Nuclear Medicine Gets Friendlier

Experimental therapies seek to poison just the disease

By JANET RALOFF

"I looked like a concentration camp survivor," recalls Sue Spenceley, describing the day 2 years ago when she arrived at the Arlington (Texas) Cancer Center. Ravaged by both Hodgkin's disease and the myriad therapies that had been directed against this lymphoma over the previous 8 years, the 5'8" woman weighed just 113 pounds and had barely enough energy to walk.

As director of medical staff support at what she describes as "a very savvy hospital" in Orange County, Calif., "I had physicians at my door—literally." Yet they hadn't been able to stop her disease.

Altogether, she suffered through 13 different regimens of radiation and chemotherapy. Some so enervated her that she would be out of breath after climbing a few stairs. Others rendered her vulnerable to infection or caused nerve damage to her fingers and feet that still persists after 7 years.

What a surprise, then, to find no unpleasantness associated with her Texas therapy. "Not only did it not wipe me out, but it actually allowed me to begin recovering from the aftermath of my last chemotherapy," she says.

With her cancer finally in check, she says, "there's nothing I wouldn't do." Last Christmas, she "skied like crazy and hiked." This therapy, she insists, "has given me my life back."

Spenceley's treatment represents a new and evolving wave of nuclear medicine that's letting physicians target increasing amounts of radiation against disease, while reducing the toxic effects on patients. Explains Huibert M. Vriesendorp, the radiation oncologist spearheading the trial that Spenceley is participating in, the overall goal is not only to improve the efficacy of cancer treatment but finally to make it "patient-friendly."

Other clinicians are applying the strategy to heart disease and arthritis (see sidebar, p. 41).

Most of these new therapies rely on an expanding arsenal of antibodies chosen for their ability to find and bind to some cell surface protein peculiar to a patient's cancer. When injected into the patient, the antibody attaches to the cancer cells and, because it is linked to a radioisotope, becomes a lethal weapon. As the isotope decays, emitting pent-up energy in the form of ionizing radiation, the cancer gets hammered.

These new nuclear therapies minimize harm to normal tissue both by using antibodies to ferry the isotopes specifically to cancer cells and, increasingly, by employing isotopes that emit beta or alpha particles (see sidebar below). Because they can travel only short distances in tissue—typically 5 millimeters or less for betas and less than one-thousandth that distance for alphas—there's far less risk than with X rays that these types of radiation will spill over to cancerfree tissue.

Ultimately, the goal of many of these new therapies is to match the scope of the high-powered but short-range radioactive particles to the size of the tumor being targeted, explains Thomas S. Tenforde of the Energy Department's Pacific Northwest National Laboratory (PNNL) in Richland, Wash.

To target clumps consisting of no more than a few cells, typical of leukemias or wandering metastatic seeds of solid tumors, alphas might be the preferred choice. For larger tumors, physicians might choose the more penetrating betas. One day, doctors may even be able to select from a family of beta emitters with different energies—and therapeutic ranges—to tailor the radiation's reach to a particular cancer's size.

A radioisotope is a single atom of an unstable element. An antibody is a much larger, Y-shaped protein. Neither has any intrinsic interest in entering a permanent relationship with the other. To bring together the reluctant mates chemically, biologists and chemists have had to engineer molecular-scale matchmakers—cages and linker molecules.

The idea is to trap isotope atoms within molecular cages, then use the linker molecules to bond one or more cages onto each antibody. The challenge, explains Tenforde, whose team is working to create new radiopharmaceuticals, has been building cages that exhibit a strong attraction for a specific isotope—indeed, a preference for it over any chemically related kin that might be found in the body.

For instance, in early April, Darrell R.

The A, B, C's of therapeutic isotopes

The three forms of ionizing radiation were named for the first three letters of the Greek alphabet: alpha, beta, and gamma. Each emanates from radioactive elements as these unstable atoms decay, shedding energy in the process of transmuting from one isotope into another. Eventually, they become stable, or nonradioactive.

The amount of energy each type of radiation carries is determined by the isotope that expelled it. The period at which half of the atoms of any given isotope have undergone this transformation is their half-life. That half-life is specific to the isotope and ranges from a few milliseconds to billions of years.

