

# Epilepsy Drug Stops Nicotine’s Addictive Effects in Animals; Also Shows Promise in Animals for Treating Cocaine Addiction

Smokers who want to kick the habit may find powerful help from a European epilepsy drug that already has shown promise in treating cocaine’s effects in animals, U.S. Secretary of Energy Bill Richardson announced at a press conference at DOE headquarters in Washington, D.C., on Wednesday, December 2.

That is the conclusion of animal studies published today in the journal *Synapse* by scientists from BNL, St. John’s University, New York University School of Medicine and the Albert Einstein College of Medicine.

“Smoking-related diseases are responsible for one in five deaths in the U.S.,” said Richardson. “With 35 million smokers trying to quit each year, and only 7 percent succeeding for more than a year, this new effort, if successful, could save millions of lives. Once again, government-funded scientists are at the forefront of the cutting-edge research enabling us to confront a major health problem.”

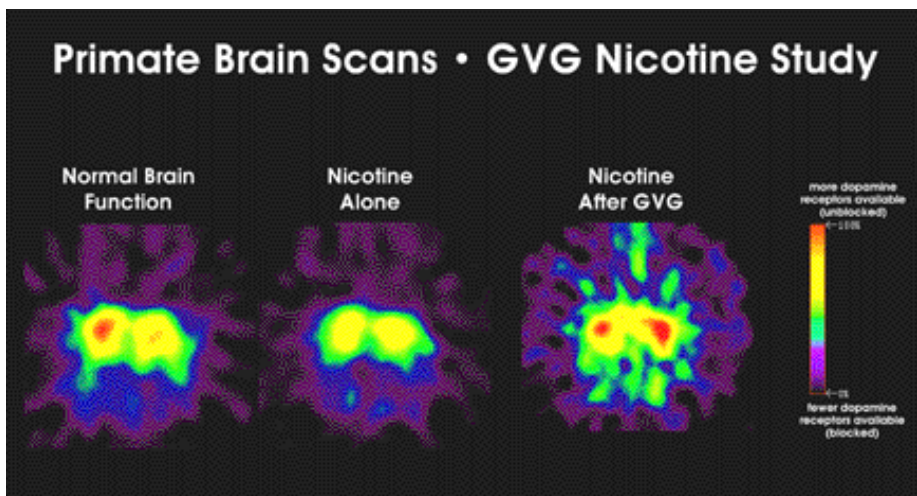
The same research team published results in August showing that the epilepsy drug — known as gamma vinyl-GABA, or GVG — looks very promising as a treatment for cocaine addiction. In animals, it prevented the dramatic changes in brain chemistry and behavior brought on by cocaine (see Bulletin, August 7, 1998).

The new paper shows that GVG does the same for nicotine. And, the dose needed to block nicotine was about one-tenth of that used to block cocaine’s effects in animals. The nicotine-blocking dose corresponds to about one-tenth to one-twentieth the dose currently used to treat epilepsy in humans. Upcoming clinical trials will determine the dosage needed in humans.

According to Alan Leshner, Director of the National Institute on Drug Abuse within the National Institutes of Health, “This study confirms the importance of the brain’s GABA system as an important target for potential anti-addiction medications like GVG. It also emphasizes that there likely are common brain mechanisms underlying addiction to all drugs and gives hope that we can develop a single medicine to use in treating addiction, whatever the primary addictive drug.”

The evidence is so strong that the scientists think GVG might work better and have fewer side effects than other stop-smoking treatments available today. It is not addictive, is not based on nicotine, and has been used safely in Europe by epileptic children for more than a decade.

“Of all the addictive drugs that exist, nicotine is the most frequently abused drug in the world, and every smoker who has tried knows how hard it is to quit,” said BNL’s Stephen



**Positron emission tomographs of the brains of primates, showing (from left) the concentration of dopamine during normal brain activity, how the concentration is affected by the administration of nicotine, and how dopamine concentrations are closer to normal if the epilepsy drug GVG is given before nicotine is administered.**

Dewey, the lead author on the paper. “We’ve shown in animals that the proper dose of GVG can stop nicotine’s addictive effects entirely.”

