RADIONUCLIDE THERAPY

Physicists and physicians are working together to devise new methods for exploiting the power of ionizing radiation to treat cancer and coronary artery disease.

Bert M. Coursey and Ravinder Nath

Each year in the US, about 200 000 patients receive therapy with radionuclides, most commonly in the form of sealed sources for treating gynecological and head and neck cancers and radiopharmaceuticals for treating thyroid cancer. Known as brachytherapy, this kind of treatment has attracted a resurgence of interest in the medical world, primarily because it offers a simple procedure for delivering high radiation doses to a tumor but minimal doses to the surrounding healthy tissue. Brachytherapy can provide this optimal dose distribution because radiation sources are implanted either in the tumor or very close to it. (*Brachys* is Greek for "near.") This advantage is not shared by external beam therapy, in which the source of radiation is about 1 m away from the patient.[1]

Recent successes with two new forms of radionuclide therapy—radioactive seeds for treating prostate cancer and radioactive sources for preventing the reclosing of arteries following balloon angioplasty—presage the treatment of hundreds of thousands of additional patients annually in the US alone. And radiopharmaceuticals containing many of the same radionuclides also offer promise for treating certain cancers that have been resistant to other types of therapy.

A brief history

Radionuclides were first used in therapy nearly a century ago, after Pierre Curie and others noticed that radium sources brought into prolonged contact with skin produced burns. Physicians used this observation to design treatments for surface lesions, such as those seen in lupus. By 1915, therapy with sealed sources of radium-226 or radon-222 had become widely available. But in the 1940s and 1950s, as concerns grew about the risks of radiation exposure to medical personnel, medical professionals lost interest in brachytherapy.

Two technical innovations began to allay those concerns. In the 1950s, so-called afterloading techniques (remote source handling with increasingly sophisticated robotics) were introduced that dramatically reduced personnel exposure. Around the same time, several new reactor-produced radionuclides with better radiation safety characteristics became available. For example, when ready supplies of cobalt-60 (which has a high specific activity, a 5.27-y halflife, and 1.25-MeV gamma rays) became available 40 years ago, external beam therapy with ^{60}Co quickly supplanted the 250-kV x-ray tubes then in use. Even today, ^{60}Co machines remain a vital and dominant treatment option for radiotherapy in developing countries. During the same period, the fission product cesium-137 became available as a safer alternative to ^{226}Ra for brachytherapy, and it is still in active use for treating gynecological cancers. (See box 1 on page 27 for information on how radioactivity is quantified.)

Radionuclide therapy remains an important treatment option today because ionizing radiation from radionuclides can kill cells, and thus inhibit growth in the benign and cancerous lesions that result from proliferative diseases. Other cytotoxic agents exist, but radiation is simply the most effective way of controlling the proliferation of cells without unacceptable morbidity. It is the treatment of choice for a large number of cancer patients.

Radiation kills cells by damaging the DNA in the cell nucleus, thereby inhibiting cellular reproduction. To damage DNA, the energy of the radiation—in the form of photons, electrons, or heavier charged particles—has to exceed a few tens of electron volts. However, if the radiation is delivered from outside the body, as in external beam radiotherapy, then photon energies of several million electron volts are needed simply to penetrate the tissues and reach the deeper-seated tumors in the body. By contrast, brachytherapy implants can be successfully performed with radionuclides that emit photons with energies as low as 20 keV. For example, palladium-103, which is used for prostate implantation, has an average energy of just 21 keV. Radiopharmaceutical therapies also allow a radionuclide to deliver its decay energy close to, or even inside, the target cells.

Clinical brachytherapy

Brachytherapy is typically practiced by an interdisciplinary team of physicians and medical physicists. Together, they must consider several factors before planning a treatment:

▷ **Size of the tumor at diagnosis.** The physical extent of the target mass (or number of target cells) is important for choosing the appropriate radionuclide. Radiation oncologists use a simple rule of thumb: If a tumor is identified with a mass of 1 mg (10^6 cells), it can usually be treated with curative intent. At that early stage, the cancer is microscopic in extent and usually undetectable by

BERT COURSEY *heads the National Institute of Standards and Technology's ionizing radiation division in Gaithersburg, Maryland.* RAVINDER NATH *chairs Yale University's division of radiological physics in New Haven, Connecticut.*

