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REPLY: My response to the concerns raised by Dr. Bianco are as follows.

1. Our study (*1*) compared FDG with fatty acid uptake in infarcted areas. Additional information concerning ^{201}Tl reinjection would certainly be of interest. In this study, we were limited to the injection of three radioactive tracers. Thallium-201 reinjection would have increased considerably the radiation dose received by the patients.
2. We are in agreement with Dr. Bianco that the comparison between wall motion obtained from ventriculography and scintigraphy by PET and SPECT has its limitations. Nevertheless, it is currently a widely accepted and available method.
3. Because of the above-mentioned difficulty of comparing functional and scintigraphic data, a division of the heart into quadrants was chosen for the comparison of wall motion and scintigraphic data, whereas for the comparison of various scintigraphic data, smaller segments (41 segments per heart) were used. The finding of disparate results by Dr. Bianco was the result of misreading. As we state in the second sentence in the Results section: "Of a total of 128 analyzed quadrants 43 (34%) exhibited ^{201}Tl defects in the redistribution tomogram. Out of these, 23 (53%) had low FDG and oPPA uptake, 13 (30%) normal FDG and oPPA uptake, 1 (2%) low FDG but normal oPPA, and 6 (14%) normal FDG but low oPPA uptake." This means that 19/43 (44%) quadrants with a defect in the ^{201}Tl redistribution tomogram exhibited normal FDG uptake. This is in agreement with 39% in the case of myocardial segments.
4. The negative correlation between free-fatty acid concentration in plasma and myocardial glucose uptake (*2,3*) is well known. The aim of the study was to evaluate the merit of scintigraphy using the iodinated fatty acid derivative oPPA against that using FDG under the metabolic condition that is technically best suited for each scintigraphic procedure. This was done by fasting in the fatty acid studies and by elevating the insulin level (by glucose load) in the FDG studies. Obviously, insulin is the major determinant of FDG uptake. The positive correlation between oPPA and FDG uptake in ^{201}Tl redistribution defects under these metabolic conditions is moderate, but significant.
5. The paper of Liedtke et al. (*4*) referred to by Dr. Bianco reports an increase of palmitate oxidation after relatively mild ischemia (60% flow reduction during 45 min) followed by 1 hr of reperfusion. Fatty acid uptake was not determined in this study. It is improbable that this experimental model characterizes the metabolic situation in patients who have had a myocardial infarction more than 4 wk prior to the study. Furthermore, oPPA traces mainly fatty acid uptake and only a minor proportion undergoes β-oxidation (*5*). Schwaiger et al. (*6*) reported that in the fasting state about one-third of the glucose extracted by the myocardium immediately enters the glycolytic pathway under control conditions. After a 3-hr occlusion and 24-hr reperfusion, the extraction of glucose increased, whereas that of nonesterified fatty acids decreased. About two-thirds of the glucose, which is extracted by the myocardium under this condition, immediately enters the glycolytic pathway. Additional studies using ^{11}C-palmitate also showed a depressed fatty acid uptake to various extents during reperfusion (*7,8*).

In general, the suitability of a tracer as a marker of myocardial viability probably depends on more complex factors, not primarily whether the substrate is the preferential one for reperfused areas. In comparison to the regional myocardial uptake of FDG, the uptake of fatty acids is, for example, much more dependent on myocardial blood flow due to the lower extraction fraction of FDG.

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Development of New Radiopharmaceuticals

TO THE EDITOR: This letter is addressed to all my colleagues in the field of nuclear medicine for their consideration and contemplation.

I have been directly involved in the commercial development of new radiopharmaceuticals for 25 years. I have lived through the transition from virtual freedom in the practice of nuclear medicine to the current restrictive environment. I now want to share with you some of my experiences, insights and perspectives.

