We presented this concept at the Society of Nuclear Medicine Annual Meeting in June 1996 (*2*) and published an article titled "Quantification of Left Ventricular Function with Thallium-201 and Technetium-99m-Sestamibi Myocardial Gated SPECT" (*3*). We are pleased that Germano et al.'s (*1*) article confirms our observations that were submitted earlier but delayed in publication.

Again, we are happy to learn that another research group has confirmed these results. We believe that gated SPECT with ^{201}Tl is both effective and reliable. Therefore, clinical sites that prefer ^{201}Tl for myocardial perfusion imaging can perform gated SPECT and obtain useful functional information that was once thought to be possible only with ^{99m}Tc-sestamibi.

REFERENCES

1. Germano G, Erel J, Kiat H, Kavanagh PB, Berman DS. Quantitative LVEF and qualitative regional function from gated thallium-201 perfusion SPECT. *J Nucl Med* 1997;38:749–754.
2. Maunoury C, Chen CC, Chua K, Thompson C, Holder LE. Quantification of left ventricular function with both thallium-201 and technetium-99m-sestamibi gated SPECT [Abstract]. *J Nucl Med* 1996;37:104P.
3. Maunoury C, Chen CC, Chua KB, Thompson CJ. Quantification of left ventricular function with thallium-201 and technetium-99m-sestamibi myocardial gated SPECT. *J Nucl Med* 1997;38:958–961.

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Is Technetium-99m-MIBI a Relevant Tracer to Tumor Response to Chemotherapy of Bone Lesions?

TO THE EDITOR: We do not agree with Taki et al.'s (*1*) conclusion that ^{99m}Tc-MIBI detects bone and soft-tissue lesions and assesses tumor response to chemotherapy comparable to ^{201}Tl. Technetium-99m-MIBI accumulation in tumors is modulated by blood flow, cell viability and the level of permeability glycoprotein (Pgp) expression (*2*). Technetium-99m-MIBI is a well-documented transport substrate for Pgp, which is induced by overexpression of the multidrug resistance (MDR) gene, which in turn is a major cause of chemotherapy resistance and failure (*3–5*). In MDR gene cells, a high concentration of Pgp on the cellular membrane induces a rapid excretion of ^{99m}Tc-MIBI; ^{99m}Tc-MIBI accumulation by MDR tumor cells remains low. This low ^{99m}Tc-MIBI uptake can help assess MDR gene overexpression (*6*).

Table 2 in Taki et al.'s (*1*) article clearly indicates such a possibility. Patients 10 and 12 had decreased ^{99m}Tc-MIBI tumor uptake postchemotherapy (−5% and −19% compared to prechemotherapy), which is consistent with MDR development. Uptake ratio of ^{201}Tl did not decrease (+21% and +1%), and the tumors did not respond to chemotherapy. Patients 23 and 25 seem more complex: ^{99m}Tc-MIBI uptake ratios increased after chemotherapy, although the tumors were nonresponsive (Table 2) (*1*). Thallium-201 uptake, however, decreased only moderately after chemotherapy (−18% and −3%, respectively), indicating residual tumor viability.

We conclude that the observation of ^{99m}Tc-MIBI uptake decrease after chemotherapy is consistent with either weakening of tumor viability or induction of MDR.

Technetium-99m-MIBI provides more information than ^{201}Tl in assessing tumor response to chemotherapy.

REFERENCES

1. Taki J, Sumiya H, Tsuchiya H, Tomita K, Nonomura A, Tonami N. Evaluating benign and malignant bone and soft-tissue lesions with technetium-99m-MIBI scintigraphy. *J Nucl Med* 1997;38:501–506.
2. Mariani G. Unexpected keys in cell biochemistry imaging: some lessons from technetium-99m-sestamibi. *J Nucl Med* 1996;37:536–538.
3. Piwnica-Worms D, Chiu ML, Budding M, et al. Functional imaging of multidrug-resistant P-glycoprotein with an organo-technetium complex. *Cancer Res* 1993;53: 977–984.
4. Luker GD, Fracasso PM, Dobkin J, Piwnica-Worms D. Modulation of multidrug resistance P-glycoprotein: detection with technetium-99m-sestamibi in vivo. *J Nucl Med* 1997;38:369–372.
5. Herbert M, Pinedon GG. P-glycoprotein a marker of cancer cell behavior. *N Engl J Med* 1995;333:1417–1419.
6. Moretti JL, Caglar M, Duran-Cordobes M, Morere JF. Can nuclear medicine predict response to chemotherapy? *Eur J Nucl Med* 1995;22:97–100.

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Time for a Change?

TO THE EDITOR: Perhaps those of us in nuclear medicine should consider following the example of the American College of Physicians (ACP) and the American Society of Internal Medicine (ASIM). The ASIM was founded by some internists who did not believe that ACP adequately addressed the socioeconomic issues of medical practice, in view of ACP's great interest in education.