© 2000 American Institute of Physics, S-0031-9228-0004-010-2

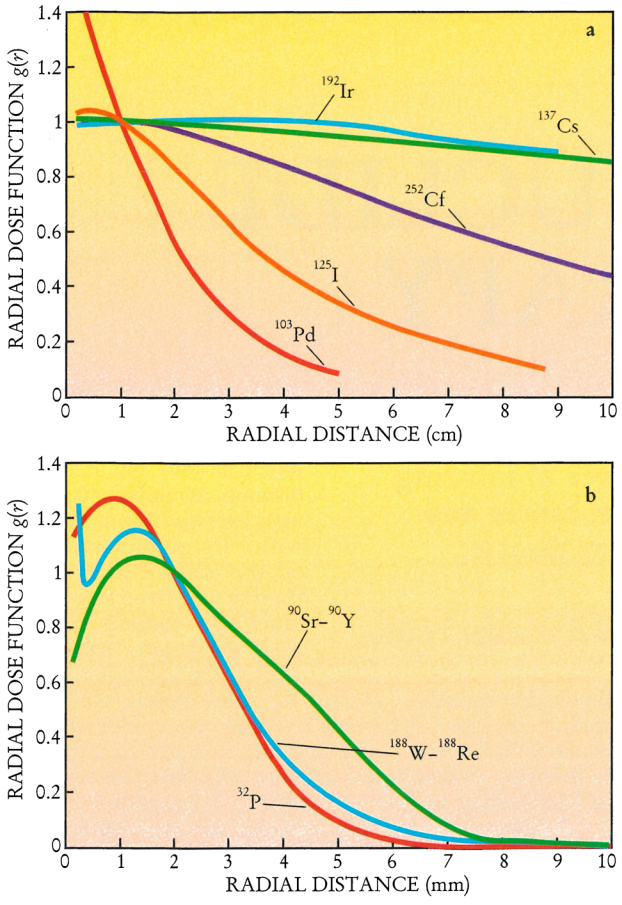

FIGURE 1. THE RADIAL DOSE FUNCTION $g(r)$ is the product of the dose at distance r (divided by the dose at a reference distance) and the distance squared.[2,3] This definition removes the $1/r^2$ dependence that is common to all the radiations, so that $g(r)$ reflects only the attenuation in tissue. (**a**) $g(r)$ for the gamma-ray emitters iridium-192, cesium-137, iodine-125, and palladium-103 and the neutron emitter californium-252 normalized at a 1-cm reference distance. (**b**) $g(r)$ for the beta emitters strontium-90–yttrium-90, phosphorus-32, and tungsten-188–rhenium-188 normalized at a 2-mm reference distance.

imaging techniques. Larger tumors are, in most cases, harder to cure, but there are many exceptions to this rule. Some large tumors are curable, whereas some tiny ones are not. Regardless of size, however, the volume of the tumor needs to be determined accurately. Advances in the physical methods used in imaging, including magnetic resonance imaging, computed tomography (CT), positron emission tomography, and ultrasound, provide radiologists with better tools to detect suspicious lesions at an earlier stage of development and to accurately localize tumors in three dimensions.

▷ **Vascularization of the tumor.** If the tumor has a good supply of blood—as is the case for a distributed soft-tissue tumor, such as a lymphoma—treatment with a radiolabeled drug or biologic agent could be possible. For solid, less vascularized tumors, it may be necessary to use sealed sources with longer-range gamma radiations. Attachment to blood vessels is not the only factor. The lack of adequate oxygen levels in less vascularized tumors makes the cancer cells in them highly resistant to photons and electrons. (The free radicals produced from water irradiated in the presence of oxygen, such as the hydroxyl radical, are the most effective agents in damaging DNA.)

▷ **Tumor-to-normal tissue dose ratio.** It is important to deliver a lethal radiation dose to the malignant cells in the target volume but a safe dose to the adjacent normal tissue. For example, in the case of prostate therapy with radioactive seeds, more than 150 gray has be delivered to the diseased prostate while the doses to the urethra, rectum, and bladder are minimized. An optimal therapeutic window exists: Too high a dose will cause unacceptable damage to the surrounding tissue, whereas too low a dose will not kill enough malignant cells in the prostate to prevent a recurrence of the tumor. Some key questions are: How wide is this therapeutic window? Can it be modified to the advantage of the patient by using radiation sensitizers for the cancer and radiation protective agents for the normal tissues? If the window is very narrow, are the available physics tools accurate enough for successful treatment without serious complications?

Choosing the right nuclide

Advances in the effectiveness of radiation therapy have been driven by parallel advances in nuclear and radiation physics. Nuclear decay data (level schemes, halflives, probabilities per decay) have helped more effective radionuclides to be introduced, while analytical and computational radiation transport methods developed for basic research and defense applications have been adapted for planning treatment. Here, we consider the role of the physicist in choosing the best radionuclide for a particular application.

