some dynamic studies which require rapid-sequential imaging with a scintillation camera.

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REFERENCE

1. KONIKOWSKI T, JAHNS MF, HAYNIE TP, et al: Brain tumor-scanning agents compared in an animal model. *J Nucl Med* 16: 200–207, 1975

REPLY

We are most appreciative of Dr. Sear's remarks on our paper "Brain Tumor-Scanning Agents Compared in an Animal Model." Dr. Sear's comments broaden the perspectives of our report to include the important aspect of radiation dosimetry. While we chose to present our data emphasizing biologic distribution, we were careful to point out that our rating system classified compounds only on this basis. However, not to overlook the importance of radiation dose, we did present whole-body dose data.

It is very true that the activity of any radiopharmaceutical administered for diagnostic purposes is limited by the whole-body and critical-organ dose to the patient. However, rating systems for radiopharmaceuticals that include radiation dosimetry, such as the one Dr. Sear presents, are based upon a generalized "population" approach. Deviations from this general rule may occur in specific medical handling of individual patients, especially in the field of cancer. The radiation dose to the patient must always be weighed against his individual needs and the information to be gained; this is a professional judgment which must be made by the physician. Dr. Sear discusses some of these considerations when he speaks of tumors near the base of the brain and of dynamic studies.

There are many ways of expressing data in animal distribution studies, such as percent dose per gram, percent kilogram dose per gram, percent dose per organ, or percent dose per 1% body weight; and certainly tumor concentration can be expressed in millicuries per gram per rad total-body dose as suggested by Dr. Sear, if one's primary concern is radiation dosimetry. This latter means of expression, however, says nothing about the relative distribution of target to nontarget areas and so is unsatisfactory from the standpoint of biologic distribution. Also, since it is based on whole-body dose, Dr. Sear's system does not take into account radiation dose to specific organs which may be critical, e.g., ^{203}Hg and the kidney.

We tried to emphasize that our data and data handling related only to biologic distribution: "Other parameters such as biological clearance and radiation decay characteristics that affect radiation dose to the patient must be considered in any type of comparison. Frequently the product having good radiation and clearance characteristics, i.e., ^{99m}Tc-pertechnetate, has poor distribution, and the substance having the best distribution pattern, i.e., ^{111}In-chloride, has other unfavorable properties."

This exchange of letters emphasizes the problem practitioners of nuclear medicine face when they attempt to optimize procedures. We think it illustrates how difficult it is to satisfy completely all members of the nuclear medicine team, e.g., the clinician, the radiochemist, the radiobiologist, the radiopharmacologist, and the radiation physicist. We thank Dr. Sear for emphasizing the radiation dose aspects of a very complex situation.

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SCINTILLATION CAMERA VERSUS RECTILINEAR SCANNER FOR LIVER IMAGING

In the abstract of a recent article (*1*), Oster et al claim "it is apparent that the multiple-view scintillation camera technique is not superior to the rectilinear two-view scans for studying the liver." However, the evidence they present fails to support this startling comment.

The authors' series consists of 125 patients, 122 of whom had liver disease proved by biopsy and only three of whom were normal. Hepatic scintigrams were performed on all patients with an unspecified scintillation camera. The scintigrams of 97 of the 122 abnormal patients were correctly called "positive," for a true-positive ratio (TPR) (*2*) of 0.8. Oster et al tell us that there were "almost no false-positive interpretations," reflecting "a degree of sophistication of interpretations." They seem to have

overlooked the fact that there were "almost no" normals in the series (only three) to have their scintigrams falsely interpreted as positive. For this reason, no meaningful false-positive ratio (FPR) (*2*) can be calculated from their data.

The authors compare their "yield of positive studies," i.e., their TPR, with that of other series from their laboratory (*3,4*) in which the patients were examined with a rectilinear scanner. Noting that the "yield of positive studies" does not differ greatly from series to series, they conclude that hepatic scintigraphy with a scintillation camera is no better than with a rectilinear scanner, even if only two views are made with the latter device. It is well established, however, that the TPR is not a fixed value, but a parameter which varies with the diagnostic "criterion level" (*5*), also called the "cut-off point" (*2*), chosen by the observer (the interpreter of the images). For this reason, the "yield of positive studies," i.e., the TPR, cannot be used alone to compare two methods of hepatic imaging, as Oster et al have done. At the very least, reference must be made to the FPR, which varies in a monotonic fashion with the TPR as the diagnostic criterion level is changed (*2,5,6*). Since the small number of normals in the series of Oster et al precludes determination of a valid FPR, their data cannot be used in any meaningful way to compare two methods of hepatic scintigraphy.

The danger of using the TPR alone to compare diagnostic tests cannot be overstated. Such a practice could lead one to conclude that randomly calling 80% of patients "positive" *without* performing an hepatic scintigram is as good a test for liver disease as hepatic scintigraphy in the hands of Oster and his colleagues, since the TPR would be about 0.8 in both cases. The only clue one would have that random diagnosis is an inferior procedure is that the FPR for random diagnosis would also be about 0.8 while (hopefully) much lower for hepatic scintigraphy.

