

Brain Glutamate Concentrations Affect Cocaine Seeking

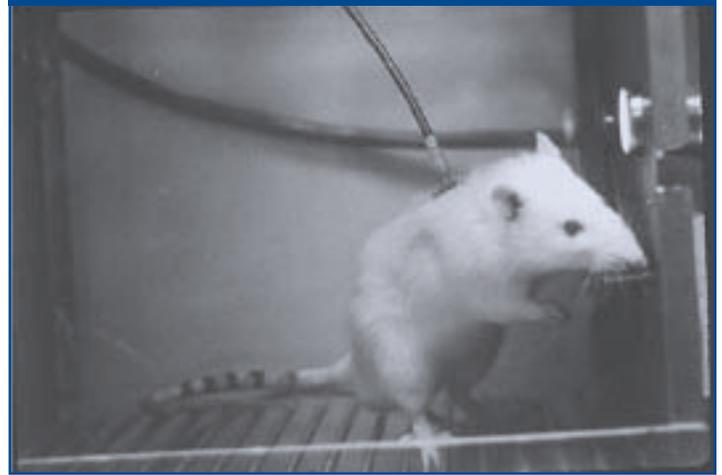
By Tom Hollon, *NIDA NOTES* Contributing Writer

NIDA-supported research has produced evidence that a medication that supplements recovering cocaine addicts' brain concentrations of the neurotransmitter glutamate may reduce their vulnerability to relapse. Although the research was done with laboratory rats, the substance used to bolster glutamate levels was acetylcysteine, a medication that is safe for humans and used routinely in emergency rooms to treat overdoses of the analgesic acetaminophen.

Dr. Peter Kalivas and colleagues at the Medical University of South Carolina in Charleston measured the glutamate concentrations in the fluid surrounding the cells in rats' nucleus accumbens (NAc) in the absence of cocaine exposure; after training the animals to voluntarily self-administer the drug by pressing a lever in their cage; and 3 weeks after removing the animals' access to cocaine. Compared with the concentrations in nonexposed animals, those during cocaine self-administration were markedly higher, and those after forced abstinence markedly lower. The investigators concluded that rats repeatedly exposed to cocaine develop glutamate concentration deficits in the NAc that persist for a considerable time after access to the drug is removed.

Dr. Kalivas and colleagues next investigated whether cocaine or acetylcysteine would restore the rats' glutamate levels and the effect on the animals' motivation to self-

A Possible Addiction Therapy, Built From the Ground Up



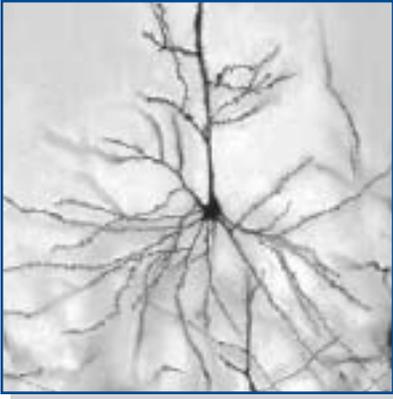
Training chambers like this one are used to study animals' responses to drugs. By pressing the lever, the rat obtains an infusion of a drug, a medication, or saline through the tube. Using such apparatus, NIDA scientists showed that cocaine abuse reduces brain glutamate levels, and treating animals with acetylcysteine reduces subsequent cocaine seeking.

administer cocaine. As in their first trials, the researchers began by training rats to press a lever to obtain cocaine, then removed the cocaine from the solution the rats received when they pressed the lever. As before, these procedures left the rats with reduced NAc glutamate concentrations; the rats also lost interest in pressing the lever because it no longer delivered cocaine. At this point the researchers injected some of the animals with a single dose of cocaine and others with a dose of acetylcysteine followed by a dose of cocaine. The initial cocaine and acetylcysteine doses both increased glutamate to the elevated levels that followed cocaine self-administration.

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Exploring the Why's of Adolescent Drug Abuse

By NIDA Director Nora D. Volkow, M.D.



Adolescence and early adulthood are periods of growth, exploration, and—for some teens and young adults—the development of drug abuse and addiction. Each day roughly 3,000 teens smoke their first cigarette. Among 30,000 teenagers polled by the National Survey on Drug Use and Health in 2002, 4.2 percent of 12- to 13-year-olds reported using an illicit drug in the past month, along with 11.2 percent of 14- to 15-year-olds, 19.8 percent of 16- to 17-year-olds, and 22.5 percent of 18- to 20-year-olds. Data gathered in 2002 by the Substance Abuse and Mental Health Services Administration show that 64 percent of patients entering treatment for drug abuse started abusing drugs at age 20 or younger.

Teen smoking illustrates the risks of early exposure to addictive drugs. A third of high school students who try smoking eventually become daily smokers. Young smokers appear to be more vulnerable to nicotine addiction than are older smokers; teen users report symptoms of dependence after smoking fewer cigarettes than adults, and they have more difficulty quitting and experience more severe withdrawal than adults who smoke similar amounts.

NIDA research is shedding light on the processes that underlie the exceptional susceptibility to addiction experienced by boys and girls who begin using drugs in adolescence. Recent animal studies provide evidence that drugs affect the developing brain differently than they do the matured brain. In one study, rats exposed to nicotine in adolescence self-administered more nicotine—as adolescents and as adults—than rats first exposed to nicotine in adulthood. In another study, rats exposed to nicotine in adolescence and given cocaine when they reached adulthood exhibited more sensitivity to cocaine's stimulant effects than did rats that were first exposed to both drugs as adults (see "Early Nicotine Initiation Increases Severity of Addiction, Vulnerability to Some Effects of Cocaine," *NIDA NOTES*, Vol. 19, No. 2, p. 8).

To strengthen prevention and treatment of drug abuse and addiction during the crucial adolescent period, NIDA has initiated a three-pronged research effort. One component of the effort will explore how developmental changes that occur in the adolescent brain may increase vulnerability to drugs, and how drugs in turn may subvert normal neurobiological maturation. We will increase support of animal studies to ascertain the successive steps in adolescent brain development and whether they differ with abstention from drugs, initiation of drug abuse, escalation to uncontrollable abuse, and relapse (RFA 04-011: "Animal

Models of Adolescent Drug Abuse: Integrative Studies of Brain and Behavioral Development").

A second component of our initiative aims to increase our ability to dissuade teens from abusing drugs by focusing on the cognitive processes—learning, motivation, judgment, and decision making—that influence choices to abuse or avoid drugs (RFA 04-009: "Behavioral and Cognitive Processes Related to Adolescent Drug Abuse"). This research will elucidate how teens perceive risk and make decisions on matters that involve risk. It will address such questions as why some young people engage in drug abuse when they have received information regarding its destructive potential. Do they assess the risks inaccurately, or do they understand the risks but weigh them more lightly than do abstaining adolescents?

