TABLE 2. PATIENTS RECEIVING MULTIPLE DOSES OF DENATURED HUMAN SERUM ALBUMIN FOR LUNG SCANNING DURING PHASE I UROKINASE TRIALS*

Radiopharmaceutical	No patients	No reactions
^{131}I-macroaggregated human serum albumin	140	None
^{99m}Tc-human serum albumin microspheres†	11	One patient experienced acute onset of choking with flushing, which rapidly returned to normal. Patient had no reaction to subsequent microspheres‡

* Dose schedule: 1, 2, 3, 7, 14 days, 3, 6 months, 1 year.
† Three patients received eight doses, two patients received ten doses, five patients received 11 doses and one patient received 12 doses.
‡ Injections in this subject were: 2/10/69; 2/11/69; 2/12/69; 2/13/69; 2/14/69; 2/17/69; 2/18/69; 2/25/69; 5/12/69—reaction; 9/26/70—no reaction; 12/2/70—no reaction.

cal intervention. Subsequently this patient received microspheres on two separate occasions without ill effects.

This patient was one of over 100 patients who were given repeat injections of microspheres in a study of pulmonary embolism. More than 100 other patients were evaluated with repeat injections of ^{131}I-macroaggregated human serum albumin without ill effects. Table 2 summarizes the patients who were treated during Phase I urokinase trials.

In summary this evidence suggests that there is a low probability of a serious allergic reaction of patients to injections of human serum albumin microspheres. Except for urokinase study patients, the probability of an individual patient receiving more than two serial doses of denatured human serum albumin is 0.056. This factor together with the low sensitizing potential of human serum albumin microspheres makes the chances of observing an allergic reaction quite small. From our data between November 18, 1968, and November 17, 1970, the estimated probability of an allergic reaction to an injection of microspheres in patients who have already had two injections is 0.003 and in all patients is 0.0007. If the data from the more than 15 other institutions which have also been using human serum albumin microspheres and have reported no reactions and our own more recent experience were included these probability estimates would be even less.

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BUCK A. RHODES
The Johns Hopkins Medical Institutions
Baltimore, Maryland

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IS IT THE BLOOD BACKGROUND?

In a recent article (*J Nucl Med* 11: 173, 1970) entitled "Failure to Detect ^{131}I Positive Thyroid Metastasis with ^{99m}Tc," the authors, Meigan and Dworkin, report a case in which metastatic lesions positive on a regular ^{131}I scan were missed on a $^{99m}TcO_4^-$ scan, supposedly because of a high blood background. We wish to point out that this failure, at least in part, may be attributed to the technical procedure followed in scanning by them.

The authors do not state clearly their reason for repeating a $^{99m}TcO_4^-$ scan after an ^{131}I scan. We presume this was a part of an overall effort to compare the two radiopharmaceuticals for the purpose of detecting metastases due to a thyroid carcinoma. In that case, a better procedure would be to perform a $^{99m}TcO_4^-$ scan first and then follow it with a ^{131}I scan. This would have avoided the problem of interference of one radionuclide to the other. The energy of ^{99m}Tc gamma rays is low (140 keV) compared with those from ^{131}I (364 keV), and therefore there will be no interference in an iodine scan due to the presence of $^{99m}TcO_4^-$. However, this is not true if an iodine scan is performed first and then followed by a $^{99m}TcO_4^-$ scan.