The team’s research also suggests that GVG may work against a variety of other addictions.

“We are gaining confidence that this approach could offer hope to all addicts, from smokers and alcoholics to hard-core heroin and cocaine users,” said team member Charles Ashby of St. John’s.

Added coauthor Jonathan Brodie of New York University (NYU), “Since the same brain chemistry changes may be common to all these addictions, it follows that a single well-aimed strategy, combined with a person’s desire to quit, could assist in defeating them all.”

To show whether GVG can be as effective in humans as it is in animals,

clinical trials are now being planned at institutions in Europe, Canada and the United States.

Though GVG is not currently approved in the U.S. to treat epilepsy, U.S. institutions can apply to conduct clinical trials under investigative new drug protocols from the U.S. Food & Drug Administration.

The research grew out of cooperative work to understand the brain’s chemical messengers, called neurotransmitters, and the effect of addictive drugs on the balance of those chemicals in the brain. One neurotransmitter in particular, called dopamine, plays a central role in the sensations and behaviors associated with all drug use.

The GVG results on cocaine were published after more than a decade of investigation that started when Dewey and NYU’s Brodie looked at the way

brain cells “talk” to one another, especially in people with schizophrenia.

Soon after receiving encouraging results on cocaine, the team began testing GVG against other addictive substances. Work on alcohol, heroin, morphine, amphetamines, and methamphetamines is nearing completion.

### Tobacco’s Addictive Hook

The researchers looked at how different doses of GVG changed nicotine’s ability to alter brain dopamine levels in rodents and primates.

They used sophisticated imaging techniques to measure dopamine concentrations in the brains of both nicotine-addicted rodents and those that had never been exposed to nicotine. And they performed brain scans on female baboons given intravenous nicotine.

“Nicotine doubles the brain’s dopamine level, sending a rush of pleasure and a signal that you should smoke over and over again,” said Dewey. “But, an appropriate dose of GVG taken before nicotine exposure can completely block nicotine’s effects on brain dopamine.”

GVG increases the levels of another brain chemical, GABA, which decreases dopamine production. So, GVG prevents nicotine from causing dramatic changes.

### Studying the Behavioral Effects

As any smoker will attest, nicotine addiction is not just a matter of the mild rush caused by smoking. The mere sight or smell of cigarettes, or of a smokers’ hangout, can bring on a craving.

This kind of behavioral effect is what makes quitting smoking so hard. So, Ashby and his colleagues tested

(continued on page 2)

## PET Imaging, Other Techniques Reveal GVG Effects

The Brookhaven-led studies of GVG, or gamma vinyl-GABA, involved research on the brains of both primates and rodents as stand-ins for the human brain, using many different biochemical and behavioral techniques.

The team’s first publication in 1992 demonstrated that GVG inhibited brain dopamine in rodents, as well as the biochemical effects of cocaine in the region of the brain that is thought to play the most important role in addiction. These studies served as the impetus to pursue GVG further in primates, and to look at its role in cocaine- and nicotine-related behavior.

The primate studies reported Wednesday (see story above) used a sophisticated medical imaging technique called PET, for positron emission tomography. PET scans are made using a large donut-shaped detector, which records faint signals from short-lived radioactive isotopes injected into the body. PET is used in hospitals and scientific institutions throughout the world for research and diagnosis. BNL researchers have used PET scans for decades to study the brain, and have made many discoveries pertaining to addiction, aging, mental illness, and normal brain function.

For the current study in *Synapse*, the researchers looked at the brain scans of primates before and after they had taken nicotine. In contrast with the primates who had been ad-

