

BNL-Led Researchers Find Drug Blocks Cocaine 'High' in Animals; May Stop Other Addictions; Clinical Trials Planned Later This Year

A team of BNL-led scientists announced on Wednesday, August 5, at a press conference held at the New York Academy of Sciences, that an inexpensive epilepsy drug may prove to be a highly effective pharmaceutical treatment for cocaine addiction.

In addition, preliminary data suggests that it may be useful for the treatment of other addictions.

These conclusions, based on animal studies, were published Wednesday in the journal *Synapse* by Brookhaven scientists and their colleagues from St. John's University (SJU), New York University (NYU), the Albert Einstein College of Medicine, and Boston University (BU).

The team showed that the epilepsy drug gamma vinyl-GABA, or GVG, blocked cocaine's effect in the brains of primates, including the process that causes a "high" feeling in humans. GVG also significantly decreased the animals drug-seeking behavior.

But GVG neither stopped the animals' routine functions, such as learning, eating and moving, nor did it cause other obvious side effects.



(Center, from left) Jonathan Brodie, NYU; Charles Ashby Jr., SJU; Stephen Dewey, BNL; and others at Wednesday's New York Academy of Sciences press conference, where cocaine-blocker findings were announced.

After more than a decade of work, "We are extremely excited about our results," said Chemist Stephen Dewey, Chemistry Department, the BNL neuroanatomist who led the research team. "If this can do for humans what it does for animals, then we may have opened the door for addicts around the world to kick their habit and for society to stop the costly cycle of addiction, violence and wasted lives. My colleagues and I are unaware of any other drug that has looked as promising."

Later this year, Brookhaven and NYU plan to begin a clinical trial to test GVG's effect on volunteer human cocaine addicts. Other institutions are also planning clinical trials.

The animal research was sponsored by DOE's Office of Energy Research and the National Institute of Mental Health, with involvement by the National Institute of Drug Abuse (NIDA).

"The Clinton Administration's war against drugs is being fought on all fronts — not just in the streets, but in the laboratory as well," said Acting Energy Secretary Elizabeth Moler. "We want Americans to know that we've got the best scientific minds in the country working hard to halt the destruction of lives and communities caused by drug addiction. Wednesday's announcement offers the thrilling prospect that we may be closing in on a major science-based victory."

"These exciting preclinical data point to a major new approach to developing medications for cocaine addiction," said NIDA Director Alan Leshner. "Since we have no medications for cocaine overdose or addiction now in our clinical toolbox, NIDA has declared developing anti-cocaine medicines our top priority."

In addition to Dewey, the following were members of the team involved in this research: Alexander Morgan, Jean Logan, and Joanna Fowler, all of the Chemistry Department; Nora Volkow, Medical Department; Charles Ashby Jr., SJU; Jonathan Brodie and Bryan Horan, NYU; Stephanie Kushner, BU; and Eliot Gardner, Albert Einstein College of Medicine.

GVG's Anti-Cocaine Effects

"While other pharmaceutical approaches to treating cocaine addiction have shown promise in animals, there

is currently no effective pharmacological treatment for cocaine addiction in humans," said Dewey. "In fact, the limited number of drugs currently being investigated in human addicts may prove to be addictive in themselves, or create tolerance and withdrawal symptoms."

GVG's anti-cocaine effects have been tested more extensively in animals than any of the previously reported drugs. The BNL-led team used a total of ten techniques, including state-of-the-art medical imaging and behavior studies, to confirm their result.

GVG was originally developed to

treat epilepsy. It is already in use in Europe and Canada, where patients have been taking it safely for several years. The U.S. Food & Drug Administration (FDA) has reviewed its safety and effectiveness for potential use in treating epilepsy in the U.S. It is expected to receive final FDA approval for epilepsy use this fall.

Wednesday's publication is the culmination of more than 12 years of investigation, which started when Dewey and co-author Jonathan Brodie, a psychiatrist at NYU's School of Medicine, began to look at the way brain cells talk to one another, especially in those afflicted with the mental illness schizophrenia. "These studies resulted directly from our early efforts to develop new treatment strategies for schizophrenia," Dewey said.

As the research progressed, Dewey and his colleagues realized that GVG might be useful in the treatment of drug addiction. They tested their surprising hypothesis over the past several years, arriving at the conclusions published on Wednesday in *Synapse*.

"Because cocaine addiction is part biochemistry and part behavior, these results confirm that it is possible to attack it on both fronts," said Charles Ashby Jr., the SJU researcher who led the behavioral component of the study.

