BROOKHAVEN BULLETIN
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BROOKHAVEN NATIONAL LABORATORY

Brookhaven Targets Cancer With Advanced Therapies

Cancer will kill an estimated 538,000 Americans in 1994, exacting a toll of fear, pain and suffering that is probably greater than for any other disease. And the costs are also great — the American Cancer Society estimates that, as of 1993, the overall annual expenditures associated with cancer in the United States were $104 billion — $35 billion for direct medical costs, $12 billion in morbidity and loss of productivity, and $57 billion due to mortality.

The approaches that BNL is taking to reduce these statistics are described in this special edition of the Brookhaven Bulletin. Drawing on the wealth of expertise available at this multidisciplinary laboratory, these approaches include experimental techniques for destroying cancerous tumors using electrons, neutrons, photons, protons and radioisotopes, and methods using radioisotopes to reduce the intense pain of cancer.

All of these approaches involve the use of radiation, which BNL administers in accordance with all applicable regulations, and, in the case of human clinical studies, only with the full understanding and informed consent of those involved.

As BNL's approaches to cancer therapy have broadened, so has the Laboratory's vision. Today, that vision focuses on making Brookhaven a center for advanced radiation therapies. As now conceived, this would involve a consortium joining BNL and major medical centers on Long Island and in New York City, along with other institutions and private investors.

Once the center opens, a cancer patient could come for treatment with the best available conventional radiation therapy. But a patient with needs beyond conventional therapy might have additional choices: Because of the many varied options for radiation therapy at BNL, a patient may wish to participate in an advanced experimental therapy that, according to preliminary studies, would offer an optimum approach to attacking the disease.

To explore the ethics, finances and other nonscientific aspects of this vision further, Laboratory Director Nicholas Samios has appointed a Medical Therapy Facility Policy Committee, chaired by Mark Sakitt, Assistant Director for Planning and Policy. "Brookhaven's tradition of excellent basic research, coupled with the unique facilities and talents that abound at our multidisciplinary laboratory, offers an unparalleled resource, promising hope — and perhaps cure — to many cancer sufferers," said Samios. "This is an exciting prospect, and I am eager to go forward with it."

Boron Neutron Capture Therapy: Clinical Trials Under Way

Every year, about 2,000 new cases of glioblastoma multiforme — a type of brain cancer that remains incurable — are reported in the U.S., and about 10,000 Americans are afflicted with it. After diagnosis, life expectancy is less than one year, and fewer than one percent of its victims survive beyond five years. Conventional radiation therapy using x-rays does not do much to improve the survival rate.

At BNL, however, Medical Department researchers have high hopes for an experimental treatment called boron neutron capture therapy (BNCT), which they have proven effective in animals with a similar brain cancer. And now, with clinical trials under way, the prospects for treatment of human brain-cancer patients with the therapy at BNL "are looking very promising," says Darrel Joel, who is involved with BNCT research, in addition to chairing Medical.

BNCT of brain tumors involves two factors: a boron-containing compound and an external source of slow neutrons. Once inside the tumor, the boron compound is irradiated with a beam of low-energy thermal neutrons of less than 0.4 electron volts (eV). The beam has the correct energy so that boron-10 can absorb, or "capture," neutrons, then fission, or split, into different parts.

The highly ionizing fission products damage the tumor cells, thus slowing or stopping the tumor's growth. The short range of the fission products restricts the radiation dose to about a one-cell diameter, reducing the damage done to normal tissue surrounding the tumor — provided that the boron is located primarily in the tumor.

From the late 1950s to early 1960s, BNCT was used to treat patients with brain tumors, first at the Brookhaven Graphite Research Reactor, then at the Brookhaven Medical Research Reactor (BMRR). The results were disappointing, due to poor tissue penetration of the thermal neutrons and poor tumor selectivity of the boron compound. Improvements in those two key areas have allowed BNL researchers to explore once again the potential of BNCT to treat glioblastoma patients.

The first improvement was the application of the boron-10 containing compound called p-boronophenylalanine (BPA) by Jeffrey Coderre, a Medical Department scientist. The compound is the precursor of a natural amino acid onto which boron-10, a nonradioactive isotope of boron, has been attached. Administered to a patient, the boronated compound moves into the brain tumor along the same metabolic pathway that the natural amino acid would have taken.

(From left) Darrel Joel, Ben Liu and Jeffrey Coderre use a direct-current plasma atomic-emission spectrometer to measure the boron concentration in a tissue sample taken from a participant in boron neutron capture therapy studies.

What makes BPA superior to other compounds developed for BNCT is that more of it — 3 to 4 times more — is deposited in the tumor than in normal brain tissue. Tumor cells were shown to be more sensitive to BNCT than was normal brain tissue. Together, these factors produced a therapeutic ratio (tumor dose/normal brain dose) of 6:1 for BNCT using BPA — significantly higher than with other boronated compounds used for BNCT elsewhere.

In studies of the tumor in animals with gliosarcoma, a type of brain cancer, over 90 percent of the tumors have been eliminated and, because little damage was done to normal brain tissue, the animals were able to live out their natural life span.