The American College of Nuclear Physicians (ACNP) was formed because it was believed by some nuclear medicine physicians that the Society of Nuclear Medicine (SNM) did not adequately address the practice concerns of physicians, being interested primarily in research and education. There remain some areas of duplication of efforts, although many important activities have been coordinated or combined.

ACP now appears to be close to joining forces with the ASIM. The members and leadership have concluded that there is really no longer a reason to have two different organizations. They want internal medicine to speak with one voice. In a survey of the 100,000 members of ACP and the 20,000 members of the ASIM, informing them of the possibility of a merger, reaction ran about 5 to 1 in favor of the merger. It might be interesting to poll members of both groups on their opinion about the desirability of a possible merger of SNM and ACNP, a merger, not a takeover of ACNP by SNM.

Not the least of the advantages of a merger of SNM and ACNP is the beautiful and luxurious building SNM now owns in Reston, VA.

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Gene Radiotherapy; Gene Targeted Versus Targeted by Gene Product

TO THE EDITOR: The editorial by Larson et al. (*1*) describes a very interesting and promising approach for in vivo detection of the expression of a gene delivered into tumor cells. In referring to a personal communication from one of the coauthors, the writers suggest the use of this approach also to deliver higher doses of therapeutic radiation to cells expressing a "marker gene." This method, which the authors call "gene-targeted radiotherapy," if demonstrated to actually work, is potentially extremely powerful. We, however, have concerns about the terminology they used to describe their approach.

The application of the methods of molecular biology have recently become more evident in nuclear medicine. This symbiosis can be extremely productive and result in significant progress in both tumor imaging and radiotherapy. As often happens in a new field, the terminology has not been standardized and different approaches are sometimes called by the same name. For example, we also have described a type of "gene-targeted radiotherapy" in an interview and article written by Kotz (*2*).

For the last 4 years, we have been developing our approach for targeting Auger-electron emitters (AEs) to specific genes using triplex-forming oligonucleotides (TFOs) as delivery molecules. This method combines the

DNA sequence-specific action of TFOs with localized damage produced by the decay of AEs such as ^{77}Br, ^{195m}Pt, ^{193m}Pt, ^{123}I, ^{125}I and others. Synthetic oligodeoxyribonucleotides (ODNs), as tools for manipulating gene expression, have drawn a great deal of attention in recent years. After entry into a cell and binding to a target DNA sequence, TFOs are capable of altering expression of the targeted gene. The target sequence can be either RNA (antisense approach) or DNA (antigene approach). In the latter, the ODN must be able to form a triple helix (or triplex) with the targeted DNA duplex. In triplex DNA, the third strand is located in the major groove of the DNA duplex and is stabilized by Hoogsteen hydrogen bonds. In general, guanine-rich polypurine/polypyrimidine sequences form the most stable triplexes. The specificity of triplex-DNA recognition is very high and is comparable with that of complementary strands pairing in Watson-Crick duplexes.

We have shown that decay of ^{125}I incorporated into a triplex-forming oligonucleotide produces double-strand breaks (DSBs) in a target DNA sequence on triplex formation in vitro (*3-5*). The breaks occur with an efficiency close to one break per decay and are localized within five-base-pairs distance from the decay site. Due to the very short range of the damage produced by AEs, the rest of the genome DNA receives a significantly smaller dose of radiation produced by the higher energy portion of ^{125}I decay spectrum. In this respect, we also have demonstrated that decay of ^{125}I in ^{125}I-ODN located in the cell nuclei, but not forming sequence-specific triplexes with genomic DNA, is almost three orders of magnitude less radiotoxic than the decay of ^{125}I incorporated into genomic DNA (*6*). DSBs produced by the decay of AEs are known to be highly cytotoxic. Therefore, the cells containing a target sequence for triplex formation should be significantly more sensitive to the AE-labeled TFO (AE-TFO) than the cells that do not contain the target sequence. For example, if a target sequence is part of a viral genome integrated into mammalian genomic DNA on infection or appears as a result of the genomic rearrangements and/or amplifications often associated with cancers, then AE-TFO directed against such sequences specifically will kill virally infected or mutated cancer cells. Alternatively, DNA single-strand breaks produced by an AE attached to the TFO through special linkers can be used to induce gene-specific mutations (*7*). This method of "gene radiotherapy" potentially results in a "knock-out" of the targeted gene.

In several of our articles, we have called our approach "radio gene therapy" and/or "gene specific radiotherapy." We believe that such terms are more relevant to our method and should be reserved for therapeutic approaches using delivery of radiotherapy to specific genes already inside a cell nucleus rather than for radiotherapy to cells transformed so as to express a marker-gene product. The less direct approach suggested by Larson et al. (*1*) is perhaps more precisely termed "transferred-gene-product-assisted radiotherapy" or some such term. As we in nuclear medicine increasingly enter into this interface of gene manipulation and radiopharmaceutical development, we must develop our new terminology to precisely describe such approaches.