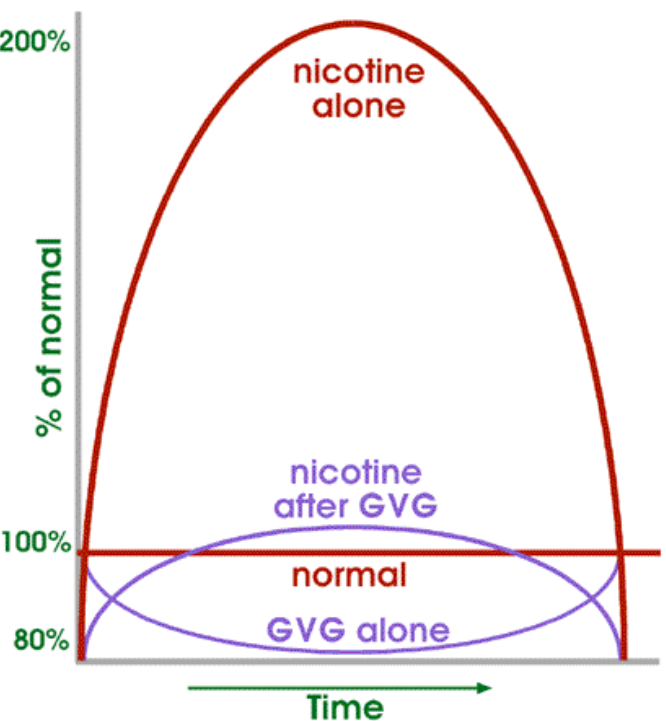
ministered nicotine but had not been given any GVG, the primates that had been given a dose of GVG before their nicotine dose showed normal levels of dopamine in the brain (see graph).

Other methods used to evaluate GVG’s effects involved rodents. For example, researchers at St. John’s University and Boston University gave rats nicotine repeatedly in order to examine their behavior when they received GVG. They also looked at the rats’ tendency to return to a place where they had gotten nicotine previously.

Called conditioned place preference, or CPP, this behavior is also important in human addiction. Recovering addicts often fall back into addiction if they are exposed to stimuli that they associate with their former use of the drug.

The primates used in this study are

### Brain Dopamine Levels



part of a resident group housed at BNL in facilities accredited by the Association for the Assessment & Accreditation of Laboratory Animal Care. All studies were sanctioned by BNL’s Institutional Animal Care & Use Committee and corresponding committees at the collaborating institutions.

— Kara Villamil

### Coming Up

**Robert Crease, BNL Historian and Associate Professor of Philosophy at the State University of New York at Stony Brook, will deliver the 341st Brookhaven Lecture, “Breakdown: The Events of 1997,” on Wednesday, December 16, at 4 p.m. in Berkner Hall. All are invited.**



## Research at BNL Into Addiction

In 1987, BNL became the first research institution to use positron emission tomography (PET) and other medical imaging techniques to investigate the brain mechanisms underlying drug addiction. Since then, Lab researchers and their collaborators and colleagues at other institutions have probed the mysteries of how drugs such as nicotine (see story, page. 1) and cocaine affect the brain and how they lure a person into the cycle of use and abuse that is addiction.

Much of this research has used medical imaging techniques of ever-increasing sophistication. BNL scientists were pioneer developers of PET technology and radiotracer drugs, the movement of which in the brain is tracked by PET scans.

Brookhaven chemists were the first to make a radiotracer incorporating cocaine that could be used for addiction studies. They also developed a fluorine-glucose compound now used in hospitals and research institutions worldwide to make images of brain function and diagnose cancer.

Using the cocaine radiotracer, BNL scientists made the first images of cocaine in the brain and the first studies linking cocaine's effects on brain function to the compulsive use of the drug. These efforts led to the first documentation of stroke-like changes in the brains of cocaine abusers and the beginning of a series of studies to map the biochemical and anatomical changes responsible for drug-addictive behaviors.

Another addiction study at BNL compared the behavior in the brain of cocaine and the psychostimulant drug methylphenidate, commonly known as Ritalin, in an effort to lay the foundation for treating addiction.

A third example of addiction research at Brookhaven showed that smokers have a marked decrease in a brain enzyme which breaks down brain chemicals involved in pleasure and reward. This result suggested that something other than nicotine may play a role in tobacco addiction.

Among the drugs being studied at BNL are: alcohol, cocaine and related drugs, heroin and opiates, and marijuana.

Lab researchers collaborate with scientists and physicians from other institutions in formulating and carrying out experiments and in recruiting volunteer human subjects.

All studies involving human subjects at BNL are reviewed by an institutional review board, which is overseen by DOE's independent human-subjects committee and observes procedures laid out in federal legislation for the protection of human subjects.