"One must always be cautious, however," said Brodie. "A serious clinical investigation is the logical consequence to this most exciting preclinical work."

Now, said Dewey, "the challenge is to see if GVG has the same effect on other addictions that involve the same set of neurotransmitters."

— Kara Villamil

Research 'Angels'

Just as no Broadway shows could run without what are called their angel backers, no research can be done without financial support.

Addiction studies at BNL are funded largely by the **U.S. Department of Energy's (DOE) Office of Energy Research** through its **Office of Biological & Environmental Research**.

DOE supports the development and use of radiotracers for positron emission tomography (PET) imaging, and advancing the use of medical imaging and other technologies to understand the processes of the human brain.

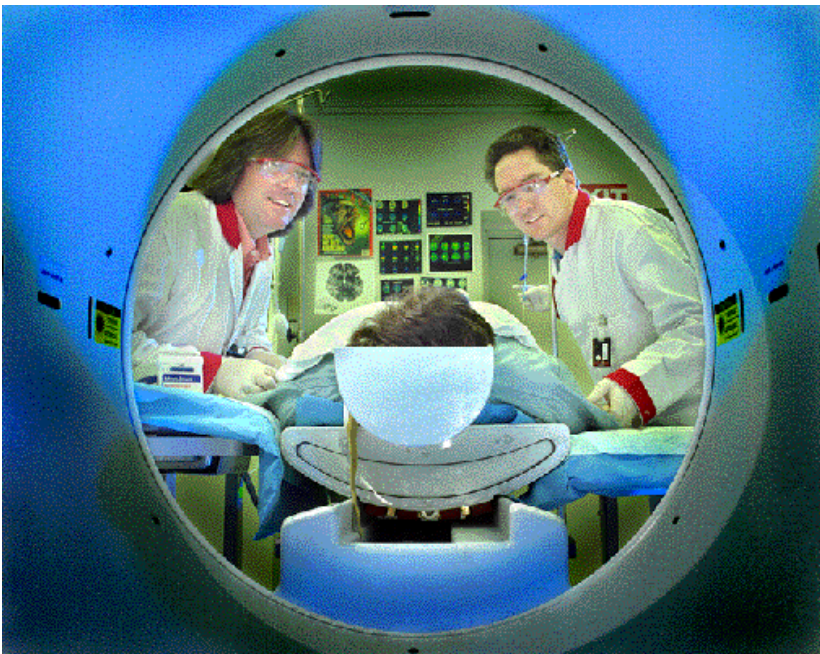
Another essential funding agency is the **National Institute on Drug Abuse (NIDA)**, which supports more than 85 percent of the world's research on drug abuse and addiction, ranging from the molecule to managed care, and from DNA to community-outreach research. NIDA also has founded a Regional Neuroimaging Center at BNL, the first outside of NIDA headquarters.

The **National Institute of Mental Health (NIMH)** is the foremost mental-health research organization in the world, with a mission of improving the treatment, diagnosis, and prevention of mental disorders such as schizophrenia and depressive illnesses, and other such conditions that affect millions of Americans.

Since the 1980s, NIMH has supported NYU and Brookhaven researchers who study the biochemical underpinnings of schizophrenia through functional PET imaging. These studies were the foundation for studies of GVG's impact on cocaine's biochemical and behavioral effects. NIMH has also funded other functional imaging research at BNL, including studies of Alzheimer's disease.

— Kara Villamil

BNL: First to Study Human Addiction Using Medical Imaging of the Brain



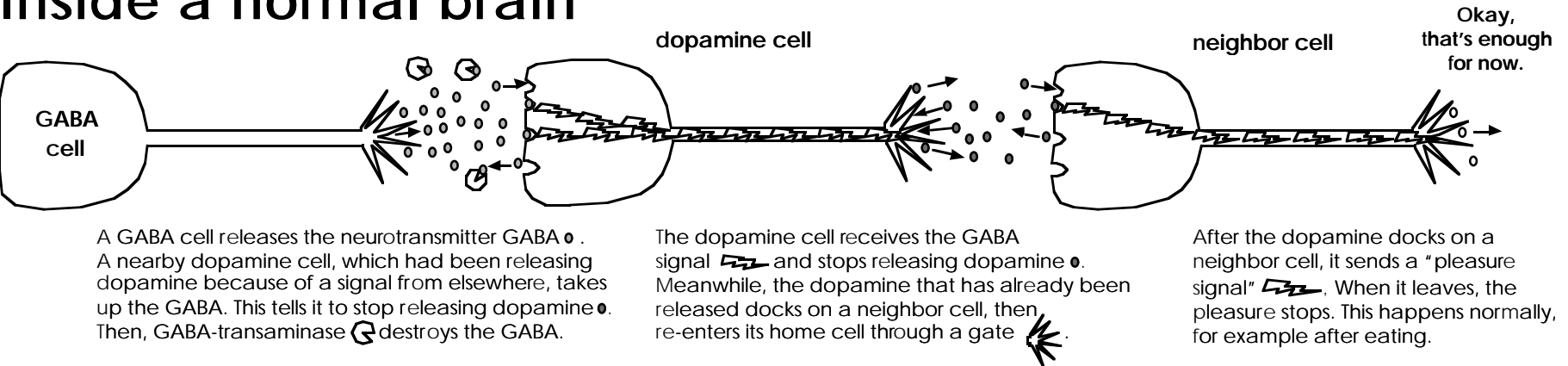
BNL's Stephen Dewey (left) and Charles Ashby Jr. of St. John's University posed using Brookhaven's positron emission tomography (PET) scanner.

