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.

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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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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