— Kara Villamil

## Lunch Concert 12/8

The Stony Brook Chamber Singers, directed by Timothy Mount, will perform seasonal music at a seasonal-specialty lunch. This will be offered at the cafeteria at noon on Tuesday, December 8, and all are invited to attend.

The 15-voice chorus, two flautists, and keyboard accompanist will present selections from Handel's *Judas Maccabeus*, carols from around the world, and secular music from the Spanish Renaissance.

## Equipment Demo

On Thursday, December 10, and Tuesday, December 15, Direct Wireless will display its products and services in Berkner Hall, 10 a.m.-2 p.m.

## RHIC Open House for Employees 12/9



**Attention Lab employees, facility-users, retirees, and guests: Wednesday, December 9, may be your last chance to get an insider's look at what BNL's Relativistic Heavy Ion Collider (RHIC) is all about. That is because RHIC construction is soon ending and operations are expected to begin in January 1999. Therefore, before the RHIC cool-down and the countdown to circulating beam begin, make time next Wednesday to take a once-in-a-lifetime tour around this really big machine and its associated detectors during the RHIC Open House. The open house features one-hour-and-ten-minute tours leaving from Berkner Hall promptly at 10 a.m., 10:35 a.m., 11:10 a.m., 11:45 a.m., 12:20 p.m., 12:55 p.m., and 1:30 p.m. In addition to the RHIC ring, open-house-goers will see one of RHIC's two major experiments — STAR or PHENIX — now under construction in their massive experimental halls. Employees are asked to check with their supervisors before leaving for the tours, and to take the bus from Berkner, since the ring area cannot accommodate any cars. For more information, contact Museum Programs Manager Janet Tempel, Ext. 4049.**

### Nicotine (cont'd.)

GVG's effect on rats' tendency to seek out a place where they had previously received nicotine, and their ability to acquire that tendency in the first place. The technique is called conditioned-place preference, or CPP.

"It was astounding," said Ashby. "Not only could GVG keep addicted animals from returning to the nicotine-associated place, but also a somewhat higher dose kept non-addicted ones from getting the habit in the first place." He commented that similar

tests have not been done on stop-smoking therapies currently on the market.

The research was funded by the U.S. Department of Energy, the National Institute on Drug Abuse and the National Institute of Mental Health. In addition to Dewey, Ashby and Brodie, the paper's authors are Bryan Horan of St. John's, Madina Gerasimov of BNL, and Eliot Gardner of Einstein.

— Kara Villamil  
*Additional information on this research is available on the World Wide Web at: [www.pet.bnl.gov](http://www.pet.bnl.gov).*

### GVG: Targeting the Brain's Communicators

GVG, or gamma vinyl-GABA, appears to prevent the effects of nicotine, cocaine and possibly other drugs in much the same way it prevents an epileptic seizure: by altering the way brain cells "talk" to one another.

In the brain, chemicals called neurotransmitters constantly float between brain cells, sending messages that travel through the brain and into the body in a process similar to the child's game "Telephone."

After neurotransmitter molecules complete their task of leaving their home brain cell and docking with a neighboring cell to convey the message, they usually return to their home cell or are eliminated in the space between cells, called the synapse. But nicotine, cocaine and many other addictive drugs wreak havoc with this process.

One neurotransmitter, called dopamine, has been described as the "feel-good" neurotransmitter. That is because drugs like nicotine and cocaine cause a pleasurable or "high" feeling by keeping dopamine molecules from reentering their home cells and thus creating floods of dopamine in the brain. This pleasurable reaction is crucial to the process by which addiction starts.

GVG is used to treat epilepsy because it increases the amount of the brain's most common neurotransmitter, called GABA, and enables better communication among brain cells. This moderates the effects of the uncontrolled neurotransmitter releases that cause epileptic seizures.

Coincidentally, GABA also reduces the level of dopamine in the region of the brain that is involved in addiction to nicotine, cocaine and other substances. Knowing this, the BNL-led research team first focused on this normal interaction between GABA and dopamine in order to lay the foundation for a novel strategy to treat drug addiction.