The third focus of NIDA's new initiative is the period of emerging adulthood, which spans the years from 18 to 25. This is a time of continued brain development, but most of all of new personal and social choices and challenges: the emergence of personal beliefs and values, exploration of career roles, and transitions involving increasing independence and shifts in relationships with parents and peers. Overall rates of drug use peak and begin to subside during these years. Most youths who abuse drugs in their teens or early twenties desist as they mature into full adults, but some do not and some initiate new abuse of additional drugs: About 25 percent of smoking, 33 percent of marijuana use, and roughly 70 percent of cocaine abuse begins after age 17. Personal, social, and demographic factors such as education, employment, and home environment all appear to influence the patterns of abuse in this period.

NIDA's sharpened focus on emerging adults will support development and testing of interventions to prevent initiation or escalation of drug abuse during this life transition (RFA 04-013: "Prevention Research for the Transition to Adulthood"). The research will draw on a broad array of academic disciplines to generate and evaluate strategies of intervening on factors ranging from interpersonal relationships—the negative influence of one intimate partner on the drug use of the other, for example—to broader social contexts, such as workplaces and college campuses.

The choices adolescents make have a profound impact. NIDA's intensified concentration on the interaction of drugs and adolescent development will sharpen our understanding of those crucial choices, and will help us provide adolescents with the information they need to choose wisely. **NN**

Behavioral Modification Changes the Brain's Biochemical Response to Cocaine, Curbs Relapse Caused by Stress

By Tom Hollon, *NIDA NOTES* Contributing Writer

The scientific view of drug addiction as a chronic brain disease rests on many studies showing that addictive drugs change the brain in ways that cause compulsive drug seeking and drug taking. NIDA research recently demonstrated that the converse can also sometimes be true: In rats, behavioral modification changed the biochemistry of the brain and thereby reduced the motivation to self-administer cocaine.

Dr. David W. Self of the University of Texas Southwestern Medical Center in Dallas and colleagues at the Yale University School of Medicine and Harvard Medical School induced cocaine dependency in a set of experimental animals and then examined the impact of the behavioral technique called “extinction training” on the rats’ behavior and glutamate receptors in one of the brain’s major communications systems. Their finding that the training increased quantities of the glutamate receptors underscores the potential effectiveness of behavioral treatments for addiction and relapse prevention.

Extinction Training and Glutamate

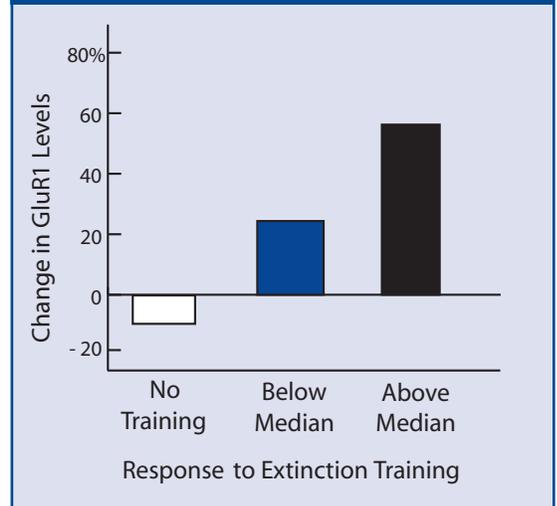
The researchers began their experiments by training rats to self-administer cocaine at will by pressing a lever. Animals trained in this way become “cocaine dependent”—that is, they develop behavioral and neurobiological changes that simulate the effects of addiction in people. The rats then underwent extinction training. In this technique, the researchers put animals into cages where they have self-administered a drug, but with a difference: Now, when the animals press the lever, no drug is

dispensed. After a number of tries—more for some, less for others—the animals lose interest in the lever. Basically, extinction training reeducates animals, teaching them that the association between pressing the lever and getting a drug no longer holds.

In their first experiment, the researchers measured how extinction training affected the frequency of the cocaine-dependent rats’ lever pressing and the supply of two glutamate receptors in the part of the brain known as the shell of the nucleus accumbens (NAc). The receptors, GluR1 and GluR2, act as relays in the brain’s glutamate system, which uses the neurotransmitter glutamate to send messages from cell to cell.

As expected, extinction training changed the rats’ behavior: Among the rats that received it, the frequency of lever pressing declined from a range of 39–44 presses in a 4-hour interval to a rate equivalent to 22–34 presses. These rats were also found to have 39% more GluR1 and 31% more GluR2 than matched cocaine-dependent rats not subjected to extinction training. Strengthening the conclusion that extinction training was responsible for these increases, the sizes of the declines in lever pressing correlated with the amount of increase in GluR1. Rats whose declines exceeded the median averaged a 58% increase in GluR1, while those whose declines were less than the median averaged a 24% increase.

Stronger Training Response Correlates With Higher Receptor Levels



Rats that responded more strongly to extinction training showed greater increases in glutamate receptor levels. Rats that did not receive training demonstrated a decrease in glutamate receptors. Percent changes shown are relative to control rats not exposed to cocaine.

“We discovered something profound—that simply allowing an animal to press a lever and not get any drug completely changed the brain’s response to cocaine,” Dr. Self says.

A second experiment confirmed the relationship between the glutamate receptors and successful extinction training. It also showed that the relationship goes the other way, too: Having more receptors at the time of extinction training increases the response to the training. In preparation for this experiment, the researchers used genetic engineering to artificially increase GluR1 and GluR2 in some cocaine-dependent rats’ NAc’s. In the first hour of train-

ing, these animals pressed levers for cocaine roughly 20 times, while animals whose receptors were not enhanced performed about 40 lever presses. The animals with the extra glutamate receptors also achieved the milestone of fewer than 20 lever presses after only 2 to 2.5 days of training, compared with more than 4 days for the other animals.

Summarizing the results of the two experiments, Dr. Self says, “There is a reciprocal relationship between extinction training and the level of glutamate receptors. Extinction training causes transient increases in glutamate receptors, while higher quantities of glutamate receptors facilitate extinction of drug-seeking behavior.”

To explain why rats with enhanced glutamate receptors are more likely to pass up cocaine, Dr. Self points to one of the key functions of the glutamate system: It helps enable an animal or a person forego short-term pleasures for the sake of safety or longer-term goals. In this situation, the prefrontal cortex, the brain’s seat of foresight and planning, releases glutamate molecules into the NAc, the brain’s pleasure center, that override the motivation for the short-term pleasure. Previous research has shown that chronic cocaine exposure reduces the cortex’s glutamate production, weakening its influence over the pleasure center. Dr. Self suggests that increasing the number of glutamate receptors in the NAc may partially compensate for the glutamate shortage by relaying more signals from the glutamate that still remains.

A more difficult question—one the researchers are pursuing now—is why extinction training increased glutamate receptors in the NAc. Although cocaine also caused glutamate shortages in rats that were taken off it without extinction training, those animals did not respond with compensatory increases in receptors.

Stress and Relapse

In a subsequent experiment, Dr. Self and his colleagues demonstrated that raising GluR1 levels in the NAc

reduced formerly dependent rats’ tendency to respond to stress by reverting to cocaine self-administration. Most surprising, the reduction in response was documented 3 weeks after the elevated GluR1 levels returned to normal.