Best known to oncologists are the gamma rays emitted by conventional radiation therapy sources such as cobalt-60. Gamma rays are photons of electromagnetic energy identical to X rays. While X rays originate from electronic transitions outside an atom's nucleus, gamma rays are emitted from the nucleus during radioactive decay. Each can easily pass through soft tissues to expose an X-ray film behind it.

Alpha particles are equivalent to helium nuclei, consisting of two protons and two neutrons. Betas are far smaller, negatively charged particles that have a mass equal to that of an electron. Dozens of radioactive elements emit an alpha or beta particle, sometimes both. Both betas and alphas disperse their cell-killing energy along their millimeter- to micrometer-long excursions through tissue. —*J.R.*

Fisher of PNNL finally constructed a cage for the alpha emitter radium-223, a decay product of actinium-227. "It's a major scientific breakthrough that will finally make it possible to use this [very short-lived] alpha emitter," Fisher declares. He points out that the achievement was realized "only after 10 years of work, including 7 years of synthesizing compounds and running stability tests on them."

So far, just a small number of successful isotope-antibody marriages have been arranged. Some of the earliest bind iodine-131, an isotope that emits low-energy gamma radiation along with a beta particle.

Dana C. Matthews of the Fred Hutchinson Cancer Research Center in Seattle has been exploring this isotope for 6 years in teenagers and adults scheduled to receive bone marrow transplants to arrest advanced leukemias. Her therapy uses an antibody that targets the CD-45 protein on white blood cells and most leukemias.

The standard treatment for these patients includes whole-body irradiation with an external beam of gamma rays. In a study begun several years ago to test how well the new therapy would be tolerated, 30 patients with advanced leukemia were given the maximum tolerable amount of external radiation, along with enough antibody-linked radioisotope to deliver 30 to 90 percent more radiation to the cancerous tissue. Though 5-year survival for patients with such an advanced cancer would ordinarily be around 25 percent, "we've gotten almost 50 percent survival," Matthews says.

Beyond cancer

Several research centers are investigating internally delivered radiation for a host of medical conditions other than cancer—notably, various forms of arthritis and coronary artery disease.

About 5 years ago, for instance, radiation oncologists at Emory University in Atlanta and Columbia University in New York launched separate studies to explore the use of radiation in patients who had received angioplasty. While this balloon-inflation procedure is designed to unclog arteries, it can unintentionally produce an injury that triggers an overzealous healing response—and a reclogging of the vessel with something akin to scar tissue.

Since radiation stops some types of cell proliferation, the researchers explored whether it might counteract the thickening of arterial walls. At Emory, Ian R. Crocker and his colleagues damaged pairs of arterial segments in several dozen pigs. Afterward, they irradiated one of those two segments in each animal with iridium-192, a gamma-ray-emitting isotope.

Six months later, the irradiated segments remained fairly open, whereas many of the nonirradiated segments had narrowed almost to the point of closure.

However, Crocker notes, "there were drawbacks to the iridium. It took about 40 minutes to deliver the treatment, and its radiation is penetrating, so you would have to move away from the bedside while the [treatment] catheter was in position." As a result, "we began thinking about how to make it more user-friendly," he says. They settled on using the isotope yttrium-90.

An Atlanta-based company is making a catheter system to shuttle metal seeds containing the isotope to the treated segments of arteries. In a small trial with 23 patients last year, the procedure inhibited the thickening of arterial walls, adding only about 6 minutes to the normal angioplasty. A slightly larger trial at the Scripps Clinic and Research Foundation in La Jolla, Calif., which used the slower iridium therapy, also dramatically inhibited the reclogging of arteries treated with angioplasty (SN: 6/14/97, p. 364).

A few months ago, the Food and Drug Administration authorized both the Emory and Scripps teams to head multicenter trials using their respective procedures. At Columbia, plans are under way for a third trial, this one using a liquid solution containing the beta-emitting rhenium-188, which is pumped to the balloon catheter as soon as an artery is unclogged.

Irradiating inflamed tissue that lines the joints, a procedure known as radiation synovectomy, remains equally experimental, despite its having been used in Europe to treat rheumatoid arthritis for more than 40 years.

PNNL

A vial of newly made yttrium-90 generates a lilac glow.

Twelve years ago, a Boston-area group received FDA approval to begin treating rheumatoid arthritis with radiation, notes Sonya Shortkroff, a team member at Brigham and Women's Hospital. Though it proved quite effective in the roughly 100 patients who were treated, she notes that "we are no longer doing it." Why? "We ran out of funding."

