size, since calcium is a strong flocculating ion. On comparison of the liver uptake of Tc-99m stannous phytate and Tc-99m antimony sulphide colloid, the higher liver concentration of the stannous phytate preparation is obvious. This greater liver uptake with the phytate preparation is probably due to the rapid movement of ionic Tc-99m stannous phytate through the lymphatic pathways into the vascular channels with the consequent formation of colloid calcium-complexed Tc-99m stannous phytate, which is then extracted by the liver. In addition, ionic stannous phytate may diffuse from the injection site across the tissues into the blood and at this point also form calcium complexes. Though there may be some colloid formation at the injection site, our hypothesis is supported by early visualization of the liver in rabbit scintigrams and the high background activity noted on scintigraphy during the first hour by Alavi and colleagues. Using the rabbit animal model and quantitated body and node uptake, we have been able to compare radiocolloids for lymphoscintigraphy and predict uptake characteristics in humans.

In reference to the work of Ege (*3*), using Tc-99m antimony sulphide colloid in internal mammary lymphoscintigraphy, Alavi et al. comment on the variable clearance of this preparation from the injection site. These absorption data were taken in patients, some with diseased lymphatics, following interstitial subcostal injection. It must be appreciated that the uptake of radiocolloid varies with the animal model studied, the injection site, and the state of the lymphatics.

There are considerable experimental and clinical data available to suggest that interstitially injected Tc-99m antimony sulphide colloid has unique features that may not be simulated by Tc-99m stannous phytate, despite apparent similarities (personal communication, W. Kaplan; our unpublished data). Unless such limitations are recognized, the substitution of Tc-99m stannous phytate for Tc-99m antimony sulphide colloid may jeopardize the quality and accuracy of the lymphoscintigraphic procedure.

GUNES N. EGE
ANN WARBICK
The Princess Margaret Hospital
Toronto, Canada

REFERENCES

*1.* ALAVI A, STAUM MM, SHESOL BF, et al: Technetium-99m phytate as an imaging agent for lymph nodes. *J Nucl Med* 19: 422–426, 1978

*2.* WARBICK A, EGE GN, HENKELMAN G, et al: An evaluation of radiocolloid sizing techniques. *J Nucl Med* 18: 827–834, 1977

*3.* EGE GN: Internal mammary lymphoscintigraphy—The rationale, technique, interpretation and clinical application: A review based on 848 cases. *Radiology* 118: 101–107, 1976

## Reply

We believe that technetium-99m stannous phytate (*1*) is a unique lymph-node imaging agent because it is different from other radiopharmaceuticals available for lymphoscintigraphy. When this agent is injected as a solution, the particles are formed in vivo in contrast to other agents that are administered as preformed particles.

In our opinion, a significant fraction of the lymph node imaging agent should be cleared from the site of injection, not only to outline all the lymph nodes along its path, but to visualize the liver and the spleen as well. The latter aspect is important to ensure that the particles have traveled through the lymphatic system and entered the systemic circulation, thereby producing a baseline pattern useful in the evaluation of abnormal states. When an agent is used that does not consistently visualize the liver/spleen (*2*), minimal decrease in lymphatic flow due to a diseased node may prevent visualization of lymph nodes proximal and distal to the abnormal site and may result in an overestimation of the extent of the involvement. Thus, the presence of extranodal activity in the liver and the spleen is probably an essential feature rather than a disadvantage with a lymph node imaging technique.

Since the particles are rapidly cleared from the circulation by the liver and the spleen, background activity is transient and minimal. Radioactivity in the liver, spleen, and kidneys in human subjects will not interfere with lymph node imaging, since these organs are usually located away from the nodes to be studied. Therefore, the statement in our paper that "Tc-99m stannous phytate appears to be a suitable agent for lymph node imaging in areas where the extranodal concentration does not interfere" is spplicable only to animals with different anatomy (such as the presence of a large bladder in rabbits) and should not be applied to human studies. An additional advantage of significant clearance of the activity from the site of injection is the reduction of radiation dose to the area of administraiton.

We did not attempt to measure the particle size of calcium stannous phytate. As part of the investigation, however, we injected prepared Tc-99m calcium stannous phytate for lymph node imaging in vitro and found that this preparation resulted in consistently poor lymph node images. In view of these findings we believe that when Tc-99m stannous phytate is used as an imaging agent, in vivo particle size cannot be inferred from in vitro particle measurements. Furthermore, one should bear in mind that the method of preparation of Tc-99m stannous phytate solution may alter its behavior in vivo. It has been shown that when Tc-99m stannous phytate is autoclaved before i.v. injection, its behavior is that of a bone-seeking agent and not as a reticuloendothelial tracer (*3*). We have used Tc-99m stannous phytate preparation (without autoclaving it) both in animals and humans and have obtained satisfactory reticuloendothelial scans (unpublished data). Our images demonstrate that the liver activity becomes apparent only after the lymph nodes are well visualized, indicating that Tc-99m stannous phytate is cleared through the lymphatics and enters the systemic circulation through the lymphatico-venous communications.

We have no experience with Tc-99m antimony sulphide colloid as a lymph-node imaging agent and no access to pertinent data, so it is not possible for us to discuss the superiority of one agent over the other.

In conclusion, more clinical and experimental data are needed before one agent can be proposed as a superior and optimal preparation for lymph node imaging.