REFERENCES

1. Larson SM, Tjuvajec J, Blasberg R. Editorial: triumph over mischance: a role for nuclear medicine in gene therapy. *J Nucl Med* 1997;38:1230–1233.
2. Kotz D. Thirty years of nuclear medicine at the NIH. *J Nucl Med* 1997;38(3):13N–26N.
3. Panyutin IG, Neumann RD. Sequence-specific DNA double strand breaks induced by triplex forming ^{125}I-labeled oligonucleotides. *Nucleic Acids Res* 1994;22:4979–4982.
4. Panyutin IG, Neumann RD. Sequence-specific DNA breaks produced by triplex directed decay of iodine-125. *Acta Oncol* 1996;35:817–823.
5. Panyutin IG, Neumann RD. Radioprobing of DNA: distribution of DNA breaks produced by decay of ^{125}I incorporated into a triplex-forming oligonucleotide correlates with geometry of the triplex. *Nucleic Acids Res* 1997;25:883–887.
6. Sedelnikova OA, Thierry AR, Neumann RD, Panyutin IG. Radiotoxicity of ^{125}I-labeled oligodeoxyribonucleotides in mammalian cells. *J Nucl Med*:in press.
7. Reed MW, Panyutin IG, Hamlin D, Lucas DD, Wilbur DS. Synthesis of ^{125}I labeled oligonucleotides from tributylstannylbenzamide conjugates. *Bioconj Chem* 1997;8: 238–243.

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Functional Brain Imaging

TO THE EDITOR: As an observer who is impressed with the work of the Basel research group with the cerebrovascular aspects of whiplash injury, I was concerned to note an illogicality in the information, which is presented in this letter.

The Basel researchers have previously reported that 77% of patients with late whiplash syndrome either with or without mild head injury could be separated from normal controls (*1*). Data were read by two independent readers blinded to the clinical diagnosis. In the latest study (*2*), the researchers claim that 100% of patients were affected. One has to wonder, why has the latest study proved more definitive? Have the independent readers become more discerning, or has the selection of subjects for investigation been changed?

I think the failure of the researchers to reconcile the results in this account with those of their previous publications is a pity. What they have discovered is quite momentous in medical history. For example, their research questions whether senile dementia could be the long-term outcome of an earlier whiplash injury. This is so important to humanity that any confusion about the legitimacy of their results might do immense harm.

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REFERENCES

1. Otte A, Ettlin ThM, Fierz L, et al. Brain perfusion patterns in 136 patients with chronic symptoms after distortion of the cervical spine using single photon emission computed tomography, technetium-99m-HMPAO and technetium-99m-ECD: a controlled study. *J Vasc Invest* 1997;3:1–5.
2. Otte, A, Mueller-Brand J, Nitzsche EU, et al. Functional brain imaging in 200 patients after whiplash injury [Letter]. *J. Nucl Med* 1997;38:1002.

REPLY: We are indebted to Dr. Gorman for pointing out an element of confusion in our recent letter to the editor (*1*). It is true that we have previously reported that 77% of 136 patients with chronic symptoms after distortion of the cervical spine with or without clinical evidence of brain injury could be separated from normal controls qualitatively by two independent readers blinded to the clinical diagnosis (*2*). This study was performed by using SPECT, ^{99m}Tc-HMPAO and ^{99m}Tc-bicisate (ECD).

It is incorrect that in the present study we claimed that 100% of patients were affected (*1*). In the study, only group-to-group differences in the perfusion (PI) and glucose metabolic indices (GMI) were presented by the p values using the Mann-Whitney U-test; neither data on qualitative image analysis nor data on specificity and sensitivity as in Otte et al. (*2*) were given. In this context, although different than the qualitative separation of patients from controls in Otte et al. (*2*), it is easy to show that even a p value of $p < 0.0001$ does not mean that 100% of patients have GMI or PI values > 2 s.d. below normal controls: It could be that only 50% have values > 2 s.d. below normal controls if the remaining 50% present with > 1 s.d. below the controls.

The additional qualitative image analysis of the 200 patients—data not given in Otte et al. (*1*)—revealed approximately 75% of patients who were affected either in the SPECT or in the PET scan, so that, overall, the recent study (*1*) proves no more definitive. In contrast, it is the first one to verify the perfusion SPECT findings of whiplash patients by glucose metabolism PET. Further studies with FDG PET and statistical parametric mapping using the method by Friston et al. (*3*) have confirmed the findings in the posterior parietal occipital region in our whiplash patient group. Of interest