After inducing cocaine dependency, genetically increasing the supply of glutamate receptors in the NAc, and a single session of extinction training,

“Perhaps extinction training teaches the animal to cope with stress by inhibiting craving, which stress normally would increase.”

the researchers gave their experimental rats a 3-week timeout. Then, they returned the rats to their training cages and administered three types of stimulus: a “priming” dose of cocaine, a light that flashes when the lever in the cage is ready to dispense cocaine, and a series of mild electrical shocks to the paw. These stimuli correspond to triggers that commonly cause addicted people to relapse—drug exposure, environmental cues associated with previous drug use, and stress. Each usually causes rats to revert to drug self-administration. Dr. Self and his colleagues found, however, that when their extinction-trained rats received foot shocks, those whose GluR1 levels were higher resumed lever pressing about 87% less frequently than those with less GluR1.

“This was really surprising,” says Dr. Self. “It suggested that glutamate

receptor increases during extinction training have long-term effects on stress-induced relapse, even after receptor quantities return to normal.”

To account for this finding, Dr. Self suggests that “there is a similarity between stress and extinction training. Foot shock is mild and basically irritates the animal, the rat equivalent of a bad day at work. Extinction is stressful too—the frustration of looking for a drug you anticipate but don’t get. Perhaps extinction training teaches the animal to cope with stress by inhibiting craving, which stress normally would increase.”

Dr. Nancy S. Pilotte of NIDA’s Division of Neuroscience and Behavioral Research agrees that behavioral changes sustained beyond the transient period of glutamate receptor elevation are an important finding. “This tells you it is extremely important to follow animals after drugs are withdrawn, a stage of addiction we know fairly little about,” she says. “We know a lot about acute affects, but very little about what happens to animals when they are no longer receiving drugs.”

Currently, no equivalent to extinction training exists for treating people. However, Dr. Self believes that in the future, virtual reality technology may make such an approach possible. “A very realistic video game might make it possible to recreate many of the anticipatory and emotional responses involved in preparing for the drug experience without ever actually receiving the drug,” he explains. “Repeated ‘virtual drug taking’ could extinguish these emotional responses by strengthening the brain pathways that exert inhibitory behavioral control over drug craving.”

Source

• Sutton, M.A.; Schmidt, E.F.; Choi, K-H.; Schad, C.A.; Whisler, K.; Simmons, D.; Karanian, D.A.; Monteggia, L.M.; Neve, R.L.; and Self, D.W. Extinction-induced upregulation in AMPA receptors reduces cocaine-seeking behaviour. *Nature* 421(6918):70-75, 2003. [NN](#)

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However, the rats given only cocaine resumed drug-seeking behavior—they began pressing the lever to try to self-administer cocaine—while those given acetylcysteine prior to cocaine did not.

“Restoration of glutamate by acetylcysteine blocked reinstatement of drug seeking in rats trained to self-administer cocaine,” Dr. Kalivas says. “This strongly indicates that susceptibility to relapse is due in part to diminished levels of extracellular glutamate associated with drug withdrawal. Our finding could well apply to people, too, since self-administration and reinstatement in animals are reliable models of addiction and relapse in humans.”

Dr. Kalivas’ findings add to a growing body of information describing glutamate’s important role in the neurobiological processes underlying drug abuse and addiction. Glutamate is a neurotransmitter, a chemical that acts as a messenger between brain cells. NIDA investigators have lately focused attention on glutamate in part because it influences levels of another neurotransmitter, dopamine, in the brain’s pleasure center, the NAc. Fluctuations in NAc dopamine levels

underlie the euphoria of initial drug use and contribute to other aspects of cocaine and other drug abuse and addiction. Glutamate signals also amplify the addictive effects of nicotine (see “Nicotine’s Multiple Effects on the Brain’s Reward System Drive Addiction,” *NIDA NOTES*, Vol. 17, No. 6, p. 1), and contribute to a condition called “long-term potentiation,” which causes brain cells that have been exposed to addictive drugs to release dopamine more abundantly in response to subsequent exposure (see “Addictive Drugs and Stress Trigger Similar Change in Brain Cells, Animal Study Finds,” *NIDA NOTES*, Vol. 18, No. 5, p. 1).

The scientists’ successful use of acetylcysteine to restore normal glutamate levels supports their hypothesis that cocaine reduces glutamate concentrations in the fluid surrounding cells in the NAc. They suspect that repeated drug exposure followed by drug withdrawal disrupts a process known as cystine-glutamate exchange: molecules of cystine enter NAc nerve cells, which pump molecules of glutamate out in exchange. The exchange normally maintains appropriate concentrations of both chemicals inside and outside the cells, but disruption by drugs may result in a shortage of extracellular glutamate. The researchers speculate that acetylcysteine rectifies this shortage because

it forms cystine molecules when it is metabolized. These molecules then enter the cells and prompt them to pump out additional glutamate.

Dr. Nancy S. Pilotte of NIDA’s Division of Neuroscience and Behavioral Research says Dr. Kalivas’s glutamate research demonstrates the value of moving beyond studies that focus on the dopamine-triggered pleasure associated with abuse and addiction. “We need to move on from thinking of dopamine as the center of the universe,” she says, adding that the payoff for broader research perspectives may be “more molecular targets for development of medications.”

Following up on the results of his animal studies, Dr. Kalivas has begun a clinical trial to determine whether acetylcysteine can control substance abuse patients’ craving for cocaine once they have achieved abstinence. He and his colleagues are also conducting further laboratory studies to evaluate whether the compound may prevent animals from seeking opioids or alcohol as effectively as it prevents them from seeking cocaine.

Source

• Baker, D.A.; McFarland, K.; Lake, R.W.; Shen, H.; Tang, X.C.; Toda, S.; and Kalivas, P.W. Neuroadaptations in cystine-glutamate exchange underlie cocaine relapse. *Nature Neuroscience* 6(7):743-749, 2003. **NN**

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Successful Trial Caps 25-Year Buprenorphine Development Effort

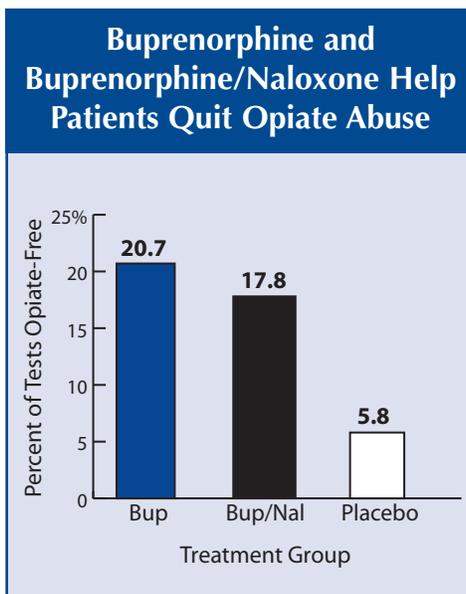
By Arnold Mann, NIDA NOTES Contributing Writer

Twenty-five years ago it would have been almost impossible to imagine a treatment for opiate addiction that could be prescribed in a physician's office, picked up at a pharmacy, and taken at home. But that scenario has been achieved after a quarter-century of collaborative effort—and the overcoming of several barriers—by NIDA's medication development program and Reckitt Benckiser Pharmaceuticals, Inc.