For example, because the gamma-ray energies of ^{60}Co, ^{137}Cs, and ^{226}Ra are too high (and therefore too penetrating), physicists continue to search for radionuclides with gamma-ray emissions that are better tailored to the treatment depth in tumors. The maximum depth of penetration is of less importance than the distribution of dose with depth,[2,4] which is often represented by the radial dose function. Several examples of the radial dose functions for beta and photon emitters are shown in figure 1. Because the interactions of radiation and condensed matter are so complex, radial dose functions cannot be accurately estimated with analytical models. Rather, they are based either on experimental data from thermoluminescent dosimeters or on computed distributions from Monte Carlo simulations.[3]

Over the past decade, iridium-192, which has a halflife of 73 days, has become remarkably popular in treatments for a great many cancers. Although ^{192}Ir has a series of gamma and x rays that contribute to the overall tumor dose, the main contribution comes from photons of around 380 keV, which have an effective range in tissue of a few centimeters. ^{192}Ir sources are typically formed into wires and seeds, which are often inserted into the tumor in intricate preselected patterns with computer-controlled remote afterloaders (see figure 2). Thanks to this method, ^{192}Ir sources of very high activity (up to 10 curies) can be used safely. This class of treatment is known as high dose rate therapy, as opposed to the traditional low dose rate therapy.

Studies continue to optimize both forms of therapy because the radiobiological response depends on dose rate. Longer-lasting, less intense irradiations allow some of the radiation damage to be repaired and, therefore, are

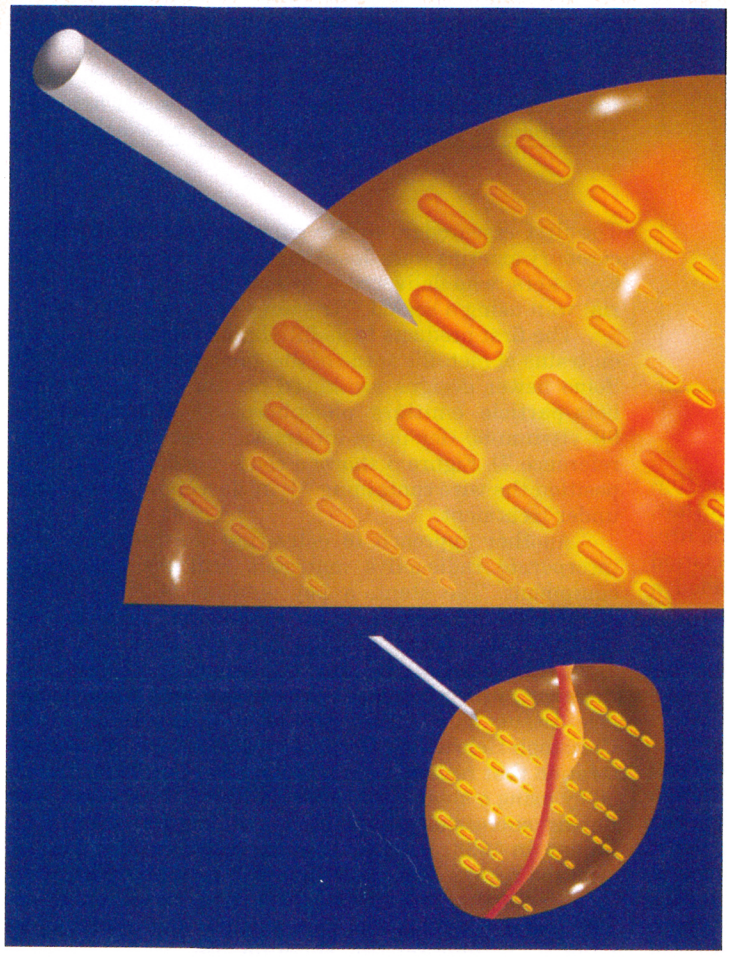

FIGURE 2. THE PLACEMENT OF RADIOACTIVE SEEDS to treat prostate cancer is shown here schematically. In a typical procedure 60–100 seeds are implanted in the prostate gland. Transrectal ultrasound imaging is used to guide the seed placement to minimize doses to the urethra, rectum and bladder. (Illustration by Jeffrey Aarons, NIST.)

less effective at killing cells. However, low dose rate brachytherapy offers some other biological advantages.