Most animal tumors can be treated with a beam of thermal neutrons because the tumors are close to the surface. For deeper tumors, such as human brain tumors, a beam of higher energy — 0.4 eV to 10 keV neutrons — is used. When the beam reaches the tumor, the neutrons have slowed into the thermal energy range and can be captured by the boron-10.

The development of this intermediate-energy, or epithermal, neutron beam is the second key to the recent success of BNCT at BNL. This beam was pioneered at the BMRR in the 1980s by BNL's late Ralph Fairchild, and, as one of only three in the world, is the most intense.

Recently, Medical's Hungyuan Liu improved the beam intensity further by rearranging the reactor's fuel elements. A second upgrade proposed by Liu will dramatically improve both beam intensity and quality. This upgrade, which could be completed within a year and a half, will radically decrease a patient's exposure time — from 30 to 40 minutes down to 2 to 3 minutes.

Approved by the BNL Human Studies Review Committee and the U.S. Food & Drug Administration, clinical trials began with a study of the distribution of BPA in patients who took the compound orally, prior to brain-tumor surgery, and the results were encouraging.

Following recent improvements in BNCT of animal tumors when the BPA was given intravenously, the biodistribution of BPA is being studied in patients who receive BPA intravenously, in a collaborative effort involving Beth Israel Hospital, New York City. If the biodistribution study is a success, patients will be treated at the BMRR in a therapy trial within 12-18 months.

Meanwhile, Joel, Coderre, Liu and others in the Medical Department continue working to determine the highest dose of neutrons that can be tolerated without causing damage to normal brain tissue. And, under a Cooperative Research and Development Agreement with Boron Biologicals, Inc., of Raleigh, North Carolina, new boron compounds are being tested, so the treatment of brain tumors can be further improved or BNCT can be applied to other types of tumors. — Marsha Belford

Also contributing to this research are: Robert Brugger, Dennis Greenberg, Michael Makar, Peggy Micca, Michiko Miura, Marta Nawrocky, Daniel Slatkin and others, all of BNL's Medical Department, and collaborators from Ohio State University, the State University of New York at Stony Brook and Oxford University, United Kingdom.

A cancer patient at the Radiation Therapy Facility is set up for treatment by, respectively, a radiotherapist, a physician, a physicist and a medical physicist: (from left) Helen Iorio, Yat Hong Lau, Lucian Wielopolski and Raymond Beers.

The Inside Stories

'They Made It Seem Easy' At the RTF, Patient Says

She was 35 years old and had no family history of the disease. She first menstruated when she was 13, never used oral contraceptives, was not exposed to other synthetic female hormones, and had birthed her first child at age 28. Before the disease's onset, she had never had large doses of radiation.

Despite not having the most common risk factors associated with the disease, D.F. found a lump in her left breast two years ago. "All of a sudden, one day it was there," she recalled, "and it was too hard and my underarm was too sore and it didn't go away." Her gynecologist referred her to a breast surgeon, from whom she learned that it was cancer.

As a result, this middle-class, native Long Islander, part-time secretary, wife of nine years and mother of three became a statistic — the one woman out of eight on Long Island who gets breast cancer.

Nationally, one out of every nine women will develop breast cancer over a lifetime, and some 15,600 women in New York State and 182,000 women in the U.S. are diagnosed with breast cancer each year.

After recovering from surgery to remove the breast lump along with 13 lymph nodes, and following four months of chemotherapy, D.F. was ready for radiation therapy. In the early stage of breast cancer, radiation following a lumpectomy has been found to be as effective as the more disfiguring mastectomy surgery in controlling local recurrence and prolonging survival.

D.F.'s only question was where to have radiation therapy. "My husband, who is knowledgeable about accelerators, insisted that I come here, to the Radiation Therapy Facility at Brookhaven, because he knew it is state of the art."

The Radiation Therapy Facility (RTF) opened in BNL's Medical Research Center in 1991, as an outpatient cancer-treatment center. As a satellite of the Department of Radiation Oncology at the University Medical Center at Stony Brook, the RTF is the second center for cancer treatment using radiation to be established within a U.S. national laboratory.

What makes the RTF state of the art is its Philips SL-25 medical linear accelerator, one of the most advanced in the world and the only one in Suffolk County. The SL-25 not only delivers more powerful, more intense and better collimated photon beams than cobalt-60 sources used elsewhere to treat cancer, but it also has a higher energy photon beam and broader range of electron beams than many other medical accelerators. As a result, patients treated at the RTF have the best chance at the most optimum outcome.

The nine electron energies allow the most accurate treatment of superficial tumors, such as skin cancer, without causing much injury to healthy tissue. While the maximum photon energy of 25 million electron volts (MeV) allows the most thorough treatment of the deepest tumors such as pelvic cancer, the 6-MeV photon beam is used to irradiate breast cancer.

Of the approximately 500 cancer patients treated to date, 15 percent have been treated for breast cancer, while the largest percentage, 45 percent, have had prostate cancer.

Each treatment session lasts only about 15 minutes — "a very long 15 minutes in the beginning, but the nurses and therapists try to make you as comfortable as possible," commented D.F. "I was never kept waiting for my treatment, the RTF is easy to get to, and you don't have to pay for parking. I don't ever want to have to go back, but they made it seem easy."

"My husband insisted that I come here, to the Radiation Therapy Facility at Brookhaven, because he knew it is state of the art."