Dr. Don Jasinski, a scientist at NIDA's Intramural Research Program (IRP), was the first to recognize the characteristics of buprenorphine—developed in the 1970s as an injectable pain medication—as useful for addiction treatment. He led the initial 1978 study demonstrating the drug's effectiveness and its acceptability to patients as a treatment for opiate dependence.

Early on, NIDA scientists realized that medications for addiction not only had to be safe and efficacious, but also had to be available in a form that would be practical for therapeutic use over the long term. NIDA worked with Reckitt Benckiser (then Reckitt & Colman) to develop noninjectable formulations of buprenorphine; by 1990, Dr. Ed Johnson and colleagues at the IRP demonstrated that a solution form of the drug administered under the tongue was safe, effective, and acceptable to patients as an opiate dependence treatment.

As with any opioid, however, there were concerns about buprenorphine diversion and the potential for abuse. NIDA again collaborated with the manufacturer, and by the mid-1990's, developed a combination tablet of buprenorphine and naloxone that would minimize the potential for abuse—a development that put the



Patients undergoing treatment for opiate addiction who received buprenorphine or buprenorphine plus naloxone were more likely to test negative for opiate abuse than patients given placebo. Craving for opiates also was reduced in the two treatment groups.

vision of take-home treatment for opiate dependence within reach. In the next decade, scientists at NIDA and Reckitt Benckiser conducted clinical trials with more than 2,400 patients that established buprenorphine's safety and efficacy in treating opiate dependence. And finally, a NIDA-funded collaborative clinical trial, codirected by Dr. Paul Fudala of the Veterans Affairs Medical Center and the University of Pennsylvania in Philadelphia, established the safety and effectiveness of the buprenorphine-naloxone combination as a prescribed take-home treatment. Data from this study and two other pivotal trials formed the basis for the U.S. Food and Drug Administration's (FDA's) approval of buprenorphine and the combination medication in 2002.

"People at NIDA knew of the great need to move opiate addiction treatment from the traditional clinic settings to individual physicians' offices. But we had to address concerns about diversion and unprescribed use. Drs. Jasinski, Johnson, and Fudala deserve a great deal of credit for their contributions to this collaborative achievement—a safe and effective take-home treatment with minimal likelihood for abuse," says Dr. Frank Vocci, director of NIDA's Division of Treatment Research and Development.

Dr. Fudala's research, a nationwide study of 472 opiate-addicted men and women, was codirected by Dr. T. Peter Bridge, then of NIDA, and was recently published. The study confirmed that the efficacy and safety of the combined therapy are equivalent to those of buprenorphine alone and superior to placebo. The combination reduces craving for and use of opiates, presents limited potential for abuse, and is suitable for office-based use, the investigators concluded.

Initial Treatment Outcomes

The study began with a double-blind phase in which 323 opiate-addicted individuals (ages 18 to 59) received one of three treatments for 4 weeks. One group of 109 patients received tablets totaling 16 mg buprenorphine and 4 mg naloxone; the second group (105 patients) received tablets totaling 16 mg buprenorphine only; and the third group (109 patients) received placebo tablets. All tablets were identical in appearance and taste. Patients reported to the clinics for dosing every weekday and took their medications home for weekends and holidays. Study patients and placebo patients also participated

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in up to 1 hour of individualized counseling per week. Opiate use was monitored through urine tests every Monday, Wednesday, and Friday.

The plan for the initial double-blind, 4-week arm of the study was to recruit 384 patients and provide each patient with 4 full weeks of therapy. However, recruitment was halted at 323 subjects because the patients receiving either medication clearly were doing better than the placebo patients. Both medication groups showed significant reductions in opiate use and craving and significant improvements in perceptions of overall health compared with those receiving placebo.

In the buprenorphine-naloxone group, the proportion of opiate-free tests was 17.8 percent; the buprenorphine group had 20.7 percent opiate-free tests; and the placebo group, 5.8 percent. The presence of cocaine, the nonopiate drug most commonly found in urine samples in this study, did not vary significantly among the three groups. Nor was there a noticeable difference among the treatment groups in drug-positive results for amphetamines, barbiturates, or methadone.

“The number of urine samples negative for drugs probably would have been higher if investigators had used the results to counsel patients. Such feedback is known to further reduce patients’ drug use, but that information was not revealed to the researchers to prevent bias. The urine test results reflect higher use at the beginning of the study—when patients are ambivalent about treatment and in the grip of addiction. It’s positive that opiate use decreased over the course of the study,” says Dr. Vocci.

Patients in both medication groups also reported reduced craving for opiates. All groups showed the same average self-reported craving level before treatment—approximately 60 on a

100-point scale. By week 4 of the study, the average craving scores fell by half for both medication groups but did not change for the placebo group. Patients receiving medications reported greater improvement in overall health and well-being than those in the placebo group—perceptions confirmed by higher weekly clinician ratings of patients’ overall health and well-being for the two buprenorphine-treated groups. Because both medications were clearly effective, the researchers halted the first phase of the study. Patients receiving placebo during this phase went on to receive buprenorphine-naloxone combination treatment in the second phase of the study.

Longer-term Efficacy

The goal of the study’s second phase was to evaluate the safety of the combination tablet in more natural conditions and over a longer term, without the restrictions associated with the double-blind condition. In this open-label portion of the study, which lasted up to 52 weeks, all patients received the combination tablet. Weekly counseling was available along with a daily dose of up to 24 mg buprenorphine and 6 mg naloxone, tailored to each patient’s individual response. The sublingual tablet was administered at the clinic each weekday for the first 2 weeks; after that, patients could take home up to a 10-day medication supply at the discretion of the investigator.

Of the 472 patients who began this phase of the study, 385 received at least 8 weeks of treatment, and 261 were treated for at least 6 months. Fourteen patients discontinued therapy because of adverse events, of which detoxification or withdrawal symptoms were the most common. Opiate-free urine samples in the open-label phase of the study ranged from 35.2 percent to 67.4 percent in multiple assessments. The overall rate of opiate use was lower than in the first phase of the study, but cocaine and benzodiazepine use remained relatively constant, the researchers reported.

The study concluded that the addition of naloxone to protect against illicit use of the treatment medication did not reduce the efficacy of buprenorphine.

“This new treatment option is historic,” says Dr. Vocci. “Congress passed the Drug Abuse Treatment Act of 2000 so that buprenorphine products, and other Schedule III, IV, and V medications approved for opioid treatment by FDA, can be prescribed by qualified doctors for the treatment of opioid addiction. This represents a change to a level of prescribing privileges that American doctors have not had since the Harrison Narcotic Act of 1914.”

