out the genetic factors in stroke and cancer. Realizing that the research community could quickly wear out its welcome by calling the vets too often, Tanner proposed that the four groups collaborate on an initial phone survey that would simultaneously seek likely subjects for each study. The collaborators first met one another in late November. In her initial telephone survey just now getting under way, Tanner is attempting to reach all the survivors from the original cohort—the 16,000 men still in "intact" pairs, and the 5000 others whose twins have died.

The collaborators suspect that the twin cohort could be invaluable for studying other diseases of old age, such as arthritis and pneumonia, once investigators learn of its existence. But with the veterans' average age now above 70, time is running out. "We're getting rather concerned about that," says Eldon Sutton, a University of Texas geneticist who heads a committee that reviews proposals to study the twins. To address that, the review committee hopes to enlist several hundred twins in one additional project: to establish permanent cell lines so that their DNA can be tested in the future as new ideas about the genetic and environmental bases of disease arise.

–David Ansley

David Ansley is a medical reporter at the San Jose Mercury News.

ADDICTION RESEARCH

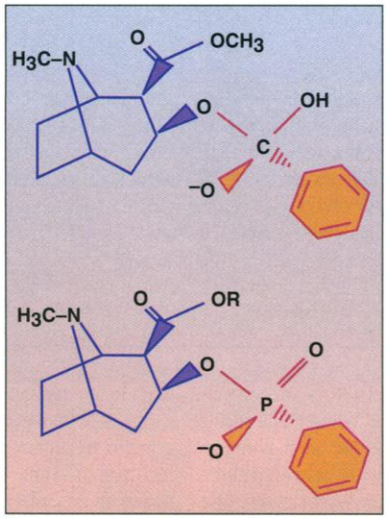
Enzyme May Blunt Cocaine's Action

Of all the common drug dependencies, addiction to cocaine, particularly in its smokable crack form, has proved the most difficult to treat. Now, in what researchers are hailing as the most promising approach in decades, a team led by physician and organic chemist Donald Landry of Columbia University's College of Physicians and Surgeons has created an enzyme that may break down the drug in the bloodstream, thus reducing its addictiveness. Although still in the test tube stage, Landry hopes that his enzyme—which may one day be administered as a vaccine—will add a new weapon to the arsenal of drug treatment. If the enzyme does indeed blunt cocaine's effects, he says, it might enable patients to forego the drug while participating in rehabilitation programs.

Experts in drug addiction say that such a treatment is badly needed. While researchers have searched for years for drugs that could block cocaine's effects or diminish a person's craving for it, their efforts have not panned out. "What we desperately need is an agent that would help a patients stay drug-free for 6 to 12 months while they're undergoing psychological and social rehabilitation," says psychiatrist Herbert Kleber of Columbia, who was the country's deputy drug czar in the late 1980s. Landry's approach, he adds, "is a totally new way of looking at cocaine addiction, and, if successful, will revolutionize the treatment."

What Landry and his colleagues have done is create a catalytic monoclonal antibody that can bind specifically to cocaine and then break it into two inert byproducts, ecognine methyl ester and benzoic acid—the same byproducts that are produced naturally when cocaine is broken down in the human body. "What I'm doing is essentially mimicking the natural degradation pathway in humans," says Landry.

To make the antibody, the researchers first immunized mice with a compound whose structure resembles that of the "transition state" for cocaine breakdown. The transition state is the high-energy, unstable intermediate through which chemicals undergoing a reaction must pass. The Landry team intended to speed up cocaine breakdown by finding an antibody that could bind to the drug and stabilize it in the transition state. The Columbia group then used antibody-producing cells from the immunized animals to hybridomas, cells that make monoclonal antibodies, and screened for those that could break down cocaine. They found one that is comparable in its activity to the enzyme that breaks down cocaine in the body. Such antibodies could be administered, he suggests, as a form of passive immunization to prevent cocaine from reaching the brain and causing the powerful "rush" that makes cocaine so addictive. The native enzyme on its own isn't active enough to do the job, but he hopes that the catalytic antibodies will improve on nature.



Antibody target. The compound used to make the catalytic antibody resembles the cocaine transition state *(above)*.

Landry began looking into the possibility of using catalytic antibodies to treat cocaine addiction in 1990 after hearing George Bush make a plea for researchers to find a way to immunize people against drug addiction. Landry then discovered that in the 1970s, Charles R. Schuster, now a senior research scientist at the Addiction Research Center of the National Institute for Drug Abuse (NIDA) in Baltimore, had actually shown that antibodies to heroin could block its effects in addicted rhesus monkeys. The problem was that once heroin bound to the antibodies, it couldn't be released again. So while the treatment works for low doses of heroin, higher doses sop up all the circulating antibodies and the treatment is no longer effective. And that's where catalytic antibodies have an edge, Landry says. Since they release the cocaine breakdown products, the catalytic antibodies themselves aren't depleted but can continue to bind and destroy more cocaine molecules.

Still, when Landry began his research, he feared that it might fall too far out of mainstream approaches to cocaine addiction to be seriously considered. "There is always that danger in trying something new," he says—although in Landry's case, instead of finding himself "off on [his] lonesome," he was able to anticipate a new trend. Indeed, at about the same time that Landry began his research, other biochemists, including Richard Lerner, president of the Scripps Research Institute and one of the inventors of catalytic antibodies, had launched similar investigations. And last fall, the National Institute on Drug Addiction issued a request for proposals for research using monoclonal antibodies and similar agents to attack cocaine addiction.

Although Landry beat Lerner to the punch, Lerner has only praise for the younger man. "It's a lovely piece of work" and has the potential to "move catalytic antibodies into the treatment of human problems for the first time," he says. But while Landry's research holds great promise, it is still in the test-tube stage. He is currently making additional, more active antibodies and hopes to begin testing them in an animal model of cocaine addiction in the next few months. "That will give us some indication if this treatment is actually effective," he says. In the best of possible worlds, human trials might begin in 5 years.

In the meantime, Landry's research has "demonstrated that what was originally just a concept—using monoclonal antibodies to treat drug abuse—is a feasibility," says Frank Vocci, director of the office of medication development at the NIDA. Far from being outside of the mainstream, Landry's work is now the leading edge.

–Virginia Morell