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, BNL researchers and their collaborators and colleagues at other institutions have probed the mysteries of how drugs such as cocaine affect the brain and how they lure a person into the cycle of abuse.

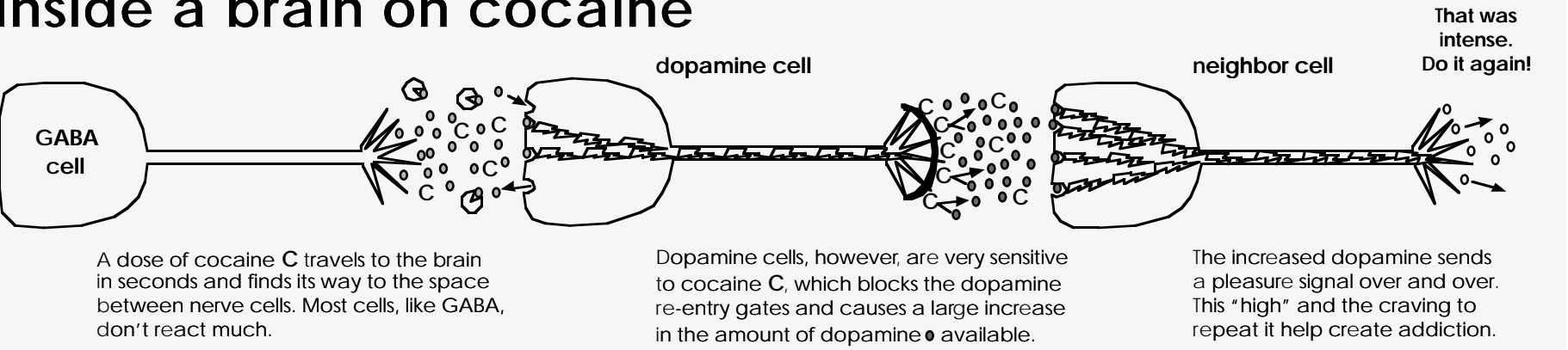
Much of this research has used medical imaging techniques of ever-increasing sophistication. BNL scientists were pioneer developers of PET technology and of the radiotracer drugs, movements of which in the brain is tracked by PET scans.

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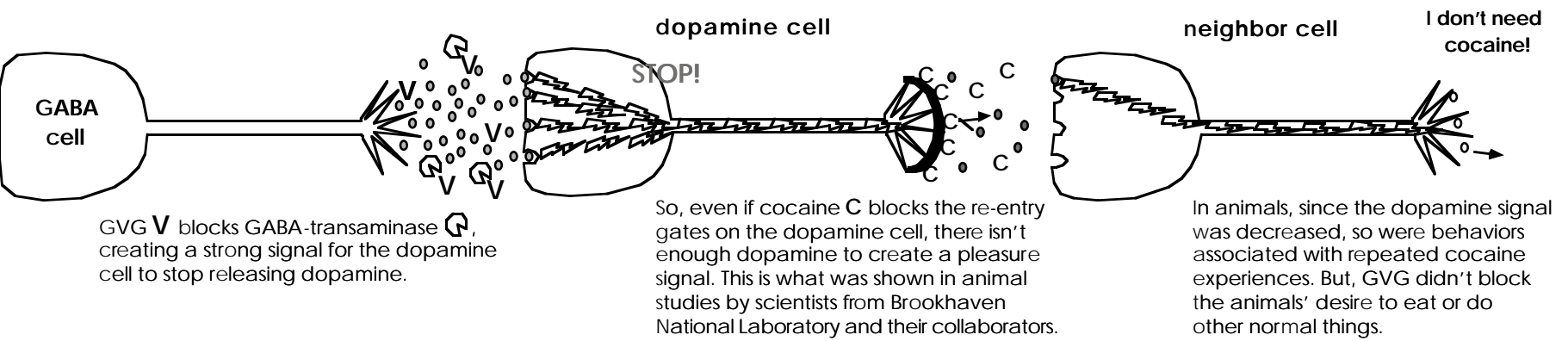
Inside a normal brain