In this article, we focus on the three applications of radionuclide therapy that are receiving the most attention—namely, prostate seed therapy, intravascular therapy, and therapeutic radiopharmaceuticals. The nuclides we discuss emit energetic photons and electrons from excited nuclear and atomic states, but in box 2 on page 29 we describe a current example of radionuclide therapy involving fast neutrons from a sealed source of californium-252.

Prostate seed therapy

In a recent report on a ten-year clinical study, prostate treatment with iodine-125 seeds was found to be as effective as surgery, with fewer of the complications (impotence and incontinence) that often accompany surgery.[5] Of the 120 000 patients in the US per year who receive some form of treatment for prostate cancer, about 10 000 are treated with seeds, a number that is expected to increase substantially.

In the radionuclide prostate treatments, 60–100 seeds are surgically implanted in a tumor volume that may be as large as 50 cm^3. Both ^{125}I, which has a 60-day halflife, and ^{103}Pd, which has a 17-day halflife, are used for prostate seeds. (The photon spectrum of an ^{125}I seed obtained with a semiconductor detector is shown in figure 3.) But the innovative use of radionuclides is just part of the reason for the current success of this treatment. Much of the credit is probably due to transrectal ultrasound imaging, which allows the urologist to observe the needle placement of the seeds in real time.

Increasing demands for seeds are leading to many new seed designs, and each manufacturer needs support from the National Institute of Standards and Technology (NIST) on air kerma standards and from physicists at universities to establish the dosimetry parameters for the sources.

Figure 4 illustrates some of the computational and imaging tools available to physicists and oncologists in designing a specific patient treatment plan. Both images show a CT scan of the pelvic area with proposed dose distributions for an interstitial seed implant (figure 4a) and

Box 1. Quantities and Units

Unfortunately, the quantities and units for radioactive sources used in therapy continue to be a source of confusion. The recent proliferation of new sources has only served to underscore the need for agreeing on a consistent set of quantities.[2,3]

Conceptually, the simplest quantity is the source radioactivity, A, which is defined by $A = \lambda N$, where λ is the decay constant and N is the number of atoms. It has units of becquerels, and 1 Bq = 1 s^{-1}. (The older unit for radioactivity is the curie, for which 1 Ci = 3.7 × 10^{10} Bq exactly.) The trouble is that the source radioactivity is rarely known and is difficult to measure—particularly if the source encapsulation attenuates the radiations in a complicated manner.

What is needed is a practical measure of source strength. Under the Système International, two dosimetric quantities are used: air kerma and absorbed dose. Both quantities have units of grays, and 1 Gy = 1 J kg^{-1}.

▷ **Air kerma** is defined as dE_{tr}/dm, where dE_{tr} is the sum of the initial kinetic energies of all the charged particles released by photons in a mass dm of dry air. Air kerma is realized by an absolute ionometric measurement, in which a finite current is measured in some known volume of dry air. The dosimetric quantity of interest for photon emitters (iridium-192, iodine-125, and others) is the air kerma strength (in units of μGy hr^{-1} m^2).

▷ **Absorbed dose.** In water at a point some reference distance from the source (say, 2 mm for a beta particle, or 1 cm for a photon), the absorbed dose is much closer to the quantity needed for treatment planning. Although it is conceptually useful, absorbed dose is difficult to realize because dose gradients near the source are large, and, as in many other physics experiments, the finite detector disturbs the measurement of interest. In practice, one usually resorts to measuring dose with passive dosimeters (radiochromic films and thermoluminescent dosimeters), whose radiation response has been calibrated in reference beams at the National Institute of Standards and Technology.

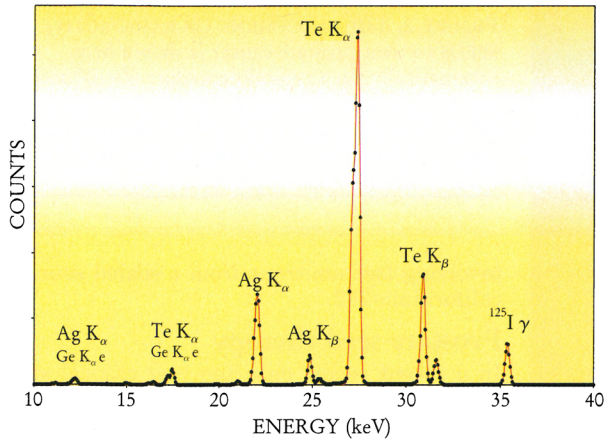

FIGURE 3. PHOTON PULSE-HEIGHT distribution for iodine-125 obtained with a semiconductor detector. Several of the ^{125}I seeds, such as the one whose spectrum is shown here, have the iodine coated on a silver substrate. In this case, the seed has a softer spectrum as a result of silver K x-ray fluorescence in the seed.

for external beam therapy with an 18-MV x-ray tube (figure 4b). A clear advantage of seed implantation is that, with careful placement, one can limit the dose to the urethra and other critical organs. The American Association of Physicists in Medicine (AAPM) has recommended a protocol for use by clinical physicists in computing patient doses from prostate implants,[2] but additional recommendations will be needed from the AAPM for the many new sources that are being introduced.

