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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.

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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

Pike et al. (2) have incorporated preparative separation and independent quality control procedures for 6-[^{18}F]fluoro-L-DOPA PET imaging ligand. After dispensing the purified 6-[^{18}F]fluoro-L-DOPA end product in "saline for injection USP" (i.e., diluted 1 to 10 for preclinical PET studies in monkeys or 1 to 100 for other in vivo and in vitro studies using small experimental animals), Chen et al. (1) have independently confirmed the quality control of end product performed by Dr. R. D. Finn and Mr. H. Richard Adams in the NIH Cyclotron Center. Moreover, this quality control data was the first to demonstrate that nonenzymatic auto-oxidation and polymerization may play a major role in causing the destruction of 6-[^{18}F]fluoro-L-DOPA (1) and 6-[^{3}H]fluoro-DL-DOPA (3) after dispensing the end product in "saline for injection USP." Several nonenzymatic metabolite peaks of 6-[^{18}F]fluoro-L-DOPA (1) were still emitting gamma radiation (unpublished results).

The results of our quality control study (1) further suggest that, similar to but not identical to their non-fluorinated congeners (4,5), both fluoro-DOPAs and fluoro-dopamines in saline may thus be auto-oxidized to reactive quinones and then polymerized to dopachrome. Additionally, our unpublished observations indicate that hydroxyl free radicals could be generated if dopamine and L-DOPA preparations are exposed to light, oxygen, and/or transition metal ions (Cu^{2+} and Fe^{2+}). It is generally believed that UV and gamma ray irradiation also promote free radical generation (i.e., OH). In fact, 6-hydoxydopa, the hydroxyl radical adduct of L-DOPA has been identified during independent quality control of 6-[^{18}F]fluoro-L-DOPA preparations by Pike et al. (2) of the MRC Cyclotron Unit.

Actual mechanisms underlying the generation of 6-hydroxydopa are still unclear (2). Hydroxyl radicals might be formed either during the irradiation of starting solutions containing L-DOPA derivatives or during the auto-oxidation of fluoro-DOPAs in the presence of tracer amounts of oxygen and/or transition metal ions. The addition of EDTA prevents auto-oxidation of 6-[^{18}F]fluoro-L-DOPA end product in saline for injection (2). A similar protective effect of EDTA on the generation of hydroxyl radicals during the radiopharmaceutical synthesis of ^{18}F-labeled fluoro-DOPA or fluoro-dopamine remains to be demonstrated.

Dunn et al. (6) described a "rapid" separation method for 6-[^{18}F]fluoro-dopamine without providing any quality control information on their intravenous radiopharmaceutical products. In their letter to the editor, however, they claimed no decrease in chemical or radiochemical purity up to 4 hr after the synthesis of 6-[^{18}F]fluoro-L-DOPA preparations. Without the chance to review the results of their new observation, we wonder where the decomposed ^{18}F-labeled fluoro-DOPA products are in their "rapid" HPLC chromatogram. We speculate that these auto-oxidized and/or decayed metabolites of fluoro-DOPA and fluoro-dopamine cannot be separated by their "rapid" HPLC separation and measured by UV detection at "220 nm" (6). Absorbance at a wavelength of 220 nm is nonspecific and thus less suitable than 280 nm UV absorbance wavelength used in the quality control of 6-[^{18}F]fluoro-dopa (2). We have detected several oxidized peaks in unprotected and saline-diluted 6-[^{18}F]-L-DOPA (1) but not in acid-diluted fluoro-DOPA or fluoro-dopamine standard (7) by using high-resolution HPLC and electrochemical amperometric detection, which is at least 500 times more sensitive than UV detection. Finally, we did not dilute our sample in 0.1 N $HClO_4$ for these auto-oxidation experiments (Figs. 5 and 6). The HPLC injector was flushed with 0.1 N $HClO_4$ after injecting 6-[^{18}F]fluoro-DOPA in saline. It appears that Drs. Dunn and Kiesewetter have misinterpreted the procedures and conclusions stated in our quality control paper. They may have missed completely the critical issues of auto-oxidation, annihilation, and oxygen radical generation in radiopharmaceuticals associated especially with PET ligands of high-specific activity.

In conclusion, fluoro-DOPA appears to be as sensitive as L-DOPA to nonenzymatic auto-oxidation reactions (Table 1) caused by oxygen, light, temperature, transition metal ions, and/or "radiation." The addition of EDTA as a preservative may be beneficial if the PET ligand is intended to be used 1–2 hr after the end of synthesis. Thus, it is recommended that the 6-[^{18}F]fluoro-L-DOPA end product be stored in a cool, dark container for immediate use in PET scanning (1). We agree with Pike et al. (2) that "the issues and problems that are raised in implementing good production practice are not always easily or immediately resolved, and deserve wider discussion by chemists involved in producing radiopharmaceuticals for PET." These current independent quality control procedures (1,2) indeed identify hydroxyl radical adduct of L-DOPA and auto-oxidation/annihilation byproducts of the 6-[^{18}F]fluoro-L-DOPA PET ligand.

TABLE 1
Nonenzymatic 6-[^{18}F]fluoro-L-DOPA Auto-oxidation: The Working Hypothesis

1. Positron annihilation:
   $6\text{-}[^{18}F]\text{-DOPA} \rightarrow 6\text{-}[^{18}O]\text{-DOPA} + \beta^+ \rightarrow 6\text{-OH-DOPA}$ (?)
2. Auto-oxidation:
   $6\text{-}[^{18}F]\text{-DOPA} + O_2 + Fe^{2+} \rightarrow O_2^{\cdot -} + H_2O_2 + {}^{\cdot}OH + Fe^{3+}$ semiquinone, quinone, zwitter ions, & dopachrome
3. Hydroxyl radical adduct:
   $O_2 \rightarrow O_2^{\cdot -} \rightarrow H_2O_2 \rightarrow {}^{\cdot}OH + \text{DOPA} \rightarrow 6\text{-OH-DOPA}$ in the presence of Radiation, UV, Cu^{2+}/Fe^{2+}
4. Anodic oxidation:
   $6\text{-}[^{18}F]\text{-DOPA} \rightarrow {}^{18}F^- + 2e^- +$ dopachrome

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