Inside a brain on cocaine



Inside a brain on cocaine after GVG



KV • © BNL • 7/98

Sanctioned Use: Animals as Models For the Human Brain

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 ten different biochemical and behavioral techniques. All studies were sanctioned by BNL's Institutional Animal Care & Use Committee and by corresponding committees at the collaborating research institutions. The research 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-related behavior. The primate studies reported Wednesday used a sophisticated medical imaging technique called PET, for positron emission tomography. PET scans are made using a large donut-shaped "camera," 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 re-

searchers have used PET scans for decades to study the brain, and, with PET, they have made many discoveries pertaining to addiction, aging, mental illness and normal brain function. **Current Study** For the current study in *Synapse*, the researchers looked at the brain scans of primates before and after they had taken cocaine. The primates that had been given a dose of GVG before their cocaine dose showed normal levels of dopamine in the brain, compared with those that had not gotten GVG. The primates are part of a resident group housed at BNL in facilities accredited by the Association for the Assessment & Ac-

creditation of Laboratory Animal Care. Other methods used to evaluate GVG's effects involved rodents. For example, researchers at St. John's University and Boston University gave rats cocaine 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 cocaine previously. Called conditioned place-preference, or CPP, this behavior is also important in human cocaine addiction. Recovering addicts often fall back into addiction if they are exposed to stimuli that they associate with their former use of the drug, for example, drug paraphernalia or an alley or house where they routinely bought or used drugs. — K.V.

For Immediate Help, Call These Numbers

- Because clinical trials to study the effects of GVG in human beings who are addicted to cocaine are not yet underway, and because GVG will only become available in this country in October for the treatment of epilepsy, GVG is not yet available to those American who are addicted to cocaine or other substances but who are seeking immediate treatment. Therefore, those in need of help now for cocaine or other addiction should contact one of following:
- **Cocaine Hotline: 1-800-COCAINE.** Provides treatment referrals and some drug information.
 - **Alcohol Hotline: 1-800-ALCOHOL.** Provides help and referrals for people with concerns about alcohol or drug use.
 - **National Drug & Alcohol Treatment Referral Service: 1-800-662-HELP.** The Center for Substance Abuse Treatment will link callers to a variety of hotlines that provide treatment referrals.
 - **NCADD Hopeline: 1-800-622-2255** Will refer the caller to a local affiliate office of the National Council on Alcoholism & Drug Dependence (NCADD). Callers can also leave their name and address to receive written information about alcohol and other drug abuse. A touch-tone phone is required.
 - In addition, Lab employees with addiction and substance-abuse problems may, during business hours, confidentially contact **BNL's Employee Assistance Program, Ext. 4567.**

Addiction Studies (cont'd.)

BNL 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 the Lab 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 BNL addiction research 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 are: cocaine-related drugs, heroin and opiates, tobacco, alcohol, and marijuana. BNL researchers collaborate closely with scientists and physicians from other institutions, both 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 the DOE's independent human subjects committee and observes procedures laid out in federal legislation for the protection of human subjects. — Kara Villamil

Summer Sundays Continue Through August 31st

Waste Management Facility Featured: Don't Waste This Opportunity!

Don't waste this opportunity: Tour BNL's state-of-the-art waste management facility this Sunday, August 9, as the mini-tour featured during the regular Summer Sunday tour.

Since its grand opening in December of last year, this facility has quietly been consolidating and packaging nearly 10,000 cubic feet of radioactive waste, 40 tons of hazardous waste and 100 tons of mixed waste for eventual shipment to processing and storage to facilities off site.

On Sunday, Lab visitors can see for themselves how the three categories of waste — radioactive, hazardous and mixed waste — are each stored separately.

Visitors will get a chance to see the buildings that house radioactive waste and hazardous waste; another building, which will not be part of the tour,

houses mixed waste, which contains both hazardous and radioactive waste.

But that's not all that mini-tour participants will see, as Operations Manager Matt LaBarge explains: "Within each building, the waste is separated and stored according to 'compatibility,' which means that flammable waste is kept in a separate room from corrosive waste such as acids. And solid waste is stored separately from liquid waste."

