Radiation Injury from Interstitial Injection of Iodine-131-Iodocholesterol

TO THE EDITOR: A 44-yr-old man was investigated for recurrent Cushing's disease. An adrenal gland scan was initiated with injection of 34-MBq of ^{131}I-iodocholesterol over a 5-min interval. Prior to injection, blood was withdrawn into the hub of the syringe to ensure correct i.v. placement. At the conclusion of the injection, the patient volunteered that the injection had been the least painful i.v. entry he had experienced. Seven days later, imaging failed to detect any radioactivity in the field of view centered on the adrenal glands. Monitoring of the injection site demonstrated essentially complete retention of the radiopharmaceutical at the site.

The patient returned 13 days later (i.e., 20 days after the injection) to inquire about the tender pruritic and erythematous patch at the injection site at which time the photograph in Figure 1 was taken. At the injection site, he had an erythematous patch measuring approximately 2 cm × 1 cm. Monitoring of the site demonstrated retention of ^{131}I (Fig. 2). On the basis of serial counts, the half-time was 5.5 days at the i.v. injection site.

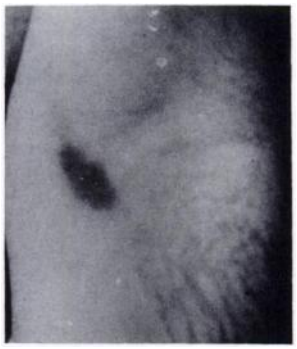

FIGURE 1
Radiation burn evident by inspection 20 days after injection.

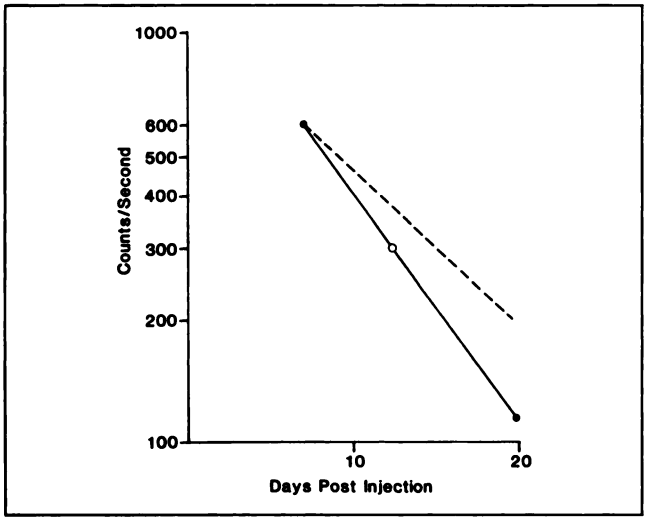

FIGURE 2. Retention of ^{131}I-iodocholesterol at the site of interstitial injection. The solid points (.) represent measurement of radioactivity over the site. The open circle (O) represents one half-time from the first measurement. The dotted line represents the decay of ^{131}I.

The absorbed dose delivered to the overlying skin cannot be precisely calculated because it has a very strong inverse dependence on the interstitial volume occupied by the injectate, and this volume is not accurately known. The absorbed dose can be estimated by treating the interstitial volume occupied by the injectate as a disk of the same area as the erythematous patch; the thickness of this volume can be roughly estimated. The volume of distribution was assumed to remain constant over time since the injectate is not water-soluble. The absorbed dose in this volume can be calculated by the method of Johns and Cunningham (*1*). Because the model assumes no activity outside the volume, the absorbed dose in the region adjacent to this volume within the range of the beta particles (i.e., the skin) can be estimated to be half the dose inside the volume. Using interstitial volumes with thicknesses of 0.5 cm and 1 cm, the dose to the skin was calculated as 490 Gy and 245 Gy, respectively. However, the most sensitive cells of the deepest dermal layer will not have been uniformly within the range of the beta particles. Only the deepest cells in the rete pegs will have been irradiated to the dose calculated from the model. The result of this microscopic scale inhomogeneity will be to decrease the average skin dose by an indeterminate factor.

This experience demonstrates a nonstochastic radiation injury from a diagnostic dose of ^{131}I-iodocholesterol. Moreover, the importance of administering a totally i.v. injection of this water-insoluble radiopharmaceutical is emphasized.

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Cardiac Clinical Utility of Fluorinated Deoxyglucose

TO THE EDITOR: The position of The Society of Nuclear Medicine (SNM) and of the American College of Nuclear Physicians (ACNP) on PET-FDG cardiac studies was recently reviewed in *JNM* by Alazraki (*1*).

The issue as discussed by Dr. Alazraki is whether FDG has efficacy for detecting coronary artery disease and for determining myocardial viability. Incidentally, there must have been a communication problem with this assertion since perfusion tracers, not FDG, are the ones used for detection of coronary stenoses.