. . . Patients treated at the RTF have the best chance at the most optimum outcome.

To ensure that the RTF's linear accelerator continues to be at the forefront of radiation treatment, several upgrades are planned. And Brookhaven scientists, in collaboration with Stony Brook researchers, will expand the preliminary studies of experimental medical treatment and imaging techniques already under way.

Meanwhile, D.F. has been cancer-free for two years — and is looking forward three more years, when she can be counted as one of the 90 percent of women with breast cancer at the same stage who have survived for five years. — Marsha Belford

Radiation Therapy Facility staff includes: Lucian Wielopolski, of BNL's Medical Department and the State University of New York (SUNY) at Stony Brook; Vivian Claeson, Helen Iorio, Yat Hong Lau, Tae Park, Eric Ramsay, Patricia Rivera and Benjamin Williams, all of SUNY Stony Brook; and Kari Johannsen, Lori Malachowsky and Denise Rodgers, and other nursing and clinical laboratory staff of BNL's Medical Department.

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ANITA COHEN, Editor
MARSHA BELFORD, Assistant Editor

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Public Affairs Office
Bldg. 134, P.O. Box 5000
Upton NY 11973-5000
Tel. (516) 282-2345; Fax (516) 282-3368

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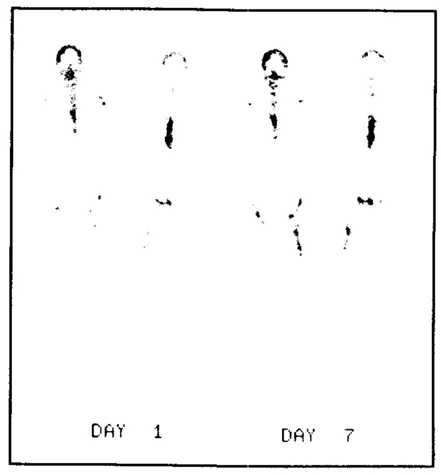
Can Tin-117m Relieve the Pain of

In approximately 60 to 80 percent of people with breast or prostate cancer and about half of those with lung cancer, the disease metastasizes, or spreads, to their bones. And, in more than half of the 320,000 new U.S. cases of metastatic bone cancer reported annually, the pain is excruciating.



(Above) Anterior and posterior whole-body images of a patient with breast cancer, which has spread to the bone, taken one and seven days after the administration of tin-117m DTPA. The darker the area, the greater the uptake of tin-117m DTPA. (Below) Pelvic and chest regions of the same patient imaged before the tin-117m DTPA study using the common bone-scanning agent, technetium-99m MDP.

While narcotic drugs can relieve this pain, they have a sedative side effect, which diminishes the quality of the patients' lives. So, the use of radioisotopes for pain relief is being explored by researchers in Brookhaven's Medical Department.

In fact, BNL researchers have developed one such compound, called tin-117m D[illegible] Tin-117m emits a number of short-ra[illegible] conversion electrons that impart a high, localized radiation dose to the bone tumor with much less radiation damage to the sensitive bone marrow.

Infused intravenously, tin-117m DTPA localizes preferentially in bone rather than in soft tissue or bone marrow, so bone tumors receive 50 times more dose than the marrow. As a result, tin-117m should not suppress the bone marrow's ability to fight infection or interfere with the blood's ability to clot, thus overcoming a major side effect of other radiopharmaceuticals also devised to deal with bone pain.

"The first pati good that he s day outdoors . .

In collaboration with the University Medical Center at Stony Brook, BNL researchers are now testing tin-117m in the first phase of clinical therapy trials approved by the U.S. Food & Drug Administration (FDA). These follow about four years of laboratory development and a 10-patient biodistribution study. This 15-patient escalating-dose trial should determine the minimum [illegible] needed for bone-pain relief and the m[illegible]mum tolerated by the marrow.

Since summer 1993, nine patients have received one infusion of 10 millicuries of this compound, and all have either been pain-free or had significantly less pain, thus requiring less narcotic medication. More patients will be studied, and all those in the trial are followed for six months or until death. Since no bone marrow toxicity has been so far observed, studies using higher doses are now being planned.

"The first patient, who had been unable to get out of bed because of his pain, felt so good that he spent the next day outdoors, and he remained pain-free until his death six weeks later from other causes," said

BNL's Neutral Beam Test Facility was completed in 1988 to test components for the Strategic Defense Initiative, using protons supplied by the Lab's 200-million-electron-volt (MeV) linear accelerator (Linac). But, with the demise of the Cold War, this defense-related research project was canceled in 1990.