As visitors will note, each building



Peter Horton

is equipped with sprinklers and a dry chemical system. In addition, each storage room has a foot-thick concrete floor, the joints of which are sealed

with PVC to prevent seepage. The concrete floor itself has a liner that has the ability to retain any liquid.

Those on the mini-tour will learn of the facility's tracking system, which employs bar codes found on the side of the waste drums. This system allows waste to be tracked from each pick-up point on site.

Besides touring this facility, visitors can take a bus tour of the site and see the Whiz Bang Science Show, a lively interactive demonstration of basic scientific principles, which is presented at 10:30 a.m., noon, 1:30 p.m., and 3 p.m. in Berkner Hall.

Organized by BNL's Museum Programs, the tours are free and open to all on Sundays through August 31st, and are offered from 10 a.m. to 5 p.m., but visitors must arrive before 3 p.m.

— Amena Saiyid

Classified

Advertisements

Placement Notices

The Laboratory's placement policy is to select the best-qualified candidate for an available position. Candidates are considered in the following order: (1) present employees within the department/division and/or appropriate bargaining unit, with preference for those within the immediate work group; (2) present employees within the Laboratory; and (3) outside applicants. In keeping with the Affirmative Action Plan, selections are made without regard to age, race, color, religion, national origin, sex, disability or veteran status.

Each week, the Human Resources Division lists new placement notices, first, so employees may request consideration for themselves, and, second, for open recruitment. Because of the priority policy stated above, each listing does not necessarily represent an opportunity for all people.

Except when operational needs require otherwise, positions will be open for one week after publication.

For more information, contact the Employment Manager, Ext. 2882; call the JOBLINE, Ext. 7744 (344-7744), for a complete list of all job openings; use a TDD system to access job information by calling (516) 344-6018; or access current job openings on the World Wide Web at <http://www.bnl.gov/JOBS/jobs.html>.

The following vacancies are exempt from the Director's hiring freeze.

- OPEN RECRUITMENT** - Opportunities for Laboratory employees and outside candidates.
- RDA8014. ASSISTANT LABORATORY DIRECTOR FOR FINANCE - Requires at least a bachelor's degree in a relevant field, MBA preferred; extensive management experience, preferably in an research environment; and excellent oral and written communication skills. In addition, requires strong interpersonal skills so as to interact successfully with all levels of staff within the Lab and outside agencies. Knowledge of government contracting processes, specifically those of DOE, is highly desirable. Will provide leadership, direction, and oversight for the financial affairs for the Lab, including financial and administrative services such as fiscal, budget, contracts and procurement, corporate policies, and resource planning. Will annually present and justify budgets to the DOE, advise management on the internal allocations of these funds, and provide leadership and implementation mechanisms for financial management systems. Will report to the Laboratory Director and function as the Lab's Chief Financial Officer. Director's Office.
- NS7552. LABORATORY TECHNICIAN POSITION - (term appointment) Under direct supervision, performs laboratory assignments relative to the radiobiology program. Duties include ordering supplies, cataloging research material, and interacting with other research groups. Good organizational and communication skills are required. Medical Department.
- DD6499. TECHNICAL POSITIONS - (two openings) Requires an AAS in an appropriate field, or equivalent experience, and DOE RCT certification. Field experience in industrial-hygiene and environmental-protection activities is highly desirable. Primary responsibilities will include performing routine and special radiological and industrial-hygiene surveys, in accordance with applicable federal regulations (10CFR835, OSHA, EPA) and BNL/ESH&H/FS/ESH procedures. Will issue respirators and personal protective equipment, write safety instructions, and participate in facility safety inspections and emergency response. Environment, Safety & Health Services Division.
- DD7528. RADIOLOGY TECHNICIAN POSITION - (on-call basis) Requires a NYS license as a diagnostic radiology technician. Primary responsibility will be to take x-rays as part of the Occupational Medicine Clinic exams. Additional duties will include performing clinical laboratory procedures (vision and hearing tests), electrocardiograms (EKG) and phlebotomy. Experience in or willingness to be trained in these secondary tasks is essential. Training will be provided. Occupational Medicine Clinic.
- DD7865. TECHNICAL POSITION - (term appointment) Requires an AAS or equivalent experience and significant experience as an electronics technician. Must be able to work from wiring diagrams, schematics, mechanical drawings and verbal instructions. Duties will include wiring, assembling and testing of equipment racks, power supplies and rf cavities. RHIC Project.