The team began working with GVG because it enhances GABA levels, and developed ways to see if the epilepsy drug would reduce the surge in dopamine produced by nicotine in both primates and rats. They also wanted to see if it would prevent the development and expression of other behaviors associated with addiction.

The studies began in the early 1990s, and preliminary results have been reported before in the journal *Synapse*. The results from the cocaine investigation were reported in *Synapse* in August, and results from studies of other addictive drugs are expected soon.

— Kara Villamil

## Outreach Workshop The Heart, Mind Connection in Heart Disease

Disease of the coronary arteries feeding the heart is the leading cause of death and disability in the U.S. To check this disease's course, medicine has encouraged changes in diet, exercise and smoking, and it has assembled an array of drugs and surgeries.

While these often work alone or in combination, another factor that affects the outcome of coronary artery disease has been identified: emotions.

To discuss "The Heart and Mind: The Psychology of Coronary Artery Disease," clinical psychologist Leslie Bowling will present an Outreach workshop next Friday, December 11, at noon in Berkner Hall. Sponsored by the Employee Assistance Program (EAP) of the Occupational Medicine Clinic, the lecture is open to all.

A psychologist and psychoanalyst, Leslie Bowling has a private practice in New York City and Sag Harbor. Following his own participation in the Dean Ornish cardiac rehabilitation program at Beth Israel Hospital, Bowling began his professional pursuit of the mind-body connection in the development and treatment of heart disease.

To register for this workshop, return the completed bottom portion of the Outreach flyer to be sent to all employees to EAP Staff Psychologist Dianne Polowczyk, Bldg. 490, by Thursday, December 10.



## Last Day for Books

Today, December 4, is the last day of the annual BERA winter book fair — so, rush to Berkner Hall between 10 a.m. to 3 p.m., grab a corner chair, and browse or buy *The New York Times* best-sellers, cookbooks, children's books and other quality hardbacks offered there at 50-75 percent off list price. For more information, call Andrea Dehler, Ext. 3347, or M. Kay Dellimore, Ext. 2873.

## DCP Help Desk

The Division of Contracts & Procurement (DCP) has established a help desk to assist requisitioners with their procurement questions. To reach the help desk, phone Ext. 3432, fax Ext. 5499 (and note "Attention: Help Desk"), or e-mail [dcphelp@bnl.gov](mailto:dcphelp@bnl.gov).

## Computer Training

The Computing & Communications Division will hold a January class on Front Page, a Web page development tool. For more information, e-mail Pam Mansfield at [pam@bnl.gov](mailto:pam@bnl.gov).





**OPEN RECRUITMENT** - Opportunities for Laboratory employees and outside candidates.

MK1111. MANAGER, RADIATION PROTECTION SERVICES DIVISION - Requires a BS in health physics or related discipline, an advanced degree preferred, certification as a health physicist by the American Board of Health Physics, and substantial experience in radiation-protection activities including at least five years of progressive management experience in radiation protection at DOE-regulated facilities and NRC-regulated facilities. In addition, must have proven track record and DOE recognition for developing, implementing, and managing a comprehensive radiation-protection program at BNL-like facilities, and strong verbal and written communications skills. Will be responsible for designing, developing, implementing, and managing the radiation-protection management system in a compliant and cost-effective manner. Will provide radiation-protection technical support services to line, facility and project managers, and will achieve a balance among compliance, internal and external customer satisfaction, and budget constraints. Environment, Safety & Health and Quality Directorate.

MK7830. SCIENTIST - (reposting) Requires a Ph.D., experience in instrumentation development for accelerator and experimental beam-line systems, expertise in ultrahigh vacuum technology, knowledge of the interface of accelerator systems with beam-line operations, and demonstrated capability of collaborating on cross-disciplinary projects and establishing independent research programs. Strong mechanical background preferred. Under the direction of E. Johnson, National Synchrotron Light Source Department.