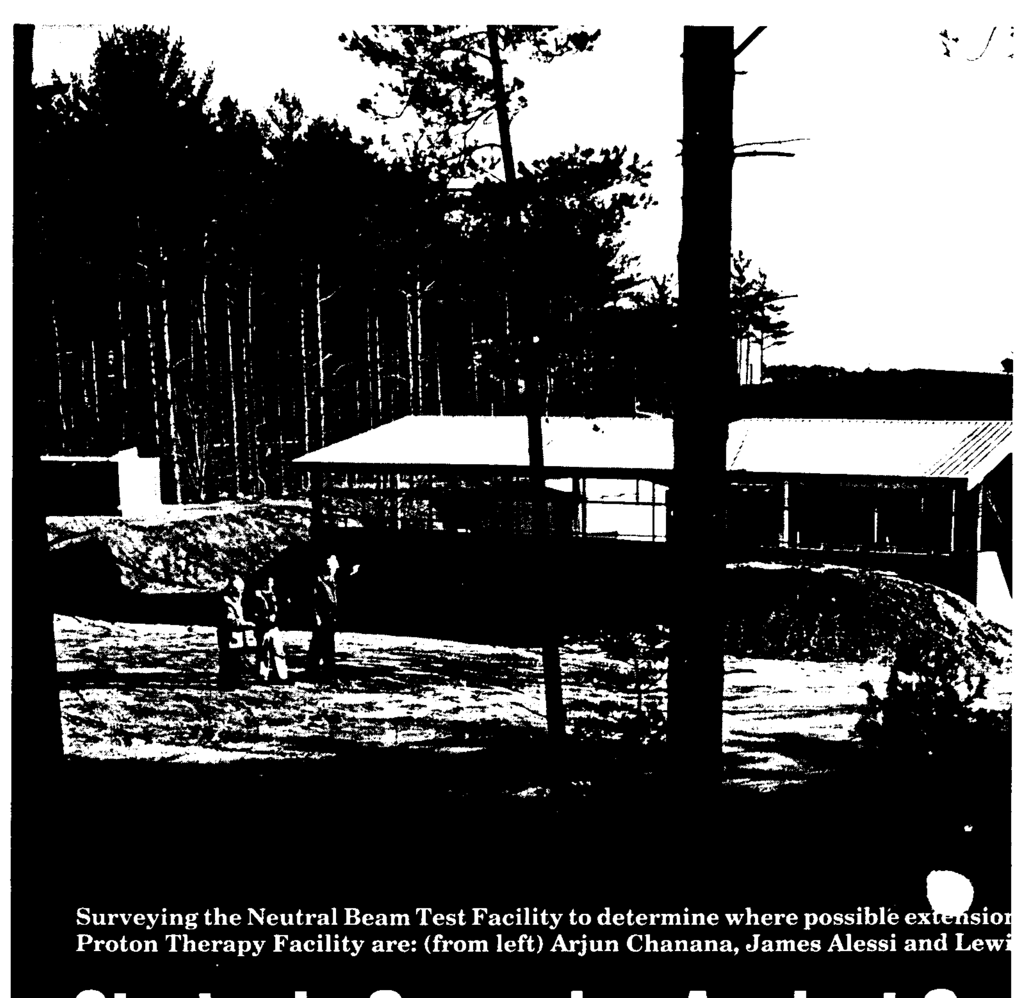
Nevertheless, the facility remains intact. And, if funding is forthcoming, it is here that a strategic campaign against cancer will be launched with protons.

While traditional x-ray or electron radiation therapy often saves the lives of people afflicted with cancer, it fails to control the disease each year in about 260,000 patients in whom the disease has not metastasized when diagnosed.

However, for many of these patients, particularly those with head, neck and spinal tumors, proton radiation therapy may improve the control of localized tumors.

To assess the feasibility of such a Proton Therapy Facility (PTF) at the former Neutral Beam Test Facility, Laboratory Director Nicholas Samios appointed a study group, headed by Arjun Chanana, Medical Department.

In its initial report, the study group has strongly recommended that a state-of-the-art PTF be established at Brookhaven. There are about 15 such facilities in operation worldwide, with the one nearest to Long



Surveying the Neutral Beam Test Facility to determine where possible extensio Proton Therapy Facility are: (from left) Arjun Chanana, James Alessi and Lewi

Strategic Campaign Against Ca

Bone Cancer?

Suresh Srivastava, who heads the Medical Department group involved in this research.

In addition, Associated Universities, Inc., holds the patent on this compound, and a radiopharmaceutical firm has expressed interest in obtaining an exclusive license on tin-117m DTPA, finishing the FDA-re- ᐧd clinical testing and then selling it w. .in the medical community. The transfer of this technology from Brookhaven to the private sector could take place as early as sometime this spring.

"Our tin compound has three major advantages over other radiopharmaceuticals already approved or being developed for this purpose," explained Srivastava.

The first advantage of tin-117m DTPA is that patients can receive this medication as outpatients. Since patients being administered tin-117m DTPA will most likely receive only 10-15 millicuries of radioactivity, the FDA does not require them to be hospitalized, thus sparing them inconvenience and expense.

