pilot trials on yttrium-90 glass microspheres through the hepatic artery for treatment of primary liver cancer. *Cancer* 1993;72:3210–3215.
28. Clarke LP, Cullom SJ, Shaw R, et al. Bremsstrahlung imaging using the gamma camera: factors affecting attenuation. *J Nucl Med* 1992;33:161–166.
29. Raoul JI, Bretagne JF, Caucanas JP, et al. Internal radiation therapy for hepatocellular carcinoma: results of a french multicenter phase II trial of transarterial injection of iodine-131-labeled lipiodol. *Cancer* 1992;69:346–352.
30. Oberfield RA, Steele G, Gollan JL, Sherman D. Liver cancer. *CA* 1989;39: 206–218.
31. Cady B. Natural history of primary and secondary tumors of the liver. *Semin Oncol* 1983;10:127–134.
32. Nelson RS, Elizalde R, Howe CD. Clinical aspects of primary carcinoma of the liver. *Cancer* 1966;19:533–537.
33. Jaffe BM, Donegan WL, Watson F, et al. Factors influencing untreated hepatic metastases. *Surg Gynecol Obstet* 1968;127:1–8.
34. Primack A, Vogel CL, Kyalwazi SK, et al. A staging system for hepatocellular carcinoma: prognostic factors in Uganda patients. *Cancer* 1975;35: 1356–1368.
35. Goldberg JA, Anderson JH, Bessent RG, et al. Glass ^{90}Y microspheres and angiotensin II for colorectal liver metastases [Abstract]. *Nucl Med Commun* 1991;12:256.
36. Kinsella TJ, Mitchell JB, Russo A, et al. Continuous intravenous infusions of bromodeoxyuridine as a clinical radiosensitizer. *J Clin Oncol* 1984;2: 1144–1150.
37. Ensminger WD, Andrews JC, Walker-Andrews S, et al. Pharmacokinetics of 5-bromo-2'-deoxyuridine (Brd Urd) applicable to hepatic arterial infusion [Abstract]. *ASCO Proc* 1989;8:77.
38. Andrews JC, Walker-Andrews SC, Juni JE, Warber S, Ensminger WD. Modulation of liver tumor blood flow with hepatic arterial epinephrine: a SPECT study. *Radiology* 1989;173:645–647.
39. Burton MA, Gray BN, Self GW, Heggie JC, Townsend PS. Manipulation of experimental rat and rabbit tumor blood flow with angiotensin II. *Cancer Res* 1985;45:5390–5393.

EDITORIAL

Microdosimetric Considerations of Hepatic Radioembolization

Tumor therapy is constrained by the demand to limit damage to normal tissue while arresting or at least slowing the growth and spread of the tumor. Chemotherapy and radiotherapy from external sources are restricted by the harm they may impose on essential body function through detriment to normal cells either near or distant from the tumor. Localizing the therapeutic intervention (be it from a chemical or physical agent) primarily to tumor cells without affecting normal cells may be approached by at least two avenues: first, by using specific cell-recognition systems for toxic agents, either through receptors or metabolic states of tumor cells that are not shared by normal cells at the tumor site when the agent is applied (*1*) and, second, by transporting the bulk of the toxic agent to the tumor, either by implanting sources within, or delivering particle sources via the blood circulation to the tumor. Both of these avenues are within the domain of nuclear medicine; two outstanding examples are the therapeutic application of monoclonal antibodies carrying a suitable radionuclide for lethal irradiation of receptor-specific tumor cells and brachytherapy, and brachyradiotherapy on the microscopic level. Radioembolization of tumor as described by Andrews et al. in this issue of the *Journal* (*2*) is a fascinating example of the latter.

Full clinical acceptance of the approach pioneered in a number of centers, especially by Andrews et al. (*2*), requires attention to the behavior and stability of microparticles in the blood circulation, the radionuclide that is bound to them, the mode of delivery of the particles to the tumor with regard to the eventual concomitant exposure of normal tissue, and finally, to the optimization of embolization of the tumor vasculature. All efforts have the common denominator of a most favorable ratio of absorbed doses to tumor cells and normal tissue. In view of the technical difficulties and the need to address them, Andrews et al.'s paper is an exemplary, careful and innovative approach to these challenging problems.