The Boston group had injected dysprosium-165, a very short-lived beta-emitting isotope, to destroy the joint tissue, or synovium. Because the tissue eventually grows back, Shortkroff notes, "it's not a cure." But a single treatment can cut or eliminate pain for some 3 to 5 years in 65 to 70 percent of patients with early-stage disease. Presumably, she says, the treatment could be repeated as needed.

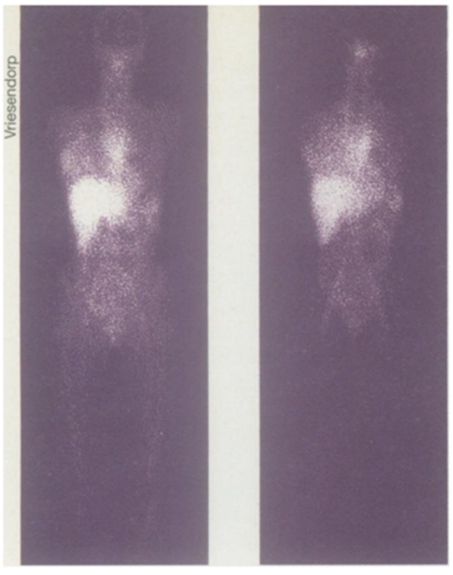
Mallinckrodt Medical, a radiopharmaceutical company in St. Louis, hopes to enter the arthritis field formally this year with a clinical trial in Europe. The firm's plan to test a novel chemical preparation containing samarium-153 just received FDA approval. This isotope, which emits beta particles and low-energy gamma rays, would also be injected directly into the joints.

Though yttrium-90 has been used successfully on rheumatoid knees in European trials, notes Joe Straus, associate director of clinical research at Mallinckrodt, it sometimes proved too powerful on inflamed fingers and other small joints, causing "radiation burns to the skin overlying those joints." Samarium's less energetic beta particles should allow the new preparation to be used in a broad range of joints, Straus says—not only the knee but also the finger, elbow, shoulder, and hip.

Hemophiliacs may derive the greatest and most lasting benefit from radiation synovectomy, says Michael E. Siegel, director of nuclear medicine at the Los Angeles County and University of Southern California Medical Center. In this population, even minor traumas that result from stepping off a curb or jumping can cause bleeding into a joint. When enough red cells get in, the tissue suffers a rheumatoid-arthritis–like inflammation that, unless treated, can cause permanent joint injury.

Because hemophiliacs lack a clotting factor to make bleeding stop, any surgery poses grave risks—and costs. The price of a hemophiliac's surgical synovectomy can run to $200,000, Siegel notes, with clotting factors accounting for much of the expense.

Injecting phosphorus-32, a pure beta emitter, into the affected joints achieves the same result without the surgery and for a cost of perhaps only $4,000, he says. Moreover, with rheumatoid arthritis patients, the autoimmune inflammation recurs as soon as the tissue grows back. "But in the hemophiliacs," he notes, "when their synovium grows back, it's normal"—and may remain so "for the rest of their lives." —*J.R.*



Colorized, whole-body image created by injecting a gamma emitter into the heart before (left) and 3 months after (right) a patient's first yttrium-90 injection to treat Hodgkin's disease. The large, bright area on the right side of the chest, which indicates where the antibody-linked gamma emitter found cancer, shows less disease after therapy.

Her group is planning studies to see whether isotopes without gamma radiation might offer even greater benefits.

While the iodine's gamma radiation is not high, Matthews notes, it does require that treated patients remain isolated in lead-insulated rooms for 4 to 10 days until the radioactive iodine decays to a point at which it no longer poses a health risk to hospital staff or visitors. Adult patients may be able to gain sufficient comfort from talking to family by phone or across chest-high shields at the door, but young children need a parent's touch, she says. "So as a pediatric oncologist, I'm very interested in getting away from the gamma component."

One gammafree isotope under investigation is yttrium-90. Over the last 8 years, Vriesendorp has been using this isotope, which emits solely betas, to treat some 130 Hodgkin's patients who have failed to benefit from all previous therapies. His regimen delivers two injections of the isotope, 1 week apart, on an outpatient basis. Even in these advanced cases, he notes, "we get a very good tumor response in two-thirds [of the patients]. The tumors shrink." Vriesendorp uses radioisotope purified from nuclear waste (see sidebar at right).