Intravascular therapy

In balloon angioplasty, an inflated catheter is used to open arteries that are occluded because of plaque formation, a life-threatening condition known as atherosclerosis. The balloon procedure is designed to crush the plaque, but it often tears the arterial wall as well. Some of the cells in the blood vessel respond to this injury by initiating repair, which often leads to restenosis (reclosing) of the artery. But if the lesion is treated with radiation (on the order of 8–30 Gy), this restenotic effect is inhibited.

In the case of most coronary angioplasty procedures, a catheter is inserted into and guided through the femoral artery in the groin until it reaches the arteries that carry blood to the heart muscle. Various devices to treat the lesion are then fed through the catheter and positioned in the coronary artery with the aid of angiographic imaging.

The first researchers to use gamma radiation in human coronary arteries were Jose Condado in Venezuela and his coworkers, who delivered a dose of 20–25 Gy to the arterial wall using a sealed ^{192}Ir source in a catheter.[6]

The first products to go into human trials were based on trains of metallic seeds of the gamma-ray emitter ^{192}Ir. Some newer designs are based on sources that use the beta-particle emitters phosphorus-32 and strontium-90–yttrium-90 (for more information, see the reviews in reference 7). Figure 5 shows a centering catheter used to position the wire containing ^{32}P in the center of the lesion under treatment.

Another approach to delivering the radiation is to incorporate radioactive materials into the angioplasty equipment. The stent, a key element of most balloon angioplasty procedures, is an expandable metallic mesh that provides mechanical support for the weakened arterial wall. In many cases, however, restenosis occurs despite the stent, which becomes incorporated into the proliferative tissue that forms around the lesion. In 1993, Christoph Hehrlein in Germany reported[8] the first demonstration that restenosis in a rabbit artery could be inhibited by using a stent impregnated with ^{32}P. Five years later, having successfully implanted a radioactive stent in a human in 1993, Hehrlein and his colleague Tim Fischell reported results from more than 250 such procedures.[9]

Stents that incorporate ^{103}Pd and vanadium-48 are also under investigation, as are other solid sources that employ ruthenium-106–rhodium-106 and tungsten-188–rhenium-188 (which take advantage of the longer halflives of the ^{106}Ru and ^{188}W parents). Other investigators are focusing on the angioplasty balloon. In this approach, the balloon is filled with a radioactive fluid, such as xenon-133 gas, or solutions of ^{32}P, ^{90}Y, rhenium-186 and rhenium-188, and holmium-166.