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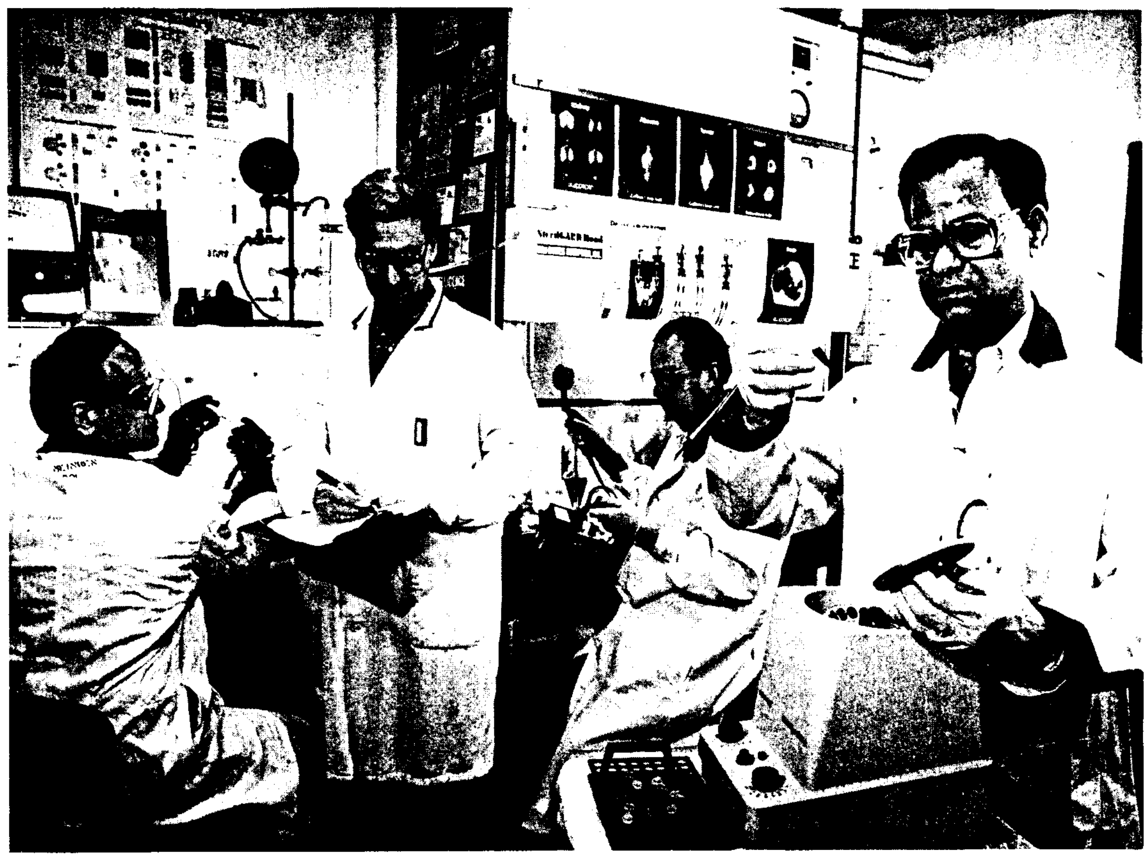
Second, in addition to giving off low-energy electrons that penetrate the bone metastases without damaging surrounding normal tissue, tin-117m DTPA also emits gamma rays, which can be used with a gamma camera to image the distribution of the compound in the patient.

Finally, this compound has the short h ife of 13.6 days. Thus, contact with li .g patients and burial of the deceased are not problems.

"Results indicate that tin-117m DTPA may be the best agent yet for the treatment of pain from osseous metastases," concluded Srivastava. "And, since the deliverable radiation dose to the tumor is three to ten times higher than that of other radiopharmaceuticals under development for this purpose, tin-117m DTPA may also prove useful for treating primary bone tumors." — Marsha Belford

Key personnel involved in this research are: Harold Atkins, Leonard Mausner, George Meinken and Beatrice Pyatt, of BNL's Medical Department; and others from BNL and the State University of New York at Stony Brook.

BLIP Upgrade: To Meet Demand For Radioisotopes



In the radiopharmaceutical laboratory preparing tin-117m DTPA for patient therapy trials now under way at Brookhaven are: (from left) George Meinken, Leonard Mausner, Johannes Klopper and Suresh Srivastava. Mausner and Srivastava are also involved in the upgrade of the Brookhaven Linac Isotope Producer, which will ensure the nation's medical community a continued supply of accelerator-produced radioisotopes.

To shore up the domestic supply of medically important radioisotopes that are produced using an accelerator, the Brookhaven Linac Isotope Producer (BLIP) is being upgraded, using $6 million approved by Congress in the present federal budget.

The U.S. Department of Energy operates two large accelerators that produce several unique radioactive forms of chemical elements used in medicine, research and industry: the Los Alamos Meson Physics Facility (LAMPF) and the Linac of BNL's Alternating Gradient Synchrotron (AGS).

Both accelerators, however, are high energy physics machines, which are not dedicated to isotope production and run only part of the year.

Given the likely closure of LAMPF in a year or two and the possible approval of a National Biomedical Tracer Facility (NBTF) with its own dedicated accelerator, the upgrade of BLIP is an interim solution to reduce U.S. reliance on foreign radioisotope production. When completed in 1996, the upgraded BLIP facility — to be renamed the Brookhaven Isotope Research Center (BIRC) — will be able to meet up to 100 percent of the U.S. demand for selected accelerator-produced radioisotopes.

"We will not only increase our production of the isotopes that we make at present, but also add to our list four isotopes that are now made only at LAMPF," said Leonard Mausner, Medical Department, who is Project Manager for the upgrade. The BLIP upgrade will raise from 12 to 16 the total number of isotopes made at BNL for distribution.

Two of the radioisotopes most used in nuclear medicine today — technetium-99m and thallium-201 — were first made at BNL.

