Evaluating Penile Blood Flow During Tumescence

TO THE EDITOR: The article by Miraldi et al. (*1*) presents a valuable model and sample data for evaluating penile blood flow during tumescence. There are, however, several points that require clarification.

First, in the results section, the authors state that for normal subjects, " . . . the abrupt change in slope of the washout curve signals a decrease in venous flow as can be seen in Figure 4." We have experience using ^{99m}Tc and ^{133}Xe simultaneously with impotent patients (*2*). In our study, the xenon washout curve of volunteers was bioexponential; it showed a sharp initial decline and then gentle decline after papaverine injection. There was no significant difference between normal volunteers and venogenic patients in the initial sharp decline. However, the second phase of the xenon washout curve following papaverine injection was different in venogenic patients. Thus, we developed the xenon penogram index that depends on the second phase of the xenon washout curve. It has been shown (*3*) that venous outflow increases because of increased arterial inflow in the early period of erection. The article indicates that venous outflow decreases immediately following papaverine injection, contrary to the physiologic findings. Several possible explanations are suggested, none of which can suitably account for the immediate decrease in the observed xenon washout rate. It seems further analysis is required.

Second, the number of patients in the reported study experiencing arterial insufficiency is unclear. Figure 5A shows this number to be five, 5B indicates four, and the Materials and Methods section states that there are three patients with "severe arterial insufficiency."

Lastly, our data (*2*) and that of Haden et al. (*4*) indicate that in some patients the xenon curve is nearly flat prior to papaverine administration. The case shown by the authors (Fig. 3A) demonstrates considerable xenon washout occurring before papaverine. Is this the case for all the patient groups, and what was the degree of variation in the xenon washout rates before papaverine?

REFERENCES

1. Miraldi F, Nelson D, Jones WT, Thompson S, Kursh ED. A dual-radioisotope technique for evaluation of penile blood flow during tumescence. *J Nucl Med* 1992;33:41–46.
2. Esen A, Kitapci M, Erbas B, Bekdik C, Remzi D. Dual radioisotopic study: a technique for the evaluation of vasculogenic impotence. *J Urol* 1992;147:42–46.
3. Tanagho EA, Lue TF, McClure RD. *Contemporary management of impotence and infertility*. Baltimore: Williams and Wilkins; 1988.
4. Haden HT, Katz PG, Mulligan T, Zasler ND. Penile blood flow by xenon-133 washout. *J Nucl Med* 1989;30:1032–1035.

Mehmet T. Kitapci
Medical College of Wisconsin
Milwaukee, Wisconsin

REPLY: Dr. Kitapci is correct in noting that the venous outflow increases after papaverine injection because of increased arterial flow. This is well shown in Figure 4 of our paper. The concern appears to be the small dip with a very fast recovery in venous flow which occurs immediately after the papaverine. As explained in the paper, this decrease in the calculated venous flow results from the abrupt change in the washout curve of the xenon. We noted in our paper that there were several possible explanations for this positive upslope that related to technique and not physiology or analysis. (See Item 1 under Results) We have now determined that the observed upslope in the washout curve is an artifact caused by partial shielding of the base of the penis, which is one of the explanations given. By repositioning the shielding such that the base of the penis is always in the field of view, the washout curve does not demonstrate a positive upslope and the resultant calculated venous flow dip does not occur.

Dr. Kitapci indicates that in his experience some patients have nearly flat xenon washout curves prior to papaverine administration. We have witnessed similar findings in patients with severe disease and note that the variation in xenon washout is quite large. The case we show is a normal patient and does demonstrate a rather significant washout before the papaverine injection. In our initial manuscript we showed curves from all three groups to demonstrate the variation, but the reviewers recommended a reduction in the number of curves. Thus, the final revised paper only contains the single normal case.

The number of patients experiencing arterial insufficiency is 5 as shown in Figure 5A. In Figure 5B there should be two values presented at the lowest point with one patient measuring 2.9 ml/min and the other 2.8 ml/min which would be indistinguishable on our graph. Unfortunately, we did not catch the error by our artist. The error is compounded in the Materials and Methods section where the number of arterial disease patients and venous leak patients were inverted. Thus, the sentence should read "5 men showed severe arterial disease" rather than 3 men, and under venous leak it should read "3 men were diagnosed as having venous leak" rather than 5 men as written. We apologize for the confusion.

We thank Dr. Kitapci for helping us clarify our results.

Floro Miraldi
A. Dennis Nelson
University Hospitals of Cleveland
Cleveland, Ohio

NRC Regulations on Departures from Manufacturer's Instructions

TO THE EDITOR: The Nuclear Regulatory Commission (NRC) recently published a final rule (*1*) to amend its regulations on the recordkeeping requirements for deviation from the package insert in the preparation of radiopharmaceutical reagent kits, elution of radiopharmaceutical generators and use of ra-

diopharmaceuticals for therapy (2). This final rule is unusual in that an expiration date was assigned to this regulation. The effective time period for this rule was set from August 23, 1992 to August 23, 1993, which is the same period of time as that for the Interim Final Rule on 10 CFR Parts 30 and 35. The inclusion of an effective time period for this final rule was necessary to allow the NRC to reconsider some of the issues raised by the American College of Nuclear Physicians (ACNP) and the Society of Nuclear Medicine (SNM) in their petition for rulemaking on 10 CFR Parts 30, 33, and 35 filed with the NRC on June 5, 1989 (3).