These intravascular radiation applications are so new

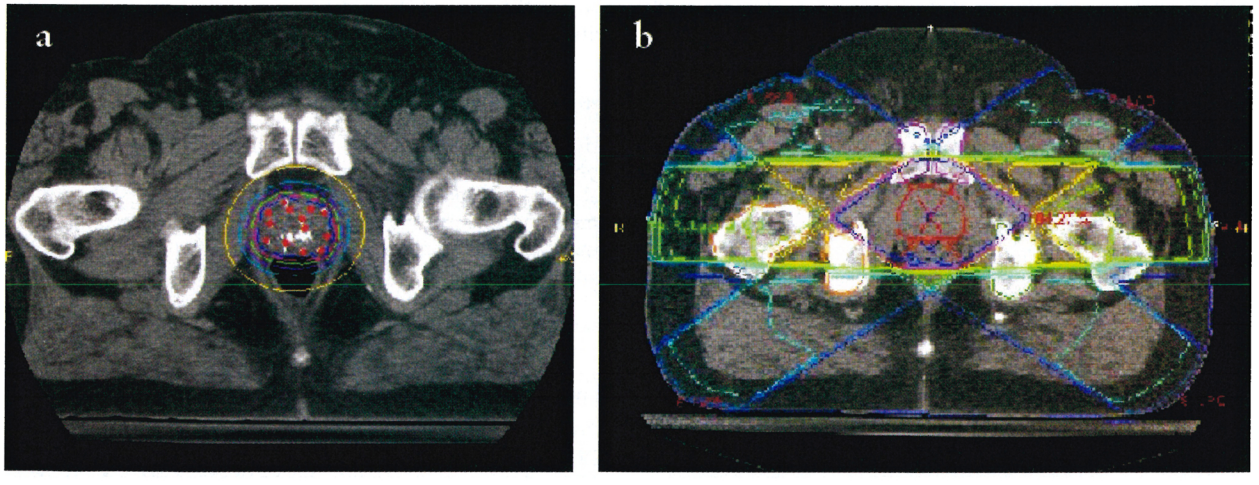

FIGURE 4. TWO-DIMENSIONAL IMAGE SLICES through a pelvis, showing radiation dose plans for prostate cancer treated with (**a**) seed therapy (the blue line is the isodose curve for 145 gray and the yellow line is 10 gray), and (**b**) external photon-beam therapy with three confocal collimated beams. These calculations by Sharron Trumpore at Yale–New Haven Hospital demonstrate the superior dose localization of brachytherapy compared with external beam therapy.

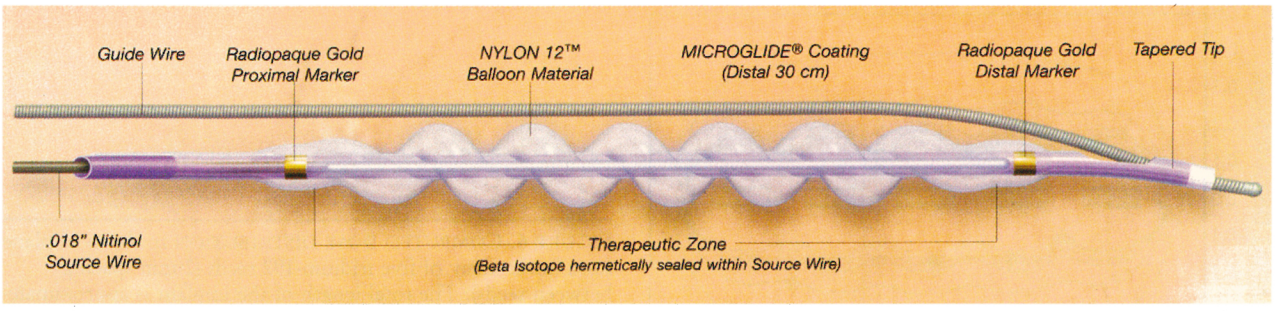

FIGURE 5. GALILEO™ CENTERING CATHETER and radioactive phosphorus-32 wire source used in prevention of restenosis. The catheter is inserted in the femoral artery and fed to the coronary artery, where the gold markers can be viewed on an angiogram. The product of the source dose rate and the dwell time in the lesion determines the dose to the arterial wall. (Courtesy of Firas Mourtada, Guidant Corp; the mention here of a commercial product does not imply its endorsement by NIST, Yale University, or PHYSICS TODAY.)

that in 1998 the number of patients treated with them per year was less than 4000 worldwide. However, intravascular radiation therapy has the potential to help 400 000 patients per year in the US alone. The trials so far have been encouraging. Paul Tierstein's group at the Scripps Clinic in La Jolla, California, recently reported the results of its two-year follow-up on the first group of patients whose angioplasty treatment involved an ^{192}Ir seed-train device.[10] The group found no evidence of late effects in these patients that would negate the short-term benefits.

Despite these and other promising early results, it is not clear just how large a volume should be irradiated to inhibit restenosis. Figure 6 shows the calculated dose distribution for a train of ^{192}Ir seeds. Gamma emitters and higher-energy beta emitters can deliver a fairly uniform dose to the arterial region where the suspect cells originate. Debates continue about beta radiation versus gamma radiation, and medium-energy versus higher-energy beta emitters. Some applications require longer-halflife nuclides, whereas others benefit from shorter-halflife nuclides. For these reasons, medical center and industry researchers will probably investigate several additional nuclides over the next few years. And if intravascular radiation therapy fulfills its early promise, a new community of users in hospitals and clinics will emerge who will require support from clinical medical physicists and health physicists for a variety of nuclides and radioanalytical procedures.