Radioisotopes are radioactive forms of a chemical element that share similar properties with their nonradioactive cousins and have been developed over the past 30 years to be used in medicine, primarily for diagnostic imaging and measurement of physiological functioning, but also for the treatment of cancer. They are usually administered to patients intravenously, and, following their localization in specific tissues or organs in the body, they can be detected externally.

In fact, two of the radioisotopes most used in nuclear medicine today — technetium-99m and thallium-201 — were first made at BNL.

While certain radioisotopes have been produced using low-to-medium-energy accelerators since 1938, other unique radioisotopes have been made at BLIP for the past 20 years. At BLIP, up to 14 targets can be simultaneously irradiated by pulses of protons that come from the 200-million-electron-volt (MeV) Linac. The Linac's primary function is to inject protons into the AGS, and the protons siphoned off for BLIP are in excess of those needed for high energy physics experiments.

In addition, this Medical Department group also has been using the neutrons from BNL's High Flux Beam Reactor to make other radioisotopes.

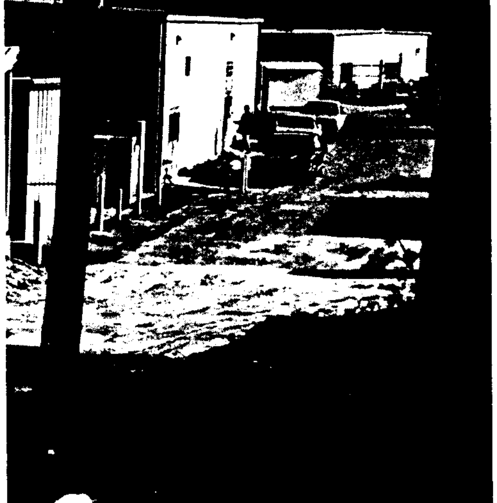
The upgrade will let BLIP operate at almost three times the present current, going from 50 to 145 microamperes. Thus, BLIP will be able to produce radioisotopes with higher specific activity, and the higher the specific activity, the more concentrated the dose of radiation administered to a patient.

In addition, users of the upgraded BLIP will be able to tune the energy of the proton beam from 66 to 200 MeV, in increments of approximately 21 MeV. This will permit studies to optimize the quality and quantity of the isotopes produced.

Finally, BLIP will expand its operations — from an average of 20 weeks a year up to 46 weeks beginning in 1996, with increased reliability — thereby permitting the increase in both the number and kinds of radioisotopes that can be made at BNL.

"Upgrading the Linac and BLIP is cheap and fast to implement, and it will provide a temporary solution until the NBTF is built," concludes Mausner. "We'll produce high yields of radioisotopes, and we will also be able to carry out realistic target development and other development projects for the NBTF." — Marsha Belford

Other BNL staff working on this upgrade include: Kathryn Kolsky, Slawko Kurczak, Henry Schnackenberg and Suresh Srivastava, Medical Department; and James Alessi and Andrew McNerny, Alternating Gradient Synchrotron Department.



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Island located in Massachusetts. At projected cancer rates, up to 4,000 patients from Long Island could benefit from proton radiation therapy annually.

"There are some tumors that are not being treated successfully with x-rays," said Chanana. "Protons can do a more effective job. The physics of protons offers the opportunity to deliver a relatively high dose of radiation to the tumor, with fewer side effects."

He added, "Construction costs of the proposed PTF at Brookhaven would be only a fraction of the cost of similar facilities planned elsewhere because we do not have to build an accelerator for protons."

At the projected cancer rates, up to 4,000 patients from Long Island could benefit from proton radiation therapy annually.

The Linac accelerates protons before pumping them into BNL's Alternating Gradient Synchrotron (AGS) for high-energy physics research. Since 1973, excess protons have been siphoned to the Brookhaven Linac Isotope Producer (BLIP), for making medical radioisotopes. The projected upgrade of both the Linac and BLIP (see story on this page) and their extended operations will provide protons for therapy almost year-round.

At the PTF, the proton energy for therapy would range from 66 MeV to 200 MeV, and, initially, about 900 patients per year could be treated at this two-treatment-room facility, which could be expanded to four rooms.

Eventually, heavy ions could be added to the arsenal of particles to be deployed in BNL's campaign against cancer. Chanana explained that heavy ions contain even more destructive power than do x-rays, electrons or protons — and that power can be pinpointed at the tumor, with relatively reduced damage to healthy tissue around the tumor.

Produced by the Tandem Van de Graaff, heavy ions are currently used for nuclear physics research at the AGS, and, by the end of the decade, will fill the Relativistic Heavy Ion Collider.

"In the future, we could siphon off heavy ions via the AGS Booster to fight cancer," said Chanana. "A heavy-ion medical therapy facility has recently been constructed in Chiba, Japan, at a cost of $300 million. Annual operating costs of the Chiba facility will be about $50 million. BNL can provide heavy ions for cancer therapy at about 10 percent of that cost."

—Diane Greenberg

Others who have contributed to this research are: James Alessi, Alternating Gradient Synchrotron Department, BNL; Victor Bond and Avraham Dilmanian, Medical Department, BNL; Lewis Snead, Department of Advanced Technology, BNL; and Lucian Wielopolski, BNL Medical Department and State University of New York at Stony Brook.