Although the NRC is eliminating the recordkeeping requirements under this final rule, they have clearly indicated in their responses to public comments that at this time they have no intention of terminating thc remainder of the Interim Final Rule (2). Thus, this final rule removes only the recordkeeping requirements related to the specific nature of the departure, i.e., a precise description of the departure, a brief statement of the reasons for the departure and the number of departures from the Food and Drug Administration (FDA) approved package inserts. The other parts of the Interim Final Rule should still remain valid. The issue of terminating the remainder of the Interim Final Rule will be addressed at a later time when the NRC has completed its consideration of the ACNP/SNM petition.

However, another difference seems to exist apart from the elimination of recordkeeping requirements between the Final Rule and the Interim Final Rule. Under the new final rule, departures from the manufacturer's instructions can be made by following the direction of an authorized user physician. The removal of the previous restrictions under the Interim Final Rule that deviations from the package insert can only be made if ". . . the departures would obtain medical results not otherwise attainable or would reduce medial risks to particular patients because of their medical condition . . ." (2) would seem to suggest that an authorized user physician may prescribe a departure from the manufacturer's instructions in the preparation of reagent kits for economic reasons. Examples of this type of departure include the addition of higher radioactivity to the reagent cold kit, allowing more unit doses to be dispensed from the same kit, and the fractionation of expensive radiopharmaceutical kits such as Ceretec™ (Amersham Corporation, Arlington Heights, IL), TechneScan MAG3™ (Mallinckrodt Medical, Inc., St. Louis, MO), and CARDIOLITE® (The Du Pont Merck Pharmaceutical Co., N. Billerica, MA) for cost reduction.

One of the major reasons that the NRC has decided to eliminate the requirements for recordkeeping related to the deviation is that both the NRC and the FDA have concluded that the major trends in departures from the package inserts have been identified based upon the documentation collected by the NRC, and they have agreed that there is no need to collect additional data. It is not clear whether the NRC had included the information with regard to the departures for economic purposes prior to their decision for amending the regulations. Even if the NRC and the FDA had not had a chance to review the documentation of deviations from manufacturer's instructions for reasons of cost saving, I believe that such departure should still be allowed under the new final rule as long as the procedures for deviation have been developed and evaluated in a scientific manner, and preferably that the procedures have been published in a peer-review professional journal. With well-established data to support the departure for cost effectiveness and the required direction for such deviation from an authorized user physician, the protection of the public health and safety can then be guaranteed, and therefore such a practice will not violate the NRC's legislative mandate.

REFERENCES

1. Departures from manufacturer's instructions; Elimination of recordkeeping requirements. *Federal Register* 1992;57:45566–45568.
2. Authorization to prepare radiopharmaceutical reagent kits and elute radiopharmaceutical generators; Use of radiopharmaceuticals for therapy. *Federal Register* 1990;55:34513–34518.
3. American College of Nuclear Physicians and the Society of Nuclear Medicine; Receipt of petition for rulemaking. *Federal Register* 1989;54: 38239–38241.

Joseph C. Hung
Mayo Clinic
Rochester, Minnesota

Correlation of Radiation Absorbed Doses to Nodal Metastases

TO THE EDITOR: In a recent study of thyroid cancer patients, Maxon et al. predicted radiation absorbed doses to nodal metastases from ^{131}I therapy and correlated them with the results of the therapy (1). They used 74 MBq (2 mCi) of ^{131}I plus conjugate views to calculate absorbed dose in a preliminary study and predicted the therapy absorbed dose by scaling with the ratio of administered activities (therapy over preliminary). In the preliminary study, patients were imaged at 24, 48 and 72 hr post-administration, instantaneous uptake was assumed and the lesion activity was plotted on semilog paper, then fit with a straight line. In 23 patients where nodal metastases were associated either with residual thyroid disease or with other metastic foci, a total of 36 lesions were analyzed quantitatively. The protocol predicted they would absorb a dose greater than or equal to 8,500 rads. Of the nodes receiving this dose, 86.1% (31/36) responded (as subsequently judged by physical examination and visual interpretation of images).

In our much smaller series, we used a pair of orthogonal views and imaged our patients after the therapy administration of radioiodine (2,3). When we had only one good view due to overlap of lesions in the other, we averaged two estimates of the volume (assuming two different ellipsoids of rotation in the good view) and found that an absorbed dose as low as 5,300 rads was sufficient to produce a response. When we had two unambiguous views, no averaging was necessary and a more accurate volume estimate was obtained. We determined that absorbed doses more than or equal to 2,400 rads (in one patient) or 3,460 rads (in another) were correlated with response. These three values are only 66% or less of the target value (8,000 rads) proposed by Maxon et al. Also, our intratherapy measurements of uptake versus time produced data sets that did not all fit a straight line. For five metastases, the peak uptake was at the first time point measured (average time 28 hr), but in four others, it was later (between 48 and 77.5 hr). Our measured effective half-life for washout averaged 1.59 days.

In view of our data, we have several questions regarding the results of the Maxon group. How well did a straight line fit the