Who Can Benefit

In the two years since the medication was approved, clinicians have gained an understanding of which patients are most likely to benefit from a take-home treatment option. Dr. Fudala cautions that buprenorphine is not likely to work well for every patient. Those less likely to benefit may include patients who require very high doses of methadone. Buprenorphine is a partial agonist, which means that in severely addicted people, it may not provide enough opiate agonist activity to treat them adequately.

Dr. Fudala says the combined agent may be especially useful for patients who do not have extremely high levels of addiction and for younger individuals, who typically have a shorter abuse history and may be using smaller amounts of an addictive substance. “We’re seeing younger and younger heroin addicts these days,” says Dr. Fudala. “It may be a good initial treatment for them, either as a medical detoxification or, if necessary, as a longer term treatment. We’ll have a better understanding of this as we gain more experience.” Another suitable population may be addicted professionals, including those in health care, who could be motivated to seek treatment in the privacy of a physician’s office setting.

Buprenorphine's suitability for office-based prescribing is based on its pharmacologic profile. Like methadone, buprenorphine activates opiate receptors, but its effects level off as the patient takes higher and higher doses; this reduces the likelihood of dangerous side effects such as severe respiratory depression. The addition of naloxone reduces the potential for abuse by illicit injection: If a combination tablet is crushed and injected by a heroin-addicted individual in an attempt to intensify buprenorphine's euphoric effect, naloxone kicks in to induce the symptoms of opiate withdrawal. Finally, buprenorphine has a relatively long duration of action and causes comparatively mild withdrawal discomfort on cessation, affording flexibility in dosing regimens and a margin of convenience for patients and physicians.

As of March 2004, 3,951 U.S. physicians were eligible to prescribe buprenorphine. Of that group, 2,848 were granted waivers of a Federal requirement for previous experience in addiction medicine. This number is growing, according to Dr. Vocci. "We had estimated that about 6,000 physicians would eventually take the training and get the waiver. So we're at about 50 percent," he says. At this time, he notes, certified physicians are restricted to treating no more than 30 patients. In October 2005, 3 years from the approval of the new drug combination, the Department of Health and Human Services and the Drug Enforcement Administration will evaluate the program and possibly adjust the restrictions. The overall picture, however, is positive, says Dr. Vocci. "Very little diversion has been reported with this new combination," he says.

Source

- Fudala, P.J., et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *New England Journal of Medicine* 349(10):949-958, 2003. **NN**

Once-A-Month Medication for Heroin Addiction?

By Kimberly R. Martin, *NIDA NOTES* Contributing Writer

A single injection of a new sustained-release formulation of buprenorphine substantially blocked heroin's effects and relieved heroin craving and withdrawal symptoms for up to 6 weeks, report researchers at the Behavioral Pharmacology Research Unit at The Johns Hopkins University School of Medicine in Baltimore.

Long-Lasting Buprenorphine Reduces Withdrawal Symptoms in Heroin-Dependent Patients



A new long-lasting, sustained-release form of buprenorphine given by a single injection reduced patients' heroin withdrawal symptoms for 4 weeks after treatment.

The study, the first to test sustained-release buprenorphine in human opioid addicts, affirms the promise of a formulation designed to increase patient adherence to treatment, ease the burden of visits to treatment providers, and reduce the risk of buprenorphine misuse.

Dr. George Bigelow and colleagues evaluated the formulation with five patients, two men and three women aged 33 to 42, who had been using heroin more than 6 years on average and were current daily users. The day before initiating buprenorphine, the researchers administered oral doses of hydromorphone as clinically needed to suppress the patients' withdrawal symptoms. The amount of hydromorphone needed to alleviate withdrawal symptoms is an objective measure of opioid dependence severity. The patients' average opioid addiction was approximately equivalent to 50 mg/day of methadone. Buprenorphine treatment consisted of a single injection of biodegradable polymer microcapsules containing 58 mg of the medication. During the following 6 weeks—a 4-week residential phase and a 2-week outpatient phase—researchers assessed the patients for signs of heroin withdrawal and patients rated their withdrawal symptoms using a standard questionnaire. No patient needed additional medication for withdrawal relief.

To test sustained-release buprenorphine's power to block the effects of heroin-like opioids, patients received weekly challenge test injections of 3 mg hydromorphone or saline under double-blind procedures. Patients' subjective ratings of various hydromorphone effects—such as feeling high, sick, or any effect—stood at zero in the first 2 weeks after buprenorphine treatment. Drug effect ratings in subsequent weeks of the study remained low—less than 25 on a 100-point scale. Moreover, the buprenorphine formulation appeared to be safe and well tolerated, with no significant side effects or signs of opioid intoxication or respiratory depression. These results suggest that sustained-release buprenorphine may prove an appealing and effective treatment option for opioid-addicted patients and their physicians.

Source

- Sobel, B.F.; Sigmon, S.C.; Walsh, S.L.; Johnson, R.E.; Liebson, I.A.; Nuwayser, E.S.; Kerrigan, J.H.; and Bigelow, G.E. Open-label trial of an injection depot formulation of buprenorphine in opioid detoxification. *Drug and Alcohol Dependence* 73(1):11-22, 2004. **NN**

Stimulant Drugs Limit Rats' Brain Response To Experience

By Patrick Zickler, NIDA NOTES Staff Writer

Fresh experience grows our brains—literally. As we navigate novel situations, our brain cells sprout new fibers and form new synapses, weaving new communication networks that enrich our repertoire of responses to life. This growth process is called structural plasticity. According to new NIDA research, amphetamine and cocaine also stimulate structural plasticity, but with a catch: At least in rats, the stimulant-drug-induced growth appears to be associated with a reduced potential for subsequent experience-driven growth.

“What we see in these animals suggests that repeated exposure to these two stimulant drugs limits the ability of later experiences to promote reorganization of synaptic connections in some brain regions,” says Dr. Terry Robinson of the University of Michigan in Ann Arbor. “If there is a similar effect in humans, some of the behavioral and cognitive changes that result from new experiences may be limited by prior exposure to drugs. This drug-triggered mechanism may contribute to the persistent behavioral and cognitive deficits associated with drug abuse and addiction.”

Dr. Robinson, at Michigan, and Dr. Bryan Kolb, at the University of Lethbridge in Alberta, Canada, and their colleagues examined the influence of cocaine and amphetamine on the growth of dendrites—filaments that grow out of brain cells and act as collectors of messages incoming from other cells. Intense proliferation of dendrite branches and spines (shorter projections that terminate in synapses) occurs when rats are put into challenging environments. In animals and people, such growth is thought to be

an important part of normal learning, transforming experience and associations into changes in brain circuitry. In the present study, the scientists looked at what happens when drug exposure precedes exposure to a new, more stimulating environment.