ABASS ALAVI
MUNI STAUM
University of Pennsylvania
Philadelphia, Pennsylvania

REFERENCES

*1.* ALAVI A, STAUM MM, SHESOL BF, et al: Technetium-99m stannous phytate as an imaging agent for lymph nodes. *J Nucl Med* 19: 422–426, 1978

*2.* EGE GN: Internal mammary lymphoscintigraphy—The rationale, technique, interpretation and clinical application:

A review based on 848 cases. *Radiology* 118: 101–107, 1976

3. HAMILTON RG, ALDERSON PO, MCINTYRE PA: Technetium-99m phytate as a bone marrow imaging agent. *J Nucl Med* 18: 563–565, 1977

## Motion-Corrected Hepatic Scintigraphy

The article by Turner et al. (*1*) is a model of the performance of the multiple-reader study. One must be cautious, however, in accepting the conclusion that the method of correction for obtaining liver images yields greater accuracy in reading than uncorrected scans. The authors have discussed the difficult problem of significance of separation of receiver operator characteristic curves in an honest and straightforward manner. Since error bars overlap for Observers Nos. 2, 3, 4, and 5 in ROC curves related to uncorrected images for virtually all points plotted, one might conclude from the study that four out of five readers found no significant difference in reading liver scans, even when employing the analog motion correction device.

For example, Turner et al. in previous correspondence noted conditional probabilities for Reader No. 3 as clearly separated on the two ROC curves for uncorrected and corrected plus uncorrected images for (pS|s) equals $0.59 \pm 0.07$ and $0.76 \pm 0.06$ at $p(S|n) = 0.04$. However, 95% confidence limits for this certainty must be examined. Two standard deviations above the lower probability of 0.59 (uncorrected scan) equals a probability of 0.73, while 2 standard deviations below the upper point of 0.76 equals 0.64, an obvious overlap. Similarly, for Observer No. 4 Turner et al. felt that the point on the ROC curve of both techniques with $p(S|n)$ of $0.21 \pm 0.06$ at $p(S|s) = 0.84$ was clearly different than that of $p(S|n) = 0.06 \pm 0.03$ at $p(S|s) = 0.86$ for the uncorrected image. However, the probability of $0.21 \pm 0.06$ means that 2 standard deviations (95% confidence limits) below that probability is a probability of 0.09, while 2 standard deviations above $0.06 \pm 0.03$, is 0.12. Clearly, there is an overlap again at the 95% confidence limits.

For each of five readers the uncorrected image yields a ROC curve that lies below that of the corrected image. At first glance one might feel that this must be statistically significant, and using the binomial expression $(0.5)^n$ (where $n = 5$), Turner et al. suggest that the probability of getting such a result, with the uncorrected curve giving poorer results than the corrected curve five out of five times is 0.03. However, this binomial test should have two "tails," since either the corrected or the uncorrected technique could have been better. The actual probability is therefore 0.0625 that five of five readers would find one or the other technique preferable.

The above discussion is not to deny that Turner et al. *may* be correct in their conclusion, for the data suggest that motion correction may provide more accurate hepatic imaging. Because of the overlap in 95% confidence limits for four out of five readers, however, and the probability in excess of 0.05 that five out of five readers might prefer the same technique, it is suggested that other definitive studies of this interesting technique should be performed before we all make this modification on our gamma cameras.

EDWARD B. SILBERSTEIN
University of Cincinnati
Cincinnati, Ohio

REFERENCE

*1*. TURNER DA, FORDHAM EW, AMJAD A, et al: Motion corrected hepatic scintigraphy: Objective clinical evaluation. *J Nucl Med* 19: 142–148, 1978

## Reply

We wish to thank Dr. Silberstein for his interest in our work and his kind remark regarding it.

Statistical testing of the separation of receiver operating characteristic (ROC) curves is difficult. Although the problem is being vigorously investigated in several quarters, and an answer may be close at hand, no method that is entirely satisfactory for clinical experiments has yet been described. In particular, we are unaware of a method that appropriately tests the separation of ROC curves generated from statistically dependent (correlated) sets of observations. For reasons outlined below, it appears to us that Dr. Silberstein's analysis is inappropriate.

In our experiment (*1*), all five observers performed better reading corrected scintigrams (CS) than reading uncorrected scintigrams (US). The strikingly superior performance of Observer 1 reading CS in contrast with his performance reading US certainly should be statistically significant. Although the improvement in performance of Observers 2 and 4 with motion correction and Observers 3 and 5 reading both types of study together was smaller, it was not trivial, especially in the region of clinical interest (i.e., the left side of the curves). The statistical significance of this improvement is uncertain, however, because we have no appropriate way of testing it. Dr. Silberstein has suggested that we look at the error bars and infer significance or lack of significance of curve separation from the presence or absence of overlap of the bars. This is inappropriate, however, because the data from which the curves were generated are correlated (*1*). Since the data are paired, the error bars underestimate the significance of the separation of the curves, and no valid conclusion about the significance of that separation can be drawn from them.

Dr. Silberstein has stated that the fact that five out of five observers performed better with motion correction than without is not significant by the sign test. He refers to a "two-tailed" sign test that yields a P value of 0.0625. In the first place, the propriety of his use of a two-tailed test is open to question. We have asked the question, "Is motion corrected scintigraphy better than uncorrected scintigraphy?" The appropriate test in this case has one "tail" and yields a P value of 0.03, a result generally considered to be statistically significant (i.e., $p < 0.05$). Furthermore, even if one chooses to use the "two-tailed" test, a P value of 0.0625 is very close to 0.05 and, therefore, a very important result, although not technically a "significant" one.

We have interpreted our data as suggesting that analog motion correction can improve the inherent detectability of mass lesions in the liver, provided that the motion correction device is properly calibrated, the spatial resolution of the imaging system and the counting rate are sufficient, the count density is high enough, and so on (*1*). In spite of the difficulties relating to the statistical analysis of the data, we continue to hold that opinion.

DAVID A. TURNER
Rush Medical College
Chicago, Illinois