Tiny Beams, Large Effects — New Research on Brain Tumor Therapy

Brain cancer is the second most common form of the disease in children. About 1,500 new cases are reported each year in the U.S., of which nearly half are incurable.

But research on an experimental treatment called microplanar beam, or microbeam, radiation therapy (MRT), conducted at BNL's National Synchrotron Light Source (NSLS) and Medical Departments, offers new hope for small children afflicted with the disease.

"Conventional radiation therapy is risky in preschool children since maturing brain tissues are particularly vulnerable to radiation," said Daniel Slatkin, Medical Department, who leads an MRT research group. "MRT is a new approach to overcome that problem."

In MRT, "microplanar" refers to the use of a wide, but microscopically thin beam of radiation. One radiation dose of 20 grays (2,000 rads), or even less, delivered rapidly in a wide beam to mammalian brain tissue may cause serious damage. But the MRT group has evidence to date that a single microbeam dose, or in some geometries many parallel microbeam doses, of up to 625 grays or more each may be given to an animal model's brain without serious consequences.

At the National Synchrotron Light Source, conducting microbeam radiation therapy experiments, Per Spanne (left front) reviews computer controls, Avraham Dilmanian (back) adjusts the subject rat's position to be viewed on a TV screen through Daniel Slatkin's (right) camera lens.

Since 1992, several MRT experiments have been performed on malignant brain tumors in rats. Results indicate that MRT can stop the growth of tumors. Over one-half of the rats that received 312 grays to each of 600 microplanar radiation volumes in and around the tumor survived at least ten weeks after the treatment, while all the untreated control rats died of massive brain tumors within two and a half weeks. The surviving rats no longer show signs of brain disease, and the only apparent side effect of MRT is minor hair loss in the treated area.

"If a brain tumor does not regrow within three months after treatment in this experimental model, it is unlikely to regrow ever again — so we are keeping close tabs on these animals," Slatkin said. "We are sufficiently encouraged to hope that MRT will eventually take its place among other useful forms of treatment for children's brain tumors."

"We . . . hope that MRT will eventually take its place among other useful forms of treatment for children's brain tumors."

Experimental precursors to this research date back to the 1950s at BNL, when the late Howard Curtis was studying the possible effects of cosmic-ray particles on astronauts. By using a microbeam pulse of 22-million-electron-volt deuterons on mice to model the radiation effects of cosmic-ray particles entering the human brain one at a time, Curtis and his colleagues discovered that they could deliver doses of 3,000 grays or more to a mouse brain without serious damage — provided the beam was only some 30 micrometers thick.

"We think, as Curtis and his colleagues previously did, that when certain kinds of vital supporting brain cells are damaged in a microbeam, nearby undamaged or minimally damaged cells can migrate into the intensely irradiated zone, then multiply to replace the damaged cells," Slatkin said. "This can take place if the irradiated volume is thin, otherwise brain tissue would not survive these high radiation doses."

Slatkin germinated the idea of MRT in 1989 with Per Spanne, then in the Department of Applied Science and now in the Medical Department, while Spanne was imaging a mouse's brain at the NSLS using a technique called synchrotron x-ray computed microtomography, which involves the use of a microbeam.

Slatkin, Spanne and Avraham Dilmanian, also of Medical, said that their team's hope is to increase x-ray energies at the NSLS by building a more energetic version of a device called a wiggler. This would allow MRT to be performed on a wider variety of brain tumors afflicting both children and adults. Until then, the team plans to work toward the goal of using the X17 beam line's existing wiggler to treat currently incurable brain tumors in young children.

— Diane Greenberg

Other collaborators in this research include: Charles Ashby, Medical Department, BNL; Stephen Dewey, Chemistry Department, BNL; Terry Button, State University of New York at Stony Brook; Jan-Olaf Gebbers, Cantonal Hospital, Switzerland; and Jean Laissue, formerly of BNL's Medical Department and now at the University of Bern, Switzerland.

Cancer Fighters: Gold and Uranium

James Hainfeld works with a purified sample of gold attached to antihuman-tumor antibodies, for experimental cancer therapy.

Gold, the glittering prize of many battles, and uranium, the lethal ingredient of atomic bombs, are being used in two separate studies at BNL as powerful potential weapons in the war against cancer.

The gold standard of electron microscope labels — a cluster of 11 gold atoms bonded to an antibody fragment — was synthesized in 1987 by James Hainfeld, Biology Department. While using the gold compound for imaging at BNL's Scanning Transmission Electron Microscope (STEM), Hainfeld noticed that the compound's special qualities, such as its ability to label almost any antibody, made it a particularly suitable compound for experimental cancer therapy.

The antibodies become gold bullets that can bind to a malignant tumor and kill its cells with a large dose of radioactivity.

In this innovative therapy, antitumor monoclonal antibodies are cloned and bind to antigens on tumor cells. Using a radionuclide of gold known as gold-199, the antibodies become gold bullets that can bind to a malignant tumor and kill its cells with a large dose of radioactivity.

For many reasons, gold-199 is potentially an ideal radionuclide for cancer therapy.