The scientists injected some female rats with amphetamine and others with saline for 20 consecutive days. Amphetamine doses were comparable to those used by individuals addicted to the drug (0.5 mg/kg amphetamine on days 1 and 20, 4.0 mg/kg on days 2 through 19). The animals were then transferred from small, single-animal cages into new housing. Some went into standard double-size cages, three animals per cage; others went into large monkey cages divided into multiple levels and appointed with wire mesh bridges and ramps, tunnels of plastic pipe, ladders, and other items to interest and challenge the rats. After the rats had lived in their new environments for 3.5 months, the researchers assessed the dendrites in two areas of their brains, the nucleus accumbens (NAc) and the parietal cortex (PC). Compared with rats exposed to saline and raised in standard housing, animals that received saline and were moved to a complex



A stained cell from the parietal cortex of a rat brain shows branching of cell dendrites—fibers that receive input from other brain cells (magnification, x250). Increased density of dendrites is a mark of structural plasticity, a process that expands communication among brain cells.

environment had an increase of roughly 11 percent in dendrite density in both brain regions. By the same standard, animals exposed to amphetamine had an increase of roughly 14 percent in dendrite density in the NAc when raised in standard housing or more stimulating housing.

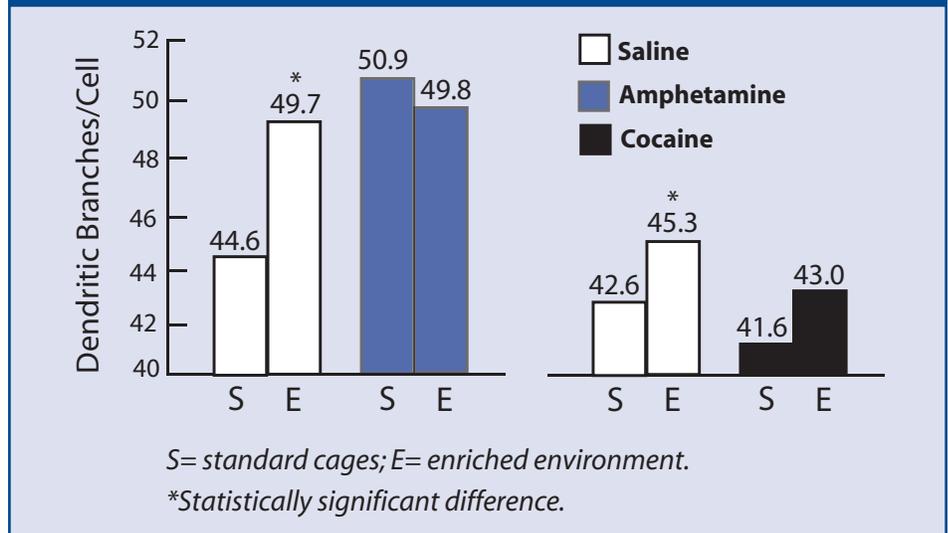
“Both amphetamine and experience in the complex environment increased the number of branches and

spines that developed on dendrites in the nucleus accumbens,” says Dr. Kolb. “However, among the animals exposed to amphetamine, those transferred to the more stimulating environment had no more overall dendritic growth in the NAc after 3.5 months than did those in standard housing.” Previous drug exposure seemed to exhaust the NAc cells’ “budget” for growth, curtailing subsequent plasticity in the NAc.

In contrast to its impact in the NAc, amphetamine did not cause dendrites to grow in the PC, a region of the brain involved in allocating and switching attention among tasks. Rats that received saline exhibited more PC dendrite growth after placement in the enriched housing than after placement in standard housing, while rats given amphetamine grew no more in one environment than the other.

The researchers repeated their experiments, this time using cocaine (15 mg/kg) rather than amphetamine. In earlier work, the researchers determined that the doses of cocaine produced transient structural plasticity. After 3 months, there was no longer any evidence of cocaine-induced

Stimulant Drugs Inhibit Brain Cell Growth In Response to Environment



Relocating rats from standard cages to an enriched environment led to a significant increase in dendrite branching in the nucleus accumbens, but not if the rats were first exposed to amphetamine or cocaine.

structural plasticity in either the NAc or the PC: Cocaine did, however, completely block the dendrite growth exhibited by saline-treated rats when both were kept in a stimulating environment for 3 months.

“This research suggests an alternative explanation for some of the cognitive and behavioral deficits associated with drug abuse,” Dr. Robinson says. “Neuropsychological deficits in addicts are traditionally seen as evidence of either frank toxicity—the equivalent of a physical lesion—or at least a kind of ‘functional lesion’ that makes certain discrete regions of the brain unable to function properly. Our results suggest that some behavioral or psychological deficits resulting from drug abuse may be caused by drugs impairing the ability of some brain regions to make the changes that enable us to learn and profit from our experiences.”

Drugs’ destructive cognitive deficits have important implications for treatment, says Dr. Susan Volman of NIDA’s Division of Neuroscience and Behavioral Research. “We need to take into account the possibility that

the cognitive capacity of drug abusers may be impaired and develop treatments that accommodate this impairment.” Dr. Volman adds that Dr. Robinson’s research does have a hopeful side: “This study examines synaptic structure and indicates that exposure to drugs alters the effects of subsequent environmental experience. That opens up the possibility that the reverse might also be true—exposure to enriching environments might alter the subsequent effect of drugs.”

For now, says Dr. Robinson, the main practical lesson of the findings is that “the brain appears to have a finite amount of plasticity. If that’s really the case, it’s important to make sure that drugs don’t get too big a share.”

Source

• Kolb, B.; Gorny, G.; Li, Y.; Samaha, A-N.; and Robinson, T.E. Amphetamine or cocaine limits the ability of later experience to promote structural plasticity in the neocortex and nucleus accumbens. *Proceedings of the National Academy of Sciences* 100(18):10523-10528, 2003. [NN](#)

“We need to take into account the possibility that the cognitive capacity of drug abusers may be impaired and develop treatments that accommodate this impairment.”

Conference Provides Overview of Consequences Of Prenatal Drug Exposure

By Patrick Zickler, *NIDA NOTES* Staff Writer

On March 23 and 24, NIDA-supported investigators met in Bethesda, Maryland, to discuss long-term consequences of prenatal exposure to drugs. The conference, “Long Term Follow-up of Prenatal Drug Exposure: Advances, Challenges, and Opportunities,” was cosponsored by the National Institute of Child Health and Human Development (NICHD) and the National Institute of Health’s Office of Research on Women’s Health. The meeting brought together more than 100 researchers involved in studying the impact of prenatal exposure to drugs on children. Conference participants described recent findings and discussed research techniques and technology that can make the most effective use of the research cohorts recruited in the past two decades.

“NIDA has long recognized the importance of studies that can follow the development of children from before birth through adolescence and early adulthood,” said Dr. Vincent Smeriglio of NIDA’s Division of Clinical Neuroscience, Development, and Behavioral Treatment. “For example, NIDA supports the Ottawa Prenatal Prospective Study, which began in 1978 and has examined the impact of prenatal tobacco and marijuana use on offspring who are now in their early twenties,” continued Dr. Smeriglio. “Other research projects, such as those designed to examine the effects of MDMA [Ecstasy] and methamphetamine over similarly long developmental periods, are just getting under way.” In all, NIDA’s prenatal drug research involves 24 studies and thousands of prenatally exposed



offspring (see “Summary of Current Prenatal Studies”).