Therapeutic radiopharmaceuticals

The first radionuclide used in the form of a therapeutic drug was ^{131}I. Shortly after World War II, the US National Bureau of Standards (the forerunner of NIST) provided ^{131}I reference materials to US companies, who began manufacturing ^{131}I-based drugs for treating hyperthyroidism and thyroid cancer. Many of these drugs are still widely used today.[11] The thyroid requires about 1 mg of iodine per week, which indicates that ^{131}I is rapidly incorporated by metabolic processes. For thyroid applications, the relatively short halflife (8.0 days) of ^{131}I is therefore an advantage, as are its medium-energy beta particles, its gamma rays that are suitable for imaging, and the ease with which it can be covalently bonded to many organic molecules.

Two other therapeutic uses of radiopharmaceuticals are attracting considerable interest—namely, palliative agents and radioimmunotherapy agents.

Some cancers, notably of the breast and prostate, can spread from their primary sites to the bone, causing a painful condition known as metastatic bone disease. The ailment may be treated palliatively by external beam therapy or by painkilling drugs, such as morphine. But

Box 2. Californium-252 Seed Sources

Neutrons were first used in cancer therapy by Ernest O. Lawrence and his brother John Lawrence, a physician, with the cyclotron at Berkeley. (See PHYSICS TODAY, May 1996, page 34.) Neutrons are a continuing source of interest because they release heavy charged particles, such as recoil protons and nuclei, as secondary radiations. These types of radiation deposit large amounts of energy per unit distance in a medium (that is, they have a higher linear energy transfer, LET). High-LET radiation is more effective than low-LET radiation in producing double strand breaks in DNA, a key process in killing cells. Moreover, high-LET radiation does not suffer from the oxygen effect that reduces the effectiveness of x- and gamma rays for treatment of hypoxic (oxygen-deficient) tumors.

Neutron-beam therapy using reactors and cyclotrons still finds some applications, but radionuclide sources of neutrons are also under investigation, particularly for use in sealed sources. As for other kinds of emitters, the challenge is to find radionuclides that have the appropriate halflives and that can be conveniently manufactured. The radionuclide that has shown the most promise is californium-252, which has a 2.6-y halflife. Thanks to recent work by Wayne State University's Mark Rivard and others, the dosimetry of such neutron sources has been put on a similar footing to the photon emitters.[4]

For both neutron beams and ^{252}Cf sources, researchers are investigating boron neutron-capture therapy (BNCT). In BNCT, the tumor site is loaded with boron-containing pharmaceuticals to boost the neutrons' cytotoxicity. Boron (that is, the stable boron-10) has this amplifying effect because it has a high neutron-capture cross section; once irradiated by neutrons, it produces charged secondaries that increase the probability of cell killing in the tumor. Seed therapy would seem to have an advantage over beam therapy in this application, because when the seed is surgically implanted, another device could be used to locally and simultaneously deliver a boronated pharmaceutical.

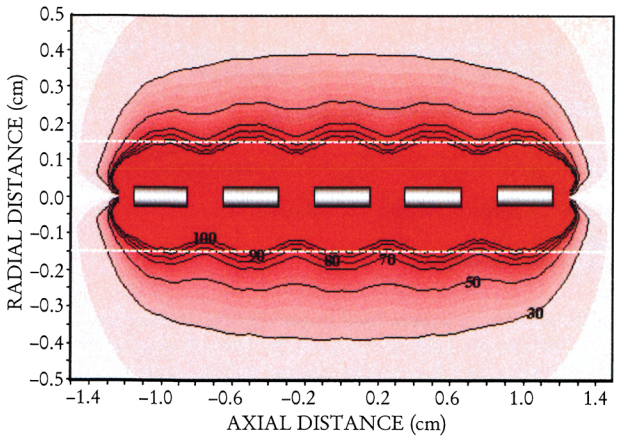

FIGURE 6. COMPUTED DOSE DISTRIBUTION in the axial plane for a linear array of five iridium-192 seeds (2-mm spacing between seeds). The total length of the implant is approximately 23 mm. These calculations by Christopher Soares at NIST show that adding additional seeds to the ends does not change the dose delivered at the reference depth of 2 mm in tissue.

increasingly, radiopharmaceuticals are being used instead.[12] In this application, the strategy is to attach high-energy beta-particle emitters with relatively short halflives to bone-seeking molecules that can be administered to the patient in the form of a drug.

^{32}P and ^{89}Sr have been mentioned for this purpose since the 1940s,[13] but only recently have radionuclide-based palliative agents come into wide general use. ^{89}Sr and samarium-153, for example, were approved in the US in 1995 and 1997, respectively. (The 50.5-day halflife of ^{89}Sr may seem a bit long for this application, but the nuclide appears to be effective.) Several other high-energy beta-particle emitters are candidates for this application, such as erbium-169, lutetium-177, and ^{188}Re, which has the advantage that it can be eluted from a commercial ^{188}W–^{188}Re generator.