Previously, up to three atoms of a radionuclide could be attached to an antitumor antibody. But, by using gold-199, each antibody can carry up to 11 atoms of gold to a tumor, thus providing more therapeutic power. Also, gold-199 is lethal for a radius of ten cells, and its half-life is only 3.1 days, properties desirable for therapy. In addition, the gold-labeled antibodies are easily imaged, using STEM.

In recent studies, Hainfeld and his colleagues intravenously injected the gold bullets into the bloodstreams of mice with colon tumors. The antibodies were provided by the Wistar Institute, in Pennsylvania.

"The antibodies attach themselves to the cancer site, but the problem is that they are also found in the liver, bone marrow and other sensitive tissues," Hainfeld said. "Doses high enough to kill the tumor would endanger other organs."

As a result, the researchers are limiting their studies to bladder carcinoma because the gold-labeled antibody can be introduced into the animal's bladder via catheterization, and, after a set time, rinsed out. "In this way, the radionuclide does not go to the bloodstream and other tissues," Hainfeld said.

In another approach, similar to boron neutron capture therapy (see article, page 1), Hainfeld and his colleagues are using antibodies tagged with uranium-235 (U-235) to accumulate preferentially in brain tumor cells, which are then irradiated.

In initial studies, the researchers found that U-235 is at least three times as effective per atom as boron in killing cells. To follow up, they replaced 5,000 iron atoms in apoferritin, an iron-storage protein, with 800 uranium atoms and attached antibodies from the Wistar Institute to these uranium-bearing proteins.

At the Brookhaven Medical Research Reactor, cell cultures treated with the U-235 antibodies were bombarded with neutrons. The U-235 nuclei were broken apart by fission, which released radiation that was powerful enough to destroy surrounding cells.

"This is promising," said Hainfeld, "but there are still several roadblocks to using U-235 that have to be overcome before we can perform clinical trials."

— Diane Greenberg

Contributing to both the gold-199 and uranium-235 research are: Kyra Carbone, Inan Feng and Frederic Furuya, Biology Department, BNL; Viswas Joshi, George Meinken, Beatrice Pyatt and Suresh Srivastava, Medical Department, BNL; and Zenon Steplewski, the Wistar Institute. Also contributing to the gold-199 research are: Kathryn Kolsky, Slawko Kurczak and Leonard Mausner, all of BNL's Medical Department. Other BNL contributors to the uranium-235 research are: Garman Harbottle, Chemistry Department; Mow Lin, Department of Applied Science; Avraham Dilmanian, Ruimei Ma and Daniel Slatkin, Medical Department.

Samarium-145: Strong Advance For Photon-Activation Therapy

It's an exciting concept for cancer therapy: Combine two agents, each powerless alone, to attack brain tumors. Called photon activation therapy (PAT), it was first developed in the early 1980s by BNL's late Ralph Fairchild and is now being pursued by researchers at BNL and Ohio State University (OSU).

So far, the results are promising: In initial clinical tests that began at OSU in the late 1980s, 12 patients with malignant brain tumors returned to normal activity after treatment, and their median survival time was 46 months instead of the usual 18 to 24 months.

In initial clinical tests . . . 12 patients with malignant brain tumors returned to normal activity.

Photon activation refers to the fact that x-rays of a limited energy range can activate iodine, thus producing large numbers of electrons that are capable of destroying tumor cells.

As tested, PAT works this way: Iodine, in the form of the drug IdUrd, is administered to each patient, in whom it localizes in brain tumor cells. An isotopic source of photons of a certain energy is then surgically implanted in the tumor, and the photons activate the IdUrd.

"The OSU clinical study worked so well," said Brenda Laster, of BNL's Medical Department, "principally because IdUrd is also a 'sensitizer,' in that it increases the apparent effectiveness of photons of any energy. But, in truth, the photons emitted by the radioisotope in IdUrd — iridium-192 — are not ideal for PAT. The radioisotope samarium-145 [^{145}Sm] will be a much better photon source because the photon energy is more suitable."

Tests conducted at BNL's National Synchrotron Light Source (NSLS) showed that PAT results should be doubly successful using samarium-145. Commented Medical's Victor Bond, "In experiments done in collaboration with William Thomlinson at the NSLS, tumor-cell destruction increased significantly at the energy of 33.4 thousand electron volts, which is similar to the energy of the samarium isotope."

Produced in BNL's High Flux Beam Reactor, the new ^{145}Sm source has many advantages. For example, it can be made available globally, and it can be reactivated and reused, thus reducing the amount of hazardous waste. "The availability of ^{145}Sm motivates us to seek other suitable drugs that might have an even greater uptake in tumor cells," said Bond.

To make the ^{145}Sm sources, the BNL researchers are working with others at Ames Laboratory. "We're hoping to be funded for a Cooperative Research and Development Agreement, which will help speed up widespread availability of this promising treatment," said Laster.

— Liz Seubert

Others who have contributed to this research are: Leonard Mausner, Medical Department, BNL; Samuel Packer, Medical Department, BNL, and North Shore University Hospital; Peter Siddons, National Synchrotron Light Source Department, BNL; Timothy Ellis, Ames Laboratory; Reinhard Gahbauer, Joseph Goodman and John Grecula, all of Ohio State University; and Gad Shani, Ben Gurion University, Israel.