inflammatory molecules secreted by the macrophage, which one disabled the phone lines?

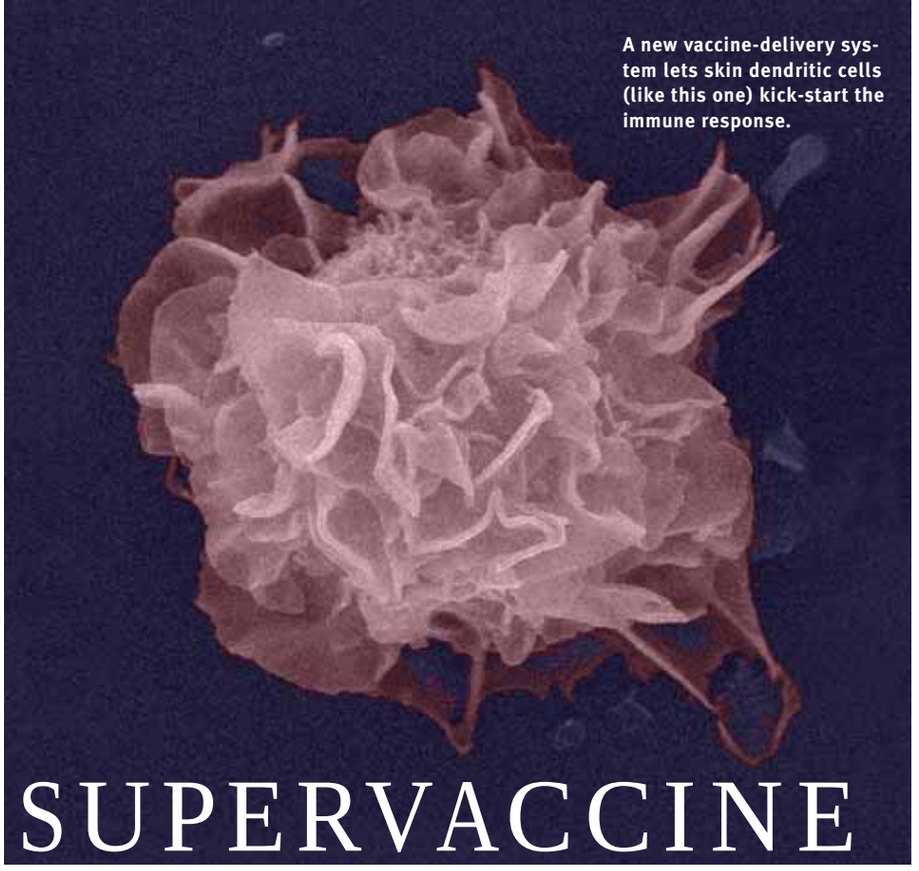
Based on studies by Pitt's former pediatric surgery chief Henri Ford that linked elevated levels of nitric oxide to NEC, Hackam's team thought nitric oxide was a likely suspect. Rippel introduced a nitric oxide blocker to the enterocytes, and sure enough, in the absence of this molecule, the phones started ringing again.

Rippel says that working with Hackam has not only fueled his interest in research, it has also benefited him as a surgeon-in-the-making.

"He really has an exceptional manner with patients," Rippel says.

Rippel is getting ready for the next phase of his scholarly project, which involves a series of imaging experiments, during which he will "tap" into the cells' communication lines.

Perhaps the secrets behind NEC travel this cellular grapevine. ■



A new vaccine-delivery system lets skin dendritic cells (like this one) kick-start the immune response.

COURTESY WATKINS

SUPERVACCINE TO THE RESCUE

HIV'S KIN DELIVERS A BETTER VACCINE | BY CAROLE BASS

An evil genius stalks the land, invading bodies and stealthily draining life from them.

Decades later, while the archvillain continues to lay waste to vast segments of humanity, its descendant—engineered in a university lab—takes on superpowers and races to the rescue. What the forefather wrought, the youth seeks to set right.

This intergenerational melodrama, worthy of a darkly illustrated superhero comic book, is playing out in a University of Pittsburgh dermatology lab.

There, researchers are exploring a new approach to vaccination that uses a modified virus. This test-tube baby is a third-generation scion of a family called lentivirus, which is better known for its most murderous member, HIV.

The researchers are finding that a souped-up lentivirus can deliver a vaccine that is both more potent and longer-lasting than existing vaccines. Eventually, they hope, it can be used to prevent a slew of infectious diseases, and even to treat cancer.

Strength and stamina aren't the only advantages of this brawny new vaccine-delivery system. Louis Falo, MD/PhD professor and chair of the Department of Dermatology at Pitt, lists others: It can be produced quickly in response to developing diseases. It's less expensive. It can probably be put into patch form so that it doesn't need refrigeration or even a needle.

Get this thing a cape and call it Supervaccine.

Falo notes that a problem with existing vaccines is the time it takes to make them.

As a result, the flu vaccine you get this year is based on viruses in circulation last year.

Falo and other researchers around the country have been experimenting with an alternative. Instead of growing, say, measles or flu virus in fertilized chicken eggs, scientists extract a gene from the disease-causing agent, copy it, and multiply it.

"The production time would be greatly reduced," Falo says, "even to the point where you might be able to make patient-specific vaccines" from the patient's own body.

But there's a hitch.

"DNA vaccines haven't been very effective," Falo says. "The problem, we think, is the delivery."

So scientists have been working on a new delivery system, using a virus to carry the antigen (that bit of the infectious agent) inside the patient. There, like any vaccine, it causes the patient to make antibodies and killer T cells.

Then there's another problem.

"The cells that they infect are actually damaged by the virus, which makes perfect sense," Falo says. "It's a virus, after all."

In particular, the virus experiments seemed to impair the skin dendritic cells (DCs). These cells, front-line sentries in the immune system, ordinarily snare an invader and take it to the lymph nodes, where the dendritic cells activate pathogen-fighting T cells.

For a virus-based vaccine that lets the dendritic cells do their job, you need a virus that can't reproduce, damage the immune system, or cause other bodily harm. You want it to simply deliver its load of whatever you're vaccinating against.

That virus should be able to lurk in the patient's system without alerting the immune system. Otherwise, the vaccine stops working after delivering its antigen load only once.

"One virus is very good at hiding," Falo says. "HIV.

"So what we did was take a member of the same family, lentivirus, and we took away all [its] ability to reproduce."

The results: In lab animals, the lentivirus vaccine produced several times the immune system response of conventional vaccines. A single injection also lasted longer.

In addition to its practical potential, the vaccine study contributes to the basic science of immunology.

Based on experiments with other viral-vector vaccines, scientists had downgraded their view of the role that skin dendritic cells play in the body's immune response.

The success of the lentivaccine suggests that skin DCs are vital after all, says the study's first author, Yukai He, an MD/PhD and Pitt assistant professor of dermatology.

"It's the first evidence that the skin DC paradigm is working in the system in initiating the T cell response."

The researchers wonder how the vaccine will perform in human skin, for which no animal offers a close approximation.

FDA approval for clinical trials is, at best, 18 months to two years away, Falo estimates. ■