The issue of the efficacy of FDG to determine myocardial viability is complex and is far from resolved. From this standpoint alone, the positions of the SNM and of the ACNP need revision.

The bases for the recommendation of using FDG to determine myocardial viability are summarized in a recent review (*2*). FDG is assumed to measure glucose metabolism. It has been postulated that in patients with chronic coronary artery disease, many of whom have myocardial infarction, PET-FDG identifies myocardial regions with low perfusion, severe contractile dysfunction but maintained or (relative to perfusion) increased uptake of FDG. The perfusion-FDG uncoupling has been designated as a mismatch. The mismatch is said to indicate PET viability and it is believed that viable tissue so defined improves after coronary artery bypass (CABG). Pathologically, the mismatch is thought to represent chronic myocardial ischemia or myocardial hibernation.

FDG measures cardiac glucose transport and phosphorylation (*3*). It has not been established that FDG provides quantitation for myocardial oxidation, glycolysis, or glycogen synthesis or degradation.

The amount of FDG taken up by the heart does not reflect the actual amount of substrate oxidized to generate ATP (*4*). When glucose is given to humans to induce a hyperglycemic-hyperinsulinemic physiology, over 57% of the extracted glucose is probably stored as glycogen (*5*). How FDG traces the underlying biochemistry of the heart in health and disease is not known.

The necessary condition of rest hypoperfusion for PET viability creates all sorts of difficulties. This would represent ischemia at rest (*6*), since there is concomitant contractile failure and compensating FDG uptake. As Gould asserts (*7*), reduction of resting myocardial perfusion occurs only with very severe stenoses and these lesions are unstable with frequent occlusion and thrombosis. Most coronary artery stenoses either occlude or have normal resting flow but reduced flow reserve. The latter is uncovered by stress/radionuclide scintigraphy and has very good probability to respond to surgery.

Most of the ventricular function data which was correlated with PET viability was obtained by conventional analyses of endocardial wall motion. Many areas were considered to be akinetic. However, magnetic resonance imaging studies would be needed to interpret the PET data, since necrotic areas with hypoperfusion could be predicted to have substantial impairment of wall thickening. This approach has been recently implemented at the National Heart Institute.

Lear (*8*) has discussed the possibility that because of PET resolution limitations noninfarcted myocardium may be overestimated with FDG, rather than being underestimated by ^{201}Tl.

Chronic myocardial ischemia is a histologic nonentity. Myocardial hibernation is a concept originally proposed by Rahimtoola (*9*). It has been recently reexamined (*10*) and there are serious doubts about the existence of such a state.

FDG imaging for myocardial viability is said to be better than ^{201}Tl perfusion imaging. However, this claim is based on studies of only 75 patients in the world's literature as discussed elsewhere (*7,11*). Although the attraction of FDG-PET is the prediction of myocardium that could be successfully improved by CABG or angioplasty, this is only part of the matter since success depends heavily on the mass of jeopardized myocardium that is revascularized in patients with chronic left ventricular dysfunction (*12*). Such information is not available in the clinic. Likewise from data such as those from the CASS study (*13*) or from postangioplasty data (*14*), it would appear that in these patients inducible ischemia or unstable angina, rather than resting ischemia, predicts good postintervention outcome.

The issue of the robustness of FDG to determine myocardial viability has been further confounded by the availability of the thallium reinjection technique. A recent study indicates that the FDG-blood flow mismatch on PET imaging identifies viability in mild ^{201}Tl defects (in which the level of ^{201}Tl itself is evidence of viability) but is less useful in identifying viable myocardium within severe fixed ^{201}Tl defects on redistribution studies. In the latter fixed defects, FDG uptake is moderately or severely reduced and the increase or lack of increase in ^{201}Tl activity after reinjection defines regions according to the presence or absence of FDG uptake by PET (*12*).

Our study (*15*) and those of Gould et al. (*16*) and Yaoita et al. (*17*) indicate that it is not uncommon to detect increased FDG uptake within regions with acute myocardial infarction. This would preclude the usefulness of this tracer in the assessment of patients with acute heart infarcts with spontaneous or pharmacologic thrombolysis.

From the foregoing discussion, it is quite obvious that the FDG-PET viability data has not been universally supported by results in other investigations and that there is a great deal of internal inconsistency in the FDG cardiac hypotheses. We agree with Gropler and Bergmann (*11*) that the available data does not permit consideration of FDG as the gold standard for myocardial viability in lieu of serial measurements of contractile function. In fact, viable myocardium can be identified by ^{201}Tl imaging (*12*) or by echocardiography during dobutamine infusion (*18*).