Even comparison of diagnostic imaging tests in terms of single sets of TPRs and FPRs may be difficult (*7,8*). While one is interested in determining the inherent detectability of lesions characteristic of the various tests, one may not be able to eliminate differences in the TPRs and FPRs which result from variations in the diagnostic criterion levels (cut-off points) chosen by the observers. For example, Oster et al cite two publications from their own laboratory (*4,9*) from which sufficient data may be extracted to calculate both the TPRs and FPRs. Poulose et al (*4*) reported that 19 of 27 rectilinear liver scans of patients with proved hepatic metastases were interpreted as showing "clear-cut focal defects," for a TPR of 0.70: only one of 57 scans of normal livers was so interpreted, for an FPR of 0.02. Fee et al (*9*) reported that 17 of 22 camera hepatic scintigrams of patients with proved liver metastases were interpreted as showing "clear-cut focal defects," for a TPR of 0.77: six of 48 scintigrams of patients with normal livers were so interpreted, for an FPR of 0.13. The TPR for examination with a scintillation camera was thus higher than the TPR for examination with a rectilinear scanner. However, the FPR for the camera scintigrams was higher than the FPR for the rectilinear scans. Since the "superior detectability" of lesions with the scintillation camera was achieved at the cost of a higher FPR, the observers of the camera studies may have used less strict subjective criteria for diagnosing "clear-cut focal defects" (i.e., a higher cut-off point) than the observers of the rectilinear scans. One cannot, therefore, say anything about the relative inherent detectability of lesions by the two methods of hepatic scintigraphy on the basis of these data.

This problem can be overcome by expressing observer performance in terms of the receiver operating characteristic (*6–8*). By this method, the TPRs for rectilinear scanning and camera scintigraphy can be compared at *any given FPR*, thus eliminating differences in the TPRs due to variations in the cut-off points employed by the observers. The receiver operating characteristic also allows evaluation of inherent lesion detectability independent of the actual frequency of lesions in the population examined (*6,8*). Furthermore, receiver operating characteristics may be used in rational selection of an "optimal" diagnostic criterion level (cut-off point) (*2,8*).

It is interesting that Oster et al point out that a change from rectilinear scanners to scintillation cameras for diagnostic liver imaging at the Johns Hopkins Medical Institutions "may have increased" the "diagnostic certainty" of the clinicians interpreting the studies. This statement suggests that a properly designed observer performance study would show the modern scintillation camera to be superior to the rectilinear scanner for diagnostic imaging of the liver.

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REPLY

We are very happy that our paper stimulated the interesting discussion by Dr. Turner. Our third study of liver scanning at Johns Hopkins differed from the previous two, referred to by Dr. Turner, in that the basic populations under study differed. In the studies by Poulose et al and by Fee et al, the basic populations were patients coming to abdominal surgery because of suspected abdominal malignancy; thus a relatively great number of patients had liver metastases at the time of surgery.

The present study population consisted of patients who had needle biopsy of the liver for various indications. The criterion for including a patient in this study was that the patient should have had a liver scan and a liver biopsy within 1 week. We can postulate some possible explanations for the low number of normal biopsies: either the clinicians have a very good index of suspicion in selecting patients for this procedure or the pathologists have a low threshold in diagnosing liver disease from needle biopsy preparations. We agree that the problem of liver imaging must take into consideration both the false positives and false negatives.

The high rate of false negatives in the study by Poulose et al using the rectilinear scanner was explained by the fact that numerous small metastases, as well as larger ones, on the liver surface could not be detected. It was hoped that the scintillation camera with its higher resolution and parallel-hole collimator and multiple views would decrease the number. Unfortunately, it did not. Despite the use of multiple views, we did not get rid of the problem of missing 20% of the lesions within the liver.

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CHEMICAL STATE OF TECHNETIUM IN VIVO (LETTER NO. 1)

In a recent article (*1*), Hambright et al state that Tc(IV) should be inert, that is, kinetically slow to substitution reactions. They invoke an inert Tc(IV) gluconate on theoretical grounds and on the basis of a competitive binding experiment between ^{99m}Tc-HEDP and 0.1 *M* gluconate. However, in a previous article (Ref. *2* of their paper) they point out that ^{99m}Tc-gluconate is dissociated by the competitive binding of ^{99m}Tc by Sephadex during a quick chromatographic analysis. The discussion of the mechanism of the inorganic reaction thus seems to contradict their previous statements about chromatographic artifacts.

They further state that the conclusion of earlier work on ^{99m}Tc chelates, including several papers by myself and others, is that "the chemistry at macro ^{99}Tc levels may be different than that shown by micro ^{99m}Tc." In fact, we had tried to show that ^{99}Tc and ^{99m}Tc reduced with stannous ion, for example, show similar reactivities with DTPA and, therefore, that the same reduced state present in ^{99}Tc-DTPA is probably present in the ^{99m}Tc radiopharmaceutical. This is similar to the authors' conclusion that ^{99}Tc and ^{99m}Tc reduced with stannous ion show similar biologic behaviors when chelated with HEDP and, therefore, that the Tc(IV) state can be assigned to the carrier-free ^{99m}Tc radiopharmaceutical. Both experiments are based on the assumption that the only variable is the concentration of technetium. However, the concentration of other species, such as stannous and stannic ion, which can affect the oxidation potential may not be held constant. Also, it has not been proved that only one oxidation state of technetium can bind to the chelating agent or give the