MK7650. SCIENTIST - Requires a Ph.D. and research experience in the area of on-line/DAQ in a large high-energy or nuclear physics experiment. Experience in C++, OO development, JAVA, CORBA, object databases, Windows NT, Sun/Solaris, and LINUX highly desirable. In developing on-line and off-line software, will work within STAR, a large detector at the Relativistic Heavy Ion Collider which is designed to study relativistic heavy ion and polarized-proton interactions. The on-line software project encompasses run control, on-line monitoring, configuration management, and on-line data bases. Under the direction of T. Hallman, Physics Department.

MK7942. POSTDOCTORAL RESEARCH ASSOCIATE - Requires a Ph.D. in organic chemistry or related discipline, and experience in synthetic organic chemistry and mass spectrometry. Will be involved in the broad area of environmental organic chemistry and organic geochemistry; specific areas of research include formation of geo-macromolecules from biological precursors, humic substances, metal-organic matter interaction in soils and sediments, and characterization of metallothioneins and related metal-binding biochemicals from bacteria. Under the direction of A. Vairavamurthy, Department of Applied Science.

MK7944. POSTDOCTORAL RESEARCH ASSOCIATE - Requires a Ph.D. in organic geochemistry or related discipline, experience in sulfur and nitrogen geochemistries, and the ability to use state-of-the-art chromatographic and spectroscopic instrumentation, including GC-MS and LC-MS. Will primarily be involved in research of sulfur geochemistry aimed at a fuller understanding of the geochemical mechanism of sulfur incorporation into sedimentary organic matter, and the role of sulfur in the preservation and diagenesis of organic matter in marine sediments. Under the direction of A. Vairavamurthy, Department of Applied Science.

NS7728. PROGRAMMER/ANALYST POSITION - Requires an MS degree or equivalent experience in computing or related field, several years' experience in C programming and data-base programming using Oracle. Duties involve working with engineers, physicists and other programmers to define data-base requirements and assist in the implementation of a control system for the Spallation Neutron Source Project. Alternating Gradient Synchrotron Department.

NS7719. ENGINEERING POSITIONS - (2 openings, reposting) - Requires a BS/MSEE and a minimum of five years' experience in the design of analog circuits, feedback systems, power electronics, power supplies, and solid-state converter technology. Experience in multi-kilowatt power supplies and fast-pulsed power techniques a plus. Alternating Gradient Synchrotron Department.

NS7721. ENGINEERING POSITIONS - (2 openings, reposting) - Requires a BS/MSEE with broad experience in the design of analog circuits and feedback systems. Experience in sophisticated instrumentation design, low-level noise immune circuit design, and computer interfacing is required. Alternating Gradient Synchrotron Department.

NS7388. PROGRAMMER/ANALYST POSITIONS - (2 openings) - Requires a bachelor's degree in computer science or related field; four to six years' programming experience (proficiency in any two of the following: VB, VB Script, C, C++, Java, Java Script or People Code), and excellent communication skills. Working knowledge of human-factors techniques, the Windows environment and Microsoft Office products is necessary, as is conceptual knowledge of object-oriented design concepts, two-tier and n-tier architectures, and relational databases. PeopleSoft experience is a plus. Financial Services Division.

DD7461. TECHNICAL POSITION - (reposting) Requires a BS in electronic technology or equivalent. Familiarity with network technology is desirable, including cabling, cable testing, network protocols, fiber optics, routers, switches, and diagnostic tools. Additional responsibilities involve assisting the computer group in maintaining NSLS control systems, which includes workstations and VME systems. Will assist in the maintenance and administration of the department's communication networks. Will also assist the staff with the installation and set-up of computers connected to the network. National Synchrotron Light Source Department.

DD4512. PHYSICIST/ENGINEERING POSITION - (reposting) Accelerator physicist/engineer to work on the operation and improvement of the existing NSLS storage rings. Areas of work include lattice modeling, orbit control, injection optimization, and study of beam intensity-limiting effects. Experience in the development of the related hardware and diagnostic equipment is desired, as well as skill in developing software application programs. Demonstrated independence in work and the ability to coordinate activities also required. National Synchrotron Light Source Department.

DD4515. TECHNICAL POSITION - (reposting) Requires a BSET or equivalent, and a thorough knowledge of digital logic concepts. Familiarity with high-speed analog circuitry and rf techniques is desirable. Requires the ability to use various types of test