At the Memorial Sloan-Kettering Cancer Center in New York, David A. Scheinberg has turned to bismuth-213, which emits only alpha radiation, to treat leukemia (SN: 2/22/97, p. 117), again on an outpatient basis.

For nearly a decade, he had tried iodine-131, but high doses killed blood-making cells, necessitating a bone marrow transplant. "That's not a feasible scheme for the majority of patients, who are either too old or lack a marrow donor," he says.

"The beauty of the alpha particle," he observes, "is that it travels only about 50 microns—which is approximately three to five cell diameters." Though his initial trial is designed to identify maximum tolerable doses for treatment, not to assess efficacy, "we've already seen significant antileukemic activity in the patients we've treated," he told SCIENCE NEWS.

To date, these antibody therapies have been directed primarily against leukemias and lymphomas, Vriesendorp notes. Not only are these cancers generally smaller and more sensitive to radiation poisoning than solid tumors, they're also bathed in the blood that can ferry the injected isotopes.

Programs are now under way to adapt these treatments to solid cancers. The Arlington team, for instance, is marrying yttrium-90 to a large antibody known as IGM.

"IGM is so big that it will not leave the bloodstream," Vriesendorp notes, "so it's not good where you need to use the vascular system to get into a tumor." It does show promise for destroying metastases in confined spaces, such as ovarian tumors that have spread to the peritoneal cavity. The soluble IGM-isotope pair can also be injected directly into a tumor. Using nude mice, "we've put it in the middle of a cancer," he says, "and over the next day or two it diffused throughout the tumor."

The IGM therapy is slated to be tested on people later this year, initially in patients with breast, colon, ovarian, or head and neck cancers. In a year or two, Scheinberg hopes to begin human trials with antibody-directed alpha-emitting isotopes targeted to tiny metastases from breast, prostate, or other solid cancers.

Antibodies aren't necessary for the beta therapy to relieve suffering in patients with tumors growing in bone. Radiologist Edward Silberstein of the University of Cincinnati Medical Center has been investigating a host of radionuclides with a natural affinity for bone, including samarium-153, strontium-89, and rhenium-186. Yttrium-90 and others are being tested in Europe.

His studies on about 150 patients indicate that each of the isotopes he's tried, "though not a cure," appears "quite effective"—reducing up to 80 percent of pain.

"We sometimes reduce the pain before the tumor [shrinks]," so some of the radiation's palliative effects must come from destroying white blood cells or other biological agents responsible for causing or signaling pain, he says.

Compared to cancers, normal tissues tend to be more sensitive to radiation and chemotherapy. Thus, Vriesendorp notes, oncologists have adopted a "no pain, no gain" philosophy.

Internally targeted radiation promises a new alternative, he says—"therapies that don't have to be given at such an industrial strength that they bring the patients to the intensive care unit and close to death."

Indeed, Spenceley argues, "if you could learn you had cancer—as horrible as that is—and know that this treatment option was available, then the diagnosis would not be as ugly as it is today." □

Rx from radwastes

In medical use for a decade, yttrium-90 is still one of the rising stars of antibody-directed radiotherapy, notes Thomas S. Tenforde of the Energy Department's Pacific Northwest National Laboratory at the Hanford site in Richland, Wash. Perhaps surprisingly, radioactive wastes from Hanford's production of plutonium for warheads are now a preferred source of this isotope. Shown below is a mixed brew of chemical and radioactive wastes, including strontium, being stored in a tank at Hanford.

When the nuclei of uranium-238 atoms break in two—while powering nuclear reactors or a bomb—they create large quantities of strontium-90. Yttrium-90 is the first product of its decay.

"We have probably the largest stockpile of strontium-90 in the United States," Tenforde says. Although there are sources of yttrium-90 other than weapons wastes, "our yttrium is the purest. The process by which it's retrieved from the strontium-90 parent is something that we patented. It leaves very few contaminants—for instance, no strontium."

Indeed, says Huibert M. Vriesendorp of the Arlington (Texas) Cancer Center, antibody therapy can give unreliable results if the isotope that's used contains contaminants. "That's one reason it's important to have the quality of isotope that comes from Hanford," he says. —*J.R.*