The largest longitudinal study of prenatal drug exposures is the Maternal Lifestyle Study (MLS), an interagency collaboration cosponsored by NICHD. “This study involves more than 1,300 children who now are entering adolescence,” observed NICHD Director Dr. Duane Alexander. “MLS has allowed us to look at the effects of prenatal cocaine exposure as well as the longer term effects of a postnatal environment involving drug abuse. The study has made significant contributions to the field of developmental science, and following these children even longer will help us assess more fully the impact of drugs on development.”

“To move forward in every aspect of prevention and treatment, we must build on our knowledge of what impact drugs have on development and on vulnerability,” said NIDA Director Dr. Nora Volkow. “That is why the focus of the research we’re discussing at these meetings is so important. It is crucial to study the effects of drugs at the earliest stages of brain development, while the fetus is still in the womb.” **NN**

Summary of Current Prenatal Studies

Studies	Total Sample (Range in Study Size)	Current Age Range
Cocaine 14 studies	5,936 (224-1,388)	1 month to 16 years
Tobacco 5 studies	1,108 (100-413)	Newborn to 24 years
Opiates 1 study	100	14 years (at final evaluation)
Marijuana 2 studies	719 (155-564)	18 to 24 years
Methamphetamine 1 study	508	Newborn to 12 months
MDMA (Ecstasy) 1 study	150	Newborn to 24 months

Experts Support CTN Dissemination Strategies

By Dr. Jeffrey Selzer and Barbara Shine, *NIDA NOTES* Contributing Writers

NIDA's National Drug Abuse Treatment Clinical Trials Network (CTN) has as its overriding mission improving the quality of drug abuse treatment. Results from the earliest CTN trials, examining such treatment methods as motivational interviewing, motivational incentives, and buprenorphine therapy, are imminent, as is the need to move those CTN research results into clinical practice. To that end, the CTN Dissemination Subcommittee met in January to discuss effective dissemination strategies.

In his welcoming remarks, NIDA Deputy Director Dr. Timothy Condon said that collaborations are already under way between NIDA and the Addiction Technology Transfer Centers (ATTCs), which are funded by the Substance Abuse and Mental Health Services Administration. Dr. Condon described groups of researchers, clinicians, and experts in technology transfer working together in “blending teams” to help clinicians adopt CTN-tested protocols. These teams have begun work to increase awareness about buprenorphine as a treatment modality and to facilitate the use of the Addiction Severity Index as an outcome assessment tool.

Dr. Everett M. Rogers, Regents Professor of Communications and Journalism at the University of New Mexico in Albuquerque, a leading expert on how innovations are dif-

fused, has studied the process for 50 years. Dr. Rogers calls the CTN an ideal “dissemination scaffold” in light of the link already in place between researchers and practitioners.

According to Dr. Rogers, characteris-

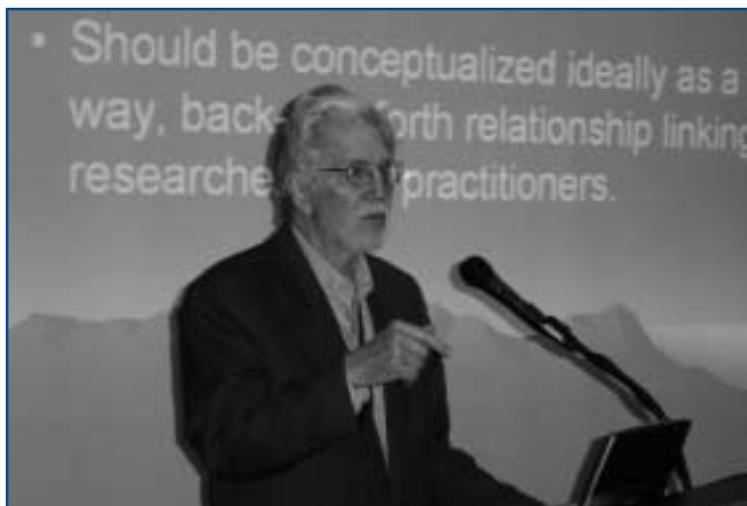
is adopted by a new user, “reinvention is inevitable.” CTN teams that have tested interventions to treat drug abuse should thus anticipate that the interventions will be modified by those who adopt them. In fact, the

CTN teams should see this process as beneficial to dissemination, according to Dr. Rogers.

Dr. Paul Roman, Distinguished Research Professor at the University of Georgia in Athens, concurred with Dr. Rogers on the importance of understanding the provider's point of view when planning to disseminate a clinical innovation. Dr. Roman is now studying how involvement in CTN research affects community treatment programs. His research has shown that treatment programs with a greater tendency to adopt innovations are those whose

managers scan the environment—journals and educational conferences—for new information and are attentive to maintaining high levels of patient satisfaction.

When the experts were asked to comment on the CTN's dissemination plans, they responded favorably: With its collaboration of researchers and providers in the design of studies, the extensive network of community treatment programs within the CTN, and the partnership between NIDA and the ATTCs, they said, the CTN is uniquely positioned to improve drug abuse treatment. **NN**



Dr. Everett M. Rogers, Regents Professor of Communications and Journalism at the University of New Mexico in Albuquerque, and an expert in the field of innovation diffusion, spoke in January at the CTN Dissemination Subcommittee meeting. Dr. Rogers noted that the CTN has a solid framework in place for disseminating innovations in drug abuse treatment.

tics of an innovation that is adopted include the following:

- It confers a **relative advantage** compared with current practice;
- It is **compatible** with other current practices;
- It is of **relatively low** complexity;
- It is possible for the potential adopter to **try before adopting**; and
- As a consequence of trying the innovation, the potential adopter sees **positive results**.

Dr. Rogers emphasized that when an innovation in drug abuse treatment

NIDA Brings “The Science of Addiction” to Times Square

Starting September 14, 2004, visitors can add the cerebral cortex and limbic system to the list of theaters, shops, and famous music sites to explore in Times Square, New York City. NIDA presents “The Science of Addiction”—a display that describes the brain and how it works, the consequences of drugs on brain and body, and facts about commonly abused drugs—at One Times Square through February 1, 2005.

The display is part of *Target America: Drug Traffickers, Terrorists and You*, an exhibit coordinated by the Drug Enforcement Administration (DEA) Museum Foundation that shows the harmful effects of illicit drugs at the societal and personal levels. Comprising contributions from private and public partners—including DEA, the Office of National Drug Control Policy, the Substance Abuse and Mental Health Services Administration, the State Department’s Bureau of International Narcotics and Law Enforcement Affairs, and the National Guard—the exhibit presents information on illicit drug production and trafficking, links with other criminal activities, the impact of drug abuse on

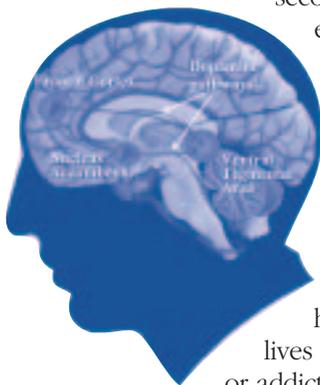
home and workplace, and the latest science on the disease of addiction.