The current regulations and restrictions imposed on the practice of nuclear medicine significantly impede growth. However, regulatory agencies are not the greatest impediment to the growth

of the practice of nuclear medicine. As Tip Taylor pointed out at the Vail High Country Meeting, there is a hierarchy of issues. From a commercial perspective, the regulatory agencies cause tactical and operational issues which raise the cost of doing business. As Tip stated, one must go to the highest level in the hierarchy (e.g., the strategic level) to identify and examine those issues that have the greatest impact in order to really understand any issue/problem

For an industry to be successful, the following three parties must be satisfied:

1. The customer: translated, the patient must benefit from the nuclear medicine procedure.
2. The retailer: translated, the practitioner of nuclear medicine must be compensated in accordance with his/her training, skills and risks.
3. The investor: translated, the company or parent organization should receive a return on his investment which is greater than investing his money in a one-year certificate of deposit (Why endure the hassle of a business if there is not a greater return?)

Growth of an industry occurs when all three parties are satisfied. I can tell you from first hand experience that the investors of the major radiopharmaceutical manufacturers are not satisfied. They have not had a reasonable, or even positive, return on their investment for many years.

The following example provides insight on how an investor thinks. Early in 1989, we were presenting the company's strategic five-year plan to an investor of our company. During the presentation, we were asked how much money an average dose generates. Dividing the annual industrial radiopharmaceutical sales (about 140 million in 1988) by the number of nuclear medicine procedures (about 7 million in 1988) yields $20. We were then asked how much the nonionic and MRI contrast agents yield? Answer: greater than $100 per patient procedure. Since drug development costs (from R&D to NDA approval), capital investment, and costs associated with production (plant costs, depreciation, compliance to regulations) are approximately the same for all these agents, we were asked why radiopharmaceuticals do not receive similar pricing. Our response was that there is a very strong tendency in the nuclear medicine community to "fight down" any price that may be charged for a radiopharmaceutical, even for those that have been around for a decade. The investor responded that based on his experience with prescribers of therapeutic drugs the other disciplines of medicine normally accept prices with only an occasional isolated comment. He did state that he felt that the "retailer" (the physician) wasn't always happy about the cost of drugs, but he (the investor) was often told that the "reluctant acceptance" was done with the knowledge that if a company recovers its costs and obtains a reasonable return on its investment, the company would reinvest into future R&D for new products (the real life blood of any industry). Without new products, the future of any industry is dim. In reality, a purchase of a product that permits a profit is an investment into the future.

During this meeting, we also reviewed projected sales for each product. The $^{99}Mo/^{99m}Tc$ generator sales/income figures popped-out as a loss leader: we could not project a profit for this item for the foreseeable future. We were then asked what would happen if we doubled the price of the generator. Our response was that there would be a deafening outcry from virtually every customer, who would show a strong intolerance to the attempt. Then we were asked how much it would raise the cost of doing a liver scan: answer, less than one dollar. An eerie silence fell over the room. Less than 9 months later I closed down the R&D facility at Emeryville. To say the least, this was one very dissatisfied and disenchanted investor.

If we look back in time, there were many dissatisified investors in the radiopharmaceutical industry: Abbott, Neisler, Cambridge, Bio-Nuclear, Iso-Med, Diagnostic Isotopes, Cintichem, NEN, P&G, 3M, and MPI, to name a few. In all cases except one, NEN, the radiopharmaceutical R&D of each of these companies was closed down, which reduced commercial domestic R&D efforts for developing new radiopharmaceuticals.

From a strategic viewpoint then, the regulatory agencies are not the greatest impediment to the growth of nuclear medicine. *The greatest impediment to the growth of nuclear medicine procedures is the inability for radiopharmaceutical manufacturers to make an equitable return on their investment.* I ask you, the practitioners of nuclear medicine, to examine your motives the next time you buy a product, haggle about the price, and/or make statements at a public forum demanding that the price of a radiopharmaceutical be reduced at least two-fold. Are you investing into the future or are you risking the lifeblood of your specialty?

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