By selecting glass microspheres with a diameter of 22 μm, which were introduced in 1987 (*3*), difficulties that arose from the premature release of the radionuclide due to the disintegration in vivo of organic polymer microspheres were overcome (*4*). Andrews et al. (*2*) solved the problem of optimal delivery of the microspheres to the site of attempted irradiation in the case of liver tumors by assessing blood flow by angiography and sulfur-colloid scintigraphy, and by blocking extrahepatic circulation from aberrant hepatic arteries by angiographic manipulations. Further increases in the ratio of microsphere deposition in tumor versus normal liver tissue could favor widespread clinical acceptance of the ^{90}Y-microsphere brachytherapy technique. Two principal kinds of modalities might be considered to enhance tumor perfusion: pharmacological and physical. The first, as mentioned by Andrews et al. (*2*), is exemplified by vasoactive drugs such as angiotensin II (*5*) and epinephrine (*6*). The second could use pre-irradiation of the tumor with 6–9 Gy from a gamma source (*7*). Localized hyperthermia may be another valuable adjuvant to radioembolization of liver tumors. A radiation sensitizer like bromodeoxyuridine has also been considered (*4*).

Having minimized the transport and trapping of microspheres outside the liver by obstructing passage into the extrahepatic circulation (e.g., into the lung) and optimizing the infusion rate, the values of absorbed doses that are eventually delivered to tumor and normal liver tissue from the ^{90}Y that was engineered to be tightly bound within the glass microspheres are of crucial importance. The heterogeneous microdistribution of particles in the circulation of the target tissue is a formidable obstacle to modeling the anticipated relation of the biological effect of radiation on the average physical absorbed dose to the tumor.

The conventional mode of express-

Received May 10, 1994; accepted June 1, 1994.
For correspondence or reprints contact: Ludwig E. Feinendegen, MD, Medical Dept., Brookhaven National Laboratory, Upton, NY 11973.

ing absorbed dose-to-tissue from incorporated radionuclides uses the MIRD concept which is based on the average energy deposited per mass of tissue (*8*). This does not adequately consider the heterogeneous microdistribution of dose from ^{90}Y in the microspheres trapped in the tumor or tissue blood vessels. A dose calculated in terms of average energy per unit tissue mass (of up to 150 Gy) was delivered to the liver (*2*) without severe impairment of liver function; this is surely far above the average organ absorbed dose of 3.5 Gy that is commonly taken as the toxicity-limiting dose from external low-LET irradiation. This large difference between the dose from radioembolization without severe hepatic impairment and the dose limit of ~3.5 Gy for liver toxicity is not explained by dose rate.

For radioembolization therapy of liver tumors, the observed tissue-sparing effect of irradiation from ^{90}Y must be put into perspective. This effect was previously investigated by Roberson et al. (*9*) and shown to be related to gross inhomogeneity of distribution of the glass microspheres in rabbit liver and liver tumors. They reported the ratio of tumor-to-normal tissue doses to vary locally by at least twofold. However, more exact information should be sought to understand tissue tolerance to irradiation from radioembolization.

Yttrium-90 is an appealing radiation source. It is a pure beta emitter with a half-time of 2.67 days and a mean energy of 930 keV. A more recent dose calculation from a planar source of ^{90}Y (*10*) indicated that 99.9% of the energy from the beta particles is absorbed within the range of about 7.4 mm from the surface of the source. At 4 mm away from the surface of the source 95% of the total dose is delivered. The mean range of dose from beta particles at the source surface (range of energy absorption to 37% of dose at surface) amounted to only 1.5 mm. Thus, each microsphere is a microsource with highly localized energy deposition. In view of the distances between capillaries in tissue and in tumor and the stochastic trapping of microspheres within the blood vessels, the delivery of dose around microspheres resembles external microbeam irradiation for which tissue-sparing effects have been reviewed (*11,12*). Therefore, even with expected destruction of cells in the radiation field of a ^{90}Y-containing microsphere, interspersed cells sufficiently far away from the microsphere may experience minimal to no damage. They are then expected to serve as seeds for initiating tissue repair, as in the case of normal vasculature as postulated for blood vessels regenerating in mouse brain following microbeam irradiation (*11*).

The validity of the calculation of range of doses absorbed around geometrically well-defined ^{90}Y sources (*10*) is measured by distance on tissue sections from ^{90}Y rod holes to junction of necrotic and viable tissue following human pituitary ablation using pituitary-implanted ^{90}Y-yttrium oxide rods (*13*). The junctions of necrotic and viable tissues were, on average, 3.48 ± 0.29 (s.d.) mm (pituitary tissue, n = 8) and 3.45 ± 0.50 (s.d.) mm (bone n = 15) from the rod surface. According to the dose range calculation cited above, about 92% of the total energy of the ^{90}Y beta particles is absorbed within 3.5 mm away from the surface of the source. Assuming correctness of dose calculation, it is interesting to note that in these experimental observations on tissue sections (*13*) there also appears to be tissue recovery at the very edge of the beta range, in that about 8% of the dose from ^{90}Y beta particles farthest away from the surface of the source is ineffective in producing tissue necrosis. This fraction of ineffective dose at the periphery of spherical or cylindrical dose distribution around the defined source may be even larger than 8% when older dose range calculations are taken into consideration. Andrews et al. report (*2*) for example, a mean tissue penetration of ^{90}Y beta particles of 2.5 mm and a maximum of about 10 mm.