A form of magic bullet therapy, radioimmunotherapy involves attaching a radionuclide to a monoclonal antibody or a smaller protein fragment that is targeted at a particular line of tumor cells. First, the radionuclide is chemically bound to a small precursor molecule called a ligand. The ligand is then attached to a monoclonal antibody, which is injected into the bloodstream. The antibody localizes in the tumor, and its radionuclide attachment emits charged particles that kill one or more tumor cells.

This form of therapy has been under intense study at medical research centers for about a decade. Because of the same attributes mentioned above for thyroid therapy, ^{131}I is one of the main nuclides that investigators have chosen to focus on. However, ^{90}Y (which has a 64-h halflife and emits 2.2-MeV beta particles) is also under investigation. For both ^{131}I and ^{90}Y, the range of the cell-killing radiation is expected to extend over several millimeters.

Mainly on theoretical grounds, researchers are also interested in alpha-particle emitters and Auger electron emitters, and several of these have been proposed as potential drug ingredients. Candidate alpha-particle emitters include[14] astatine-211, bismuth-212 and bismuth-213, and fermium-255. Some of these have active daughter nuclides that emit additional alpha and beta particles in the tumor volume. Auger emitters are expected to be more effective in killing cells because of the high linear energy transfer (LET) of the low-energy (that is, less than 1 keV) electrons.[15] The two nuclides most often mentioned are ^{125}I and indium-111. There are, however, many other possibilities, including other radioindiums (^{114m}In) and radioplatinums (^{193m}Pt, ^{195m}Pt).

Advances in this field must come not only from carefully selecting the appropriate radionuclide, but also from better targeting strategies that ensure higher specificity for the target cells and lower radiation doses to normal tissue. For example, antibody fragments or smaller protein fragments—as opposed to complete antibody molecules—have been found to localize faster in tumors.

Looking ahead

The three classes of therapeutic radionuclides that we have focused on here—sealed sources for prostate therapy, sources for intravascular therapy, and radiopharmaceutical therapies—are poised for rapid growth over the next few years. Of course, major considerations in healthcare today are costs and reimbursements. Perhaps some of these procedures will be rather costly. However, in the case of prostate cancer treatment, radioactive seed therapy actually costs less than the alternatives of surgery and beam radiotherapy. Still, widespread acceptance of these procedures will depend primarily on how successful they are compared with the alternative therapies.

For medical physicists and for research physicists in nuclear and radiation sciences, radionuclide therapy offers many challenging opportunities to discover and develop more of these lifesaving applications of medical science and technology.

References

1. S. Nag, *Principles and Practice of Brachytherapy*, Futura, Armonk, N.Y. (1997).
2. R. Nath, L. L. Anderson, G. Luxton, K. A. Weaver, J. F. Williamson, A. S. Meigooni, Medical Physics **22**, 209 (1995).
3. R. Nath *et al.*, Medical Physics **26**, 119 (1999).
4. M. J. Rivard, J. G. Wierzbicki, F. van den Heuvel, R. C. Martin, R. R. McMahon, Medical Physics **26**, 87 (1999).
5. J. C. Blasko, P. D. Grimm, H. Radge, D. Schumacher, in *Prostate Cancer*, M. S. Ernstoff, J. A. Heaney, R. E. Peschel, eds., Blackwell Science, Cambridge, Mass. (1998), p. 137.
6. J. A. Condado, O. Curdiel, R. Espinoza, J. G. Brito, M. L. Harrison, L. R. Joyner, S. L. Liprie, Journal of the American College of Cardiology **288A**, (1994).
7. R. Waksman, *Vascular Brachytherapy*, 2nd ed., Futura, Armonk, N.Y. (1998).
8. C. Hehrlein, M. Zimmermann, J. Merz, Circulation **88**, 651 (1993).
9. T. Fischell, C. Hehrlein, Herz **23**, 379 (1998).
10. P. Tierstein *et al.*, Circulation **99**, 243 (1999).
11. C. A. Gorman, International Symposium on Radioiodine, Thyroid **7**, No. 2 (1997).
12. "Radionuclides and Bone Palliation," special issue of Applied Radiation and Isotopes **49**, No. 4 (1998).
13. H. L. Atkins, Applied Radiation and Isotopes **49**, 277 (1998).
14. S. Mirzadeh, Applied Radiation and Isotopes **49**, 34 (1998).
15. J. G. Kereiakes, D. V. Rao, Medical Physics **19**, 1359 (1992). ■