Meigan and Dworkin took the precaution of avoiding this interference by performing a technetium scan 5 days post iodine scan and thereby assumed that no iodine or minimal iodine was left by that time. We calculated that 5 days interval is not sufficient to give an insignificant iodine level and there there may be a substantial amount of iodine present at the time of a technetium scan. The authors do not give the 24-hr

uptake of iodine in metastases and thyroid bed. However, from our experience as well as others (*1*) this value may range from 2 to 10% of the injected dose. On this assumption, the amount of iodine left on the sixth day post injection can be easily calculated and will range from 10 to 50 μCi. Moreover, all of this will be localized in thyroid bed and metastases. The amount of technetium present at the time of scan can also be computed as follows: In a normal thyroid, the pertechnetate uptake at ½ hr ranges between 1 and 3% of the injected dose. Therefore this value cannot be expected to be more than 1% for a person whose thyroid has been removed. Also, if this value is higher than 1%, then correspondingly the 24-hr uptake for iodine will be expected to be higher than the postulated 10%. Thus the amount of technetium present at the time of scan will be in the range of 50 μCi or less which is of the same order as the amount of iodine present on the sixth day. The result of this large amount of iodine present (even if one takes lower limit 10 μCi) will be to degrade the resolution of the collimator badly because of (A) the scattered contribution of iodine gamma rays [which incidentally is worse in the range of technetium gamma rays (*2*)] and (B) the increased septal penetration of iodine gamma rays for a low-energy collimator. The evidence of this degradation in resolution is present in their technetium scan. Compare the size of metastasis denoted by C in their Fig. 1 with Fig. 2. The size in Fig. 2 is twice as big as in Fig. 1. The likelihood that this metastatic lesion has grown twice its size in 5 days is remote. We feel that this is due to degradation of the resolution of the collimator. If now one applies this degradation of resolution on lesions A, B, D, and E, and the large amount of activity in the heart blood pool, one will obtain a scan of Fig. 2. Therefore, one cannot blame the high blood background alone as the probable cause for not seeing the metastatic lesion E.

RAMESH CHANDRA
JOSEPH HERNBERG
PHILIP BRAUNSTEIN
New York University Medical Center
New York, New York

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THE AUTHORS' REPLY

The case we reported was obviously not part of a carefully planned study. We completely agree that a better procedure would be to perform the ^{99m}Tc-pertechnetate scan initially. This fact notwithstanding, the point made by our paper remains unchallenged. The point is that where thyroid uptake of ^{99m}Tc-pertechnetate is *low* (as in the case of a hypothyroid patient after thyroidectomy), a small island of remaining uptake may be "lost" in a sea of background radioactivity.

Because of space limitations we will agree that on Day 5 an equal number of microcuries of ^{131}I and ^{99m}Tc will be found in the various lesions 30 min after ^{99m}Tc-pertechnetate administration. In fact, there would probably be less ^{131}I due to the fact that ^{131}I is not only lost by physical decay but is also lost by biologic metabolism. Overlooked by Chandra et al is this latter process which would be accelerated in this patient due to the elevated TSH levels associated with hypothyroidism and also due to the fact that thyroid cancer has a more limited capacity to store ^{131}I in the form of thyroid hormone. Another point overlooked by the writers is that Fig. 1 shows the almost complete absence of radioiodine in the regions usually associated with the heart and great vessels. At 5 days post ^{131}I the amount of radioiodine in these areas would diminish even further. One obviously cannot claim to have scatter in these areas from nonexistent radioiodine.

Some review of basic physics appears to be in order. The counting rate of a given quantity of ^{131}I will fall by 75% or more if counted at the collimator focal point, using first an ^{131}I collimator and ^{131}I channel settings and then using a ^{99m}Tc collimator and ^{99m}Tc channel settings. This is due to the fact that counting rates tend to be much lower when counting Compton scatter than when counting at the photo peak (assuming equivalent window settings). Add to that the fact that the ^{99m}Tc photons have a higher efficiency of interaction with the sodium iodide crystal. Taken together, these facts yield the following: A given number of microcuries of ^{99m}Tc counted with a ^{99m}Tc collimator on the ^{99m}Tc channel will yield approximately a tenfold higher counting rate than an equal number of microcuries of ^{131}I counted under the same circumstances. Thus the contribution of ^{131}I counts to Fig. 2 (see original paper) over the areas visualized in Fig. 1 is about 10%. As one moves away from these areas, the ^{131}I contribution to the counting rate falls away rapidly. There is no doubt