The SNM and the ACNP are well advised to wait until the FDA determines whether FDG is useful for the determination of cardiac viability and estimates the incremental gain of FDG imaging relative to perfusion scintigraphy.

Note Added in Proof: Reference 15 now accepted for publication is: Sebree L, Bianco JA, Subramanian R, et al. Discordance between accumulation of C-14-deoxglucose and T1-201 in reperfused myocardium. *J Mol Cell Cardiol* 1991;23:in press.

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REPLY: It is gratifying to learn that Lines From the President is read by the membership and even generates letters to the editor. Unfortunately, I think that Dr. Bianco did not understand the discussion in Lines From the President (*J Nucl Med* 1990;31:26A, 30A) concerning regulation of cyclotron-produced radionuclides. The issue was not "whether FDG has efficacy for detecting coronary artery disease for determining myocardial viability," as stated in Dr. Bianco's letter. My discussion dealt with politics, not science. The issue was *whether FDA has legitimate authority to regulate cyclotron radiopharmaceuticals produced in a clinical facility for patient use in that institution*, or whether the regulatory authority rests with the states under laws governing the practices of medicine and pharmacy. The Society of Nuclear Medicine and the American College of Nuclear physicians believe that *the regulatory authority for cyclotron radiopharmaceuticals produced in the same institution where they are to be used legitimately belongs with the states, not the FDA.* In fact, PET/cyclotron practice currently is governed under the rules of practices of pharmacy and medicine as there is no FDA NDA for [^{18}F]FDG, ^{13}N-ammonia, or any other cyclotron-produced nuclides used in patients. Only commercial firms, which wish in future to be involved in commercial distribution of these radiopharmaceuticals, legitimately fall under FDA regulation and must deal with NDA products.

Naomi Alazraki
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Stability of 6-[^{18}F]Fluorodopa Preparations

TO THE EDITOR: We wish to comment upon the issue of the stability of 6-[^{18}F]fluoro-L-dopa, with special reference to the compound as produced at the National Institutes of Health (NIH).

In a paper presented in this *Journal*, Chen et al. (*1*) investigated the stability of the 6-[^{18}F]fluorodopa produced at the NIH. The authors prepared a diluted solution of the radiopharmaceutical formulation in saline (1:100) and analyzed this solution for chemical decomposition by high-performance liquid chromatography (HPLC) with electrochemical detection. They found that 6-[^{18}F]fluorodopa in this dilute saline solution, or diluted in 1% acetic acid, decreases in chemical purity by 20% after 1 hr and by 50% after 4 hr when stored in light at room temperature. These nonenzymatic oxidation mechanisms resulted in at least two new mass peaks as determined by electrochemical detection. The addition of EDTA (0.15%) to the formulation prevented these nonenzymatic oxidation mechanisms.

We wish to report that the quality control and stability studies conducted in the Cyclotron/Radiochemistry Section of NIH on several batches of 6-[^{18}F]fluorodopa indicate no decrease in chemical or radiochemical purity up to 4 hr from the end of synthesis. No color change or precipitate was noted in the vial containing the original pharmaceutical formulation when stored in an amber vial at room temperature for up to 4 hr. Thus, we are in concurrence with Pike et al. (*2*), who report that their preparations of 6-[^{18}F]fluorodopa maintain radiochemical purity for at least 1 hr without the need for added stabilizers. Our method was analysis of a 10-μl aliquot of the final radiopharmaceutical formulation by HPLC, without dilution, using a high speed C-18 analytical column with gradient elution, mass detection by UV (220 nm), and radioactivity detection (NaI) (*3*).

We think the discrepancy between the results reported by Chen et al. and ours is due to the method of handling the sample. Chen et al. reported in their experimental section that the evaluated samples were prepared by taking 10 μl of the end product and diluting 1:100 with 0.1 N $HClO_4$. One hundred microliters of this dilution were injected onto the HPLC system. Furthermore, the sample used for the long-term stability studies was a 1:100 dilution in saline, which was periodically injected onto the HPLC system. This long-term stability study was reported to show a 20% decrease in purity after 1 hr exposure to light at room temperature. Presumably, the increase in the percent impurities found in the Chen et al. analysis is a direct result of the dilution of the 6-[^{18}F]fluorodopa relative to the amount of dissolved oxygen. In our analyses, we do not dilute the formulation, but use it directly.

We conclude that our 6-[^{18}F]fluorodopa remains stable for up to 4 hr without the addition of Na_2EDTA or any other preservative when the formulation is stored in an amber vial at room temperature and the pH of the final formulation is between 6 and 7.

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REPLY: With the safety of patients and good production practices of radiopharmaceuticals in mind, both Chen et al. (*1*) and