PEREGRINE Goes to Work

WHO knew decades ago that the storehouse of data on nuclear science and radiation transport that Lawrence Livermore was developing would one day be applied to cancer treatment? In the early 1990s, Livermore researchers began combining that huge database with Monte Carlo statistical techniques to create PEREGRINE, a new tool for analyzing and planning radiation treatment for tumors. Approved for use by the U.S. Food and Drug Administration last September, PEREGRINE—named for the patron saint of cancer patients—is beginning to find its way into hospitals and clinics.

In July 1999, Livermore licensed the PEREGRINE technology to the NOMOS Corporation of Sewickley, Pennsylvania, to commercialize it. NOMOS has been developing advanced radiation therapy solutions in the fight against cancer since the early 1990s and is a leader in the new field of inverse planning for radiation treatment. "NOMOS is very innovative," according to physicist Rosemary Walling, program manager for PEREGRINE at Livermore.

PEREGRINE is equally innovative. While several dose calculation systems dot the radiation planning landscape, PEREGRINE is the first to exploit the mathematical power of Monte Carlo statistics (see *S&TR*, October 1999, pp. 14–15, and May 1997, pp. 4–11). It took the computing revolution of the 1980s and 1990s to make Monte Carlo fast enough for use by clinicians.

When patients receive radiation therapy, they are bombarded by billions to trillions of particles. PEREGRINE Monte Carlo radiation transport algorithms determine the dose deposited in the patient by following the path of representative particles as they travel through the body. The probabilistic laws of modern physics prevent scientists from knowing the exact fate of each particle, but they do allow scientists to predict a distribution of how these particles, and their daughter products, interact in matter. By sampling millions of the trillions of particles that enter the body and recording the energy deposited by each as it travels through the body, PEREGRINE's Monte Carlo statistical method develops an accurate representation of the dose distribution.

The Livermore team and NOMOS worked together to prepare all necessary documents for FDA approval. NOMOS submitted the application to the FDA in October 1999 and got the good news not quite a year later.

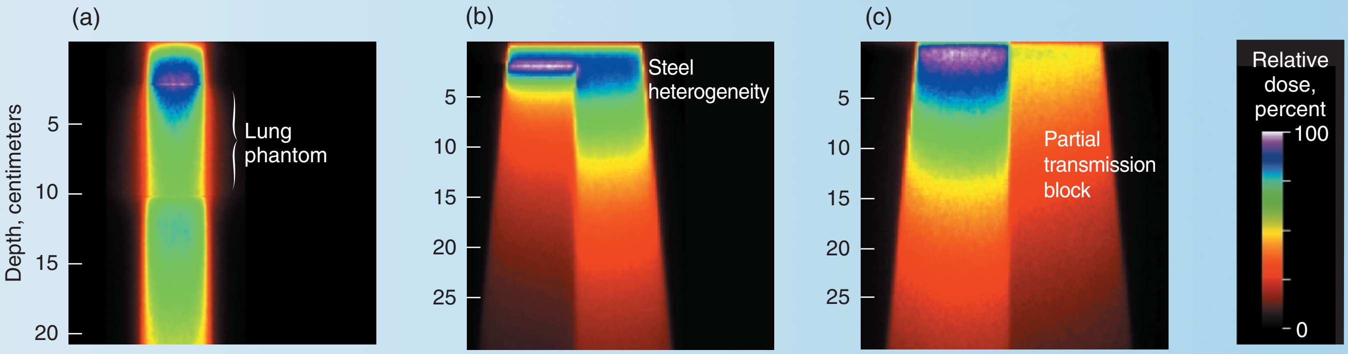
Former Secretary of Energy Bill Richardson announced FDA approval at NOMOS headquarters on October 6, 2000. "PEREGRINE could change the way cancer is treated in America," he said. "This technology was developed through advances resulting from nuclear weapons research and with the multidisciplinary scientific expertise of a Department of Energy national laboratory. This is an excellent example of turning swords into plowshares."