On the exhibit’s entrance floor, visitors can explore topics covered by DEA; NIDA’s display is located on the second floor. The exhibit also features the “Memorial Wall”—a large photo-mural acknowledging the many people who have lost their lives to drug abuse or addiction. NIDA developed text information and graphics for the mural, which highlights the powerful impact of addiction at the personal level.

Using well-designed graphics, the display guides the viewer through a sequence of logically developed information about drug addiction—from the reasons for taking drugs, to the known risk factors for addiction and the vulnerability of the developing adolescent brain, to factors known to facilitate prevention. A section on treatment high-

lights the link between scientific discoveries and therapeutic advances and emphasizes the potential of the brain to recover partially from the disease. This section describes NIDA programs that test therapies for addiction in communities and the criminal justice system. Visitors can view the range of free publications provided by the Institute and can obtain information on how to order or download these from the NIDA Web site.

The DEA Museum designed the exhibit with students in mind, but organizers view the educational goal more broadly. Sponsoring organizations can hold seminars, presentations, press conferences, and other events in the third-floor auditorium. Free admission, the Times Square location, and flexible exhibit hours (open 7 days a week from 9 a.m. to 8 p.m.) make *Target America: Drug Traffickers, Terrorists and You* and “The Science of Addiction” a must-see for anyone who wants to learn about the many-sided consequences of illegal drugs. For more information, contact Exhibit Educator Amy Bloustone at 212-337-1265. **NN**



Leader in Drug Abuse and Addiction Research Honored

Dr. Mary Jeanne Kreek has been awarded the Columbia College of Physicians & Surgeon’s Alumni Gold Medal for Distinguished Achievements in Medicine. Dr. Kreek is the first awardee from the drug addiction research field and the fourth woman to receive this award. She is Professor and Head of the Laboratory of the Biology of Addictive Diseases, Rockefeller University Hospital, The Rockefeller University, and Principal Investigator and Scientific Director of a NIDA Research Center in New York City.

The award cites Dr. Kreek’s pivotal work helping more than 2 million former heroin abusers worldwide

overcome their addiction. “I was deeply honored to receive this award,” says Dr. Kreek. “Forty years ago, we first concluded, contrary to the then-accepted concept, that addiction is a metabolic disease of the brain with behavioral manifestations.

“Over the last 15 years, we have been able to identify many molecular neurobiological changes that are related to the development of specific addictive diseases. During the last 6 years, we have begun to elucidate specific molecular genetic variants that contribute to human addictive diseases.” Dr. Kreek concludes, “This work has all been supported by NIDA research grants, for which we are

extremely grateful.”

A graduate of Wellesley College, Dr. Kreek received her M.D. degree from the Columbia University College of Physicians & Surgeons. She joined the Rockefeller Institute in 1964 and, with Dr. Vincent P. Dole and the late Dr. Marie Nyswander, performed initial studies of methadone for the chronic management of heroin addiction. These studies led to development of the first effective pharmacotherapy for addiction treatment. **NN**



Dr. Mary Jeanne Kreek

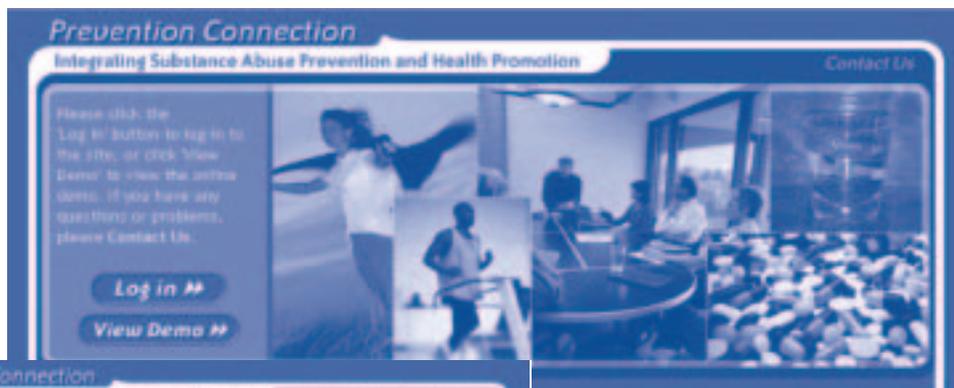
Web-Based Program Trains Practitioners To Add Prevention Messages to Wellness Programs

In the last 20 years, drug abuse prevention strategies have increased dramatically in number and in scientific sophistication. Prevention training programs have not kept pace, especially in the area of equipping health professionals to deliver prevention education to adults.

To make up this lag, ISA Associates of Alexandria, Virginia, offers *Prevention Connection*:

Substance Abuse Prevention Training for Health Promotion Practitioners. The Web-based training program was developed and tested under a NIDA-supported Small Business Innovation Research (SBIR) grant. It uses an interactive, multimedia approach to train wellness professionals to integrate substance abuse prevention materials and messages into health promotion programs across a range of topics—from stress management to healthy eating, active lifestyle, and parenting skills.

“Research shows that by integrating substance abuse messages into health promotion programs in the workplace and community, we can reach a much larger audience and reduce substance abuse,” says Dr. Royer Cook, principal investigator for the project. “Unfortunately, many health practitioners do not know enough about substance abuse or how to incorporate relevant information into their programs. With *Prevention Connection*, any English-speaking health practitioner with an Internet connection can learn in just hours how to integrate substance abuse prevention messages and materials into a wellness program.”



Screen captures from the *Prevention Connection* Web site.

Prevention Connection emphasizes that health promotion and health education practitioners can weave substance abuse prevention information seamlessly into other health promotion programs without losing the program’s impact on the targeted health behavior. In addition to hands-on exercises that allow practitioners to build their own program outlines, *Prevention Connection* helps wellness professionals understand the importance of integrating substance abuse prevention with health promotion and shows how substance abuse prevention makes good business sense.

Practitioners will appreciate *Prevention Connection’s* indepth look at the leading substance abuse prevention models and theories, descriptions of innovative workplace prevention programs, and facts about drugs

and their effects. ISA tested the program with members of the Worksite Health Promotion and Health Educator Groups of the American College of Sports Medicine, who found it engaging and effective.

In the past two decades, ISA has completed eight NIDA-funded SBIR projects. Two more prevention projects are in development: One targets prescription drug abuse, and the other is a DVD-based program for young adults in the workplace.

For More Information . . .

The current annual licensing fee for an individual *Prevention Connection* user is \$495; group rates are available. To order *Prevention Connection* or to get more information about this and other employee-focused health promotion programs offered by ISA Associates and the Center for Workforce Health (www.centerforworkforcehealth.com), please contact Dr. Tracy McPherson (tmcpherson@isagroup.com) or Dr. Cook (rcook@isagroup.com) at 703-739-0880. **NN**

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