Andrews et al. (*2*) have shown the potential usefulness of radioembolization therapy of hepatic tumors. It is expected that localized tumor therapy will improve further by applying the data from modes of dose calculation that diverge from the MIRD concept and are based instead on microdosimetric considerations (*14*). As stated by Andrews et al. (*2*), the in vivo assessment of tissue sites of ^{90}Y deposition (*15*) promises to be helpful in these advances provided the nature of ^{90}Y source with potential microscopic heterogeneity of distribution in tissue, is taken into account. This will require a description of the number and activity of particles, and their microscopic distribution in normal and tumor tissues. Stable nuclides of high atomic number, such as ^{187}Au, might be usefully incorporated into the particles to aid in the radiographical assessment of their distribution and concentration in tissue.

ACKNOWLEDGEMENTS

The author thanks D.N. Slatkin for review of this manuscript and Mrs. A. Ruggiero for her secretarial help.

Ludwig E. Feinendegen
Brookhaven National Laboratory
Upton, New York

REFERENCES

1. Feinendegen LE. Contributions of nuclear medicine to the therapy of malignant tumors. *J Cancer Res Clin Oncol* 1993;119:320–322.
2. Andrews JC, Walker SC, Ackermann RJ, Cotton LA, Ensminger WD, Shapiro B. Hepatic radioembolization with yttrium-90 containing glass microspheres: preliminary results and clinical follow-up. *J Nucl Med* 1994;35:1637–1644.
3. Ehrhardt GJ, Day DE. Therapeutic use of yttrium-90 microspheres. *Nucl Med Biol* 1997;14: 233–242.
4. Wollner IS, Knutzen CA, Ullrich KA, et al. Effects of hepatic arterial yttrium-90 microsphere administration alone and combined with regional bromodeoxyuridine infusion in dogs. *Cancer Res* 1987;47:3285–3295.
5. Gray BN, Burton MA, Kelleher DK, Anderson J, Klemp P. Selective internal radiation (SIR) therapy for treatment of liver metastases: measurement of response rate. *J Surg Oncol* 1989; 42:192–196.
6. Burton MA, Gray BN, Klemp PF, Kelleher DK, Hardy N. Selective internal radiation therapy distribution of radiation in the liver. *Eur J Cancer Clin Oncol* 1989;25:1487–1492.
7. Order SE, Klein JL, Leichner PK, Frincke J, Lollo C, Carlo DJ. Yttrium-90 antiferritin—a new therapeutic radiolabeled antibody. *Int J Radiat Oncol Biol Phys* 1986;12:277–281.
8. Loevinger R, Budinger TF, Watson EE. *MIRD primer for absorbed dose calculations*. New York: Society of Nuclear Medicine; 1988:128.

9. Roberson PL, Ten Haken RK, McShan DL, McKeever PE, Ensminger WD. Three-dimensional tumor dosimetry for hepatic yttrium-90-microsphere therapy. *J Nucl Med* 1992;33:735–738.
10. Lueders C, Kopeč M, Morstin K, Schmitz T, Feinendegen LE. Die Radiosynoviorthese. Anwendung und durchführung unter besonderer berücksichtigung dosimetrischer aspekte. *Akt Rheumatol* 1992;17:74–81.
11. Slatkin DN, Spanne P, Dilmanian FA, Sandborg M. Microbeam radiation therapy. *Med Phys* 1992;19:1395–1400.
12. Slatkin DN, Spanne P, Dilmanian FA, Nawrocky MM, Gebbers JO, Laissue JA. Microplanar beam radiotherapy [MRT] of malignant brain tumors in rats. *In: National synchrotron light source 1993 annual report*, BNL-52415, 1994: in press.
13. Talbot IC, Slatkin DN, Arnot RN, Doyle FH, Joplin GF. Pituitary ablation by yttrium-90 implantation: some postmortem and clinical observations. *Int J Appl Rad Isot* 1980;31:695–701.
14. International Commission on Radiation Units and Measurements. Microdosimetry. *ICRU report 36. 1983.*
15. Herzog H, Rösch R, Stöcklin G, Lueders C, Quaim GM, Feinendegen LE. Measurement of pharmacokinetics of yttrium-86 radiopharmaceuticals with PET and radiation dose calculation of analogous yttrium-90 radiotherapeutics. *J Nucl Med* 1993;34:2222–2226.