The FDA Decides

One of the biggest pieces of documentation that went to the FDA was a set of clinical measurements prepared in conjunction with cancer researchers at the University of California at San Francisco (UCSF). These measurements were important for verifying PEREGRINE's accuracy as a treatment tool. In radiation therapy, the goal is to maximize the radiation dose that hits the tumor while minimizing the dose to surrounding, healthy tissue. No clinical trials were performed for FDA approval. Rather, clinicians at UCSF used their accelerators (which create the radiation beam) to take measurements in water "phantoms" using various beam directions and angles as well as the many types of modifiers that are used to change the shape of the beam to match the needs of a particular tumor.

UCSF also took measurements with layers of various materials above and in the water phantom. PEREGRINE is unique in being the only dose calculation code that can examine radiation activity where different kinds of materials, such as bone, soft tissue, and air (in our lungs), meet. NOMOS staff took measurements in solid phantoms to duplicate bone and other materials.

Christine Hartmann-Siantar, program leader for the PEREGRINE project at Livermore, is shown with John Friede, chairman and chief executive officer of NOMOS Corporation during the announcement of FDA approval for PEREGRINE.



Images resulting from some of the PEREGRINE measurements taken by the staff at the University of California at San Francisco. They demonstrate how effectively PEREGRINE can handle different materials and shapes: (a) heterogeneities in the lung, (b) a steel prosthesis, and (c) a partial transmission block to protect healthy tissue during radiation treatment.

The NOMOS submission to FDA requested what is known as 510(k) approval. A 510(k) is a premarketing notification demonstrating that the device to be marketed is as safe and effective as another legally marketed device. In the submission, PEREGRINE was compared to other radiation treatment dose calculation systems. What makes it work as well as it does—Monte Carlo mathematics—is significantly different from the means of calculating dose in other systems, but its end use as a planning tool for today's clinics is substantially the same.

PEREGRINE's dose calculation capability will be used with a radiation treatment planning system. A radiation oncologist, medical physicist, radiation therapist, or dosimetrist will use the two together to design a series of radiation treatments that can be reviewed by the patient's physician prior to treatment. PEREGRINE is being used with CORVUS, an inverse planning system created and marketed by NOMOS.

The City of Hope Cancer Center in Los Angeles was the first customer to purchase PEREGRINE, and UCSF, Livermore's long-time collaborator, was the first to take delivery. Numerous other hospitals, including one in Belgium, are beginning the commissioning process. The first patients to benefit from PEREGRINE will likely begin to receive treatment this summer.

Pushing Frontiers

Medical physicist Christine Hartmann-Siantar is program leader for PEREGRINE at Livermore. She says, "Our goal has always been to get what is known as ubiquitous distribution of PEREGRINE. We want to see it in as many clinics as possible, from university centers to community hospitals. This way, every patient will have access to the most accurate radiation dose calculation method."

The Livermore team is now working with NOMOS to add more types of accelerators and more accelerator radiation energy levels to PEREGRINE's database. They are also continuing to work with UCSF, expanding PEREGRINE's capabilities to include electron radiation treatment. Treatment with photons is the most commonly used because photons can travel deep into the body. Electrons are useful for tumors close to the surface because electrons deposit their energy within a few centimeters of the skin.

The PEREGRINE team has also begun a quality assurance project with UCSF to examine the photon radiation dose that exits the body on the side away from the beams. Known as portal imaging, it could be used to check where a small dose goes before the full dose is administered. Portal imaging would also be an excellent tool for periodic use as the full series of treatments are given to assure that the dose being received is the one the radiation oncologist planned.

Hartmann-Siantar joined the Laboratory in 1993 with the goal of applying Livermore's nuclear data and computational know-how to radiation treatment. "I got a chance to work with some of the best computer scientists, engineers, and physicists in the Laboratory," she says. "Without them, PEREGRINE never would have happened."

PEREGRINE team members have won many awards for their work. Hartmann-Siantar added another in February 2000 as one of four first-ever recipients of the Edward Teller Fellowship Award. Working with the team, she is using the fellowship to study how radiation damages DNA. At the time of the award, Hartmann-Siantar said, "I am very excited to have an opportunity to push new frontiers in science." She and her team have already pushed a few, and they aren't stopping yet.

—Katie Walter

Key Words: cancer treatment, Monte Carlo mathematics, PEREGRINE, U.S. Food and Drug Administration.

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