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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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

hereby especially, the hypometabolism in this region did not correlate with the cortex area in the MR scan.

Another point raised by Dr. Gorman is the question whether whiplash injury could "trigger" Alzheimer's disease-like pathology. Up to now this was only speculation. Nevertheless, there is increasing evidence of a link between head injury and the subsequent onset of Alzheimer's disease. Deposits of amyloid beta-proteins are found not only in cases of dementia pugilistica but in some patients dying after a single episode of severe head injury (*4*). A tenfold increase in the risk of Alzheimer's disease was associated with both apolipoprotein E epsilon 4 and a history of traumatic head injury, compared to a twofold increase in risk with apolipoprotein E epsilon 4 alone, whereas head injury in the absence of an apolipoprotein E epsilon 4 allele did not increase risk (*5*).

Because of head restraints, whiplash trauma today also produces a head impact that can lead to direct brain damage. However, the question whether senile dementia could be the long-term outcome of an earlier whiplash injury remains open.

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Technetium-99m-HMPAO Brain SPECT in Systemic Lupus Erythematosus with Central Nervous System Involvement

TO THE EDITOR: We read with great interest the article by Lin et al. (*1*) about brain SPECT in systemic lupus erythematosus. After working for the past 2 years on a similar group of patients, we formed conclusions similar in some aspects, but different in others, which may be the result of a different methodological approach. We previously reported a part of our observations (*2,3*); the rest of this material is in preparation to be published.

We performed brain SPECT using a triple-head gamma camera, MRI and anticardiolipin antibody (ACA) assays in 66 systemic lupus erythematosus, 14 Sjögren's syndrome, 12 diffuse scleroderma and 4 mixed collagenosis patients. In most, an acetazolamide stress test was performed 3 days later. SPECT results were compared with a group of 25 healthy volunteers. Brain SPECT was abnormal in 91% of systemic lupus erythematosus patients, with MRI abnormal in only 26%. Until that point, our observations are in agreement with those of Lin et al. (*1*). In our opinion, however, although visual interpretation may sometimes be superior to semiquantitative, some subtle changes may be overlooked in visual analysis, especially regarding intrahemispherical asymmetries. We found diffuse hypoperfusion of both frontal lobes when compared to HMPAO cerebellar uptake and healthy control subject indices in 30% of systemic lupus erythematosus, 50% of Sjögren's syndrome and none of diffuse scleroderma patients. This correlated well with cognitive impairment assessed by psychometric tests.

Also, analysis of interhemispherical asymmetries revealed significant problems, which are underlined by the authors. We believe that the subtle changes seen on images of systemic lupus erythematosus parients require comparison to physiological asymmetries of a healthy volunteer database and visual interpretation is not sufficient. As in systemic lupus erythematosus, at least in our patient group, diffuse HMPAO uptake defects are more frequent than focal ones and comparison with healthy control subject results seem to be particularly important, especially in analyzing basal ganglia HMPAO uptake, where, even in healthy subjects standard deviation of interhemispherical HMPAO may be high (s.d. = 8.7% in our material). Therefore, basal ganglia SPECT results should be interpreted with caution. Another problem is ACA assay results. The authors did not find correlation with clinical findings. How did the correlation with SPECT images look? This is important because thrombo-embolic brain infarcts are more frequent in ACA patients (*4*). This was consistent with our SPECT findings, where 9 of 12 patients with ACA had multiple focal HMPAO uptake defects (more than five per patient) resembling multi-infarct dementia.

Last, but not least, there is the problem of future guidelines in systemic lupus erythematosus brain research. What is the appreciable in Lin et al.'s (*1*) article is the size of the patient groups, subdivision to different pathological groups and insight into basal ganglia. The other interesting points seem to be cerebrovascular reactivity in systemic lupus erythematosus, reversibility of cerebral blood flow (CBF) changes and comparison with other connective tissue diseases. Lin et al. (*1*) describe improvement in brain perfusion in a patient after methylprednisolone therapy. During control scanning after steroid therapy, we found brain perfusion improvement in 12 of 20 patients, no change in 6 and new hypoperfused areas in 2. Of 6 ACA-positive patients, none showed improvement. Another crucial point might be reactivity to acetazolamide-induced hypercapnia, as carbon dioxide is the most important physiological regulator of regional CBF redistribution. We found it altered (no change or paradoxical HMPAO uptake improvement in 48% of patients). In comparing systemic lupus erythematosus with the other connective tissue diseases, we found a pattern similar to systemic lupus erythematosus in mixed collagenosis, multifocal-defect pattern but not hypofrontality in Sjögren's syndrome and little or no CBF changes in diffuse scleroderma. This may be related to different pathological mechanisms.

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REPLY: We thank Dr. Lass et al. for their comments and agree that comparison with a normal database of ^{99m}Tc-HMPAO brain SPECT may be the best way to diagnose central nervous system (CNS) involvement in systemic lupus erythematosus patients. Establishment of a normal database, however, is an enormous task. Dr. Lass collected 25 healthy volunteers, but this may not be enough. Dividing the normal control subjects into different age groups is necessary since age may affect the regional blood flow in the brain tissue (*1,2*). In addition, the use of steroids