which has a range of particle sizes, and some of the smaller particles will certainly be capable of passing through an SN to second-tier nodes. The data of Gulec et al. suggest that onward passage to second-tier nodes may have occurred in their series of 32 patients. They reported that 1 patient had six SNs in the axilla, 2 had five SNs, 2 had four SNs and 7 had three SNs. Using ^{99m}Tc-antimony sulfide colloid for mammary lymphoscintigraphy in 159 patients with breast cancer, we have seen 122 patients with one SN in the axilla, 7 with two SNs in the axilla, none with three SNs in the axilla and 1 with four SNs in the axilla (*3*). We have never seen a patient with five or six axillary SNs. This suggests that some of the axillary SNs reported by Gulec et al. were, in fact, second-tier nodes. Not all "hot" nodes are true SNs, and without lymphoscintigraphy it is not possible to distinguish SNs from second-tier nodes (*4*). Using lymphoscintigraphy, lymph channels can be seen entering the SNs on dynamic images, whereas nonSNs are seen receiving tracer that has already passed through an SN.

The inadequacy of microfiltered ^{99m}Tc-sulfur colloid as a tracer for mapping lymphatic drainage from a primary tumor site is also illustrated by the small number of internal mammary (IM) SNs detected by Gulec et al. Only 3 patients (9%) showed drainage to IM nodes. We found that 35% of patients with breast cancer had IM drainage, and, overall, 15% had direct drainage to the supraclavicular fossa (SCF) (*5*). Gulec et al. did not report SCF drainage in any of their patients, even though 21 of 32 patients (66%) had upper quadrant tumors. In our patients with upper quadrant lesions, 20% showed direct drainage to SCF nodes. Some of the difficulty Gulec et al. had in identifying drainage to the IM and supraclavicular node fields may have been caused by their use of the gamma probe as a crude rectilinear scanning device, without lymphoscintigraphy. Nevertheless, these data suggest that ^{99m}Tc-sulfur colloid is not providing a full picture of the pattern of lymphatic drainage from the breast and is not the best tracer to use for breast lymphatic mapping procedures, including SLNB.

Gulec et al. also state that the success rate of sentinel lymph node identification in breast cancer using a radiocolloid and a gamma-detecting probe is related to the volume of radiocolloid injected. This is perhaps true using microfiltered ^{99m}Tc sulfur colloid and is testimony to its limitations as a tracer for mapping lymphatic drainage. Initial studies with small volumes of tracer showed high failure rates in identifying draining SNs, and increased volumes have been used in attempts to force the tracer into the lymphatic capillaries. Recent publications are encouraging the injection of larger and larger volumes, and Gulec et al. state that injecting 8 mL means a "hot" node will be found in the axilla in 100% of patients. Such volumes are obviously nonphysiological; therefore, there must be doubt that all "hot" nodes found using this approach are actually true SNs draining the primary tumor. Large volumes of tracer will cause the tracer to pass along tissue planes in the breast away from the tumor, thus the tracer may enter lymphatic capillaries quite a distance from the primary tumor. Using ^{99m}Tc-antimony sulfide colloid, we found tracer migration through the lymphatics to SNs in 92% of patients, using four peritumoral injections with volumes of only 0.1–0.2 mL per injection site (*5*). Failure to identify draining lymph nodes was usually associated with metastatic disease in the lymphatic vessels or draining lymph nodes. Thus, successful sentinel lymph node identification is not injection-volume related but primarily tracer related, when using physiological injection volumes.

Most researchers who have studied the pattern of lymphatic drainage from tumor sites in different parts of the breast have found that approximately 90% of all tumors include the axilla as a draining node field, with varying drainage also to the IM, supraclavicular and interpectoral nodes (*5,6*). Thus, any SLNB methodology that finds hot "sentinel" nodes in the axilla of 100% of patients with breast cancer is, by inference, forcing radiocolloid to drain incorrectly to the axilla in about 10% of patients. Such "hot" nodes are not true SNs.

Finally, we make a plea to all those applying the SLNB technique in patients with breast cancer to remember that the primary aim is to accurately map lymphatic drainage from the primary tumor to the draining SNs and then to selectively remove those nodes. The goal should not be to ensure that axillary lymph nodes are radiolabeled at any price and then to remove such "hot" nodes.

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Roger F. Uren
Robert B. Howman-Giles
Missenden Medical Centre
Camperdown

John F. Thompson
Sydney Melanoma Unit
Camperdown, Australia

REPLY: We thank Drs. Uren, Thompson and Howman-Giles for their comments regarding our preliminary report of sentinel lymph node biopsy (SLNB) for breast cancer using unfiltered ^{99m}Tc-sulfur colloid (uTcSC) (*1*). They raise several interesting points and conjectures that we would like to comment on.

The first and most important observation to be made regarding their comments is that not all radiocolloids are available in all places. Antimony sulfide colloid, formerly approved in the U.S. for investigational use, is no longer available to clinicians in North America. Unfortunately, discussions of this and other unapproved radiocolloids such as nanocoll, interesting and stimulating as they may be, remain largely academic for those of us who live and work on this continent. Hopefully, this regrettable situation will change. As a consequence of this, however, proponents of various radiocolloids in different parts of the world inevitably "talk past each other"; to some extent the letter of Uren et al. and our response to it are examples of this.

In referring back and forth to SLNB experience in melanoma and breast cancer patients throughout their letter, Uren et al. imply that SLNB for these two diseases is essentially the same procedure. This is not the case. For SLNB in melanoma, preoperative lymphoscintigraphy (LS) is important for identification of all lymph node basins that contain sentinel lymph nodes (SLNs). It is almost exclusively in the melanoma experience that dynamic LS has played a significant role in determining which radiolabeled node in a given basin is "sentinel," or at least the first SLN in line to receive drainage from the primary tumor.

In breast cancer, LS with either filtered (220 nm) ^{99m}Tc-sulfur colloid (fTcSC) or uTcSC is much less useful, because the radiocolloid injection site around the primary tumor often overlaps one or more of the regional lymph node basins, thereby interfering with or precluding external imaging. The size of the diffusion zone does not vary with volumes of radiocolloid injectate > 4 mL (*2,3*). The issue of SLNs in multiple basins is not as critical in breast cancer as in melanoma, the authors' data (*4*) notwithstanding (more on this below). Moreover, in that the axillary lymphatics are oriented obliquely with respect to the x, y and z axes, more often than not the preoperative skin marking of an SLN by orthogonal localization techniques is imprecise. Most of the time there is a discrepancy of as much as several centimeters between the LS-directed skin marking and the actual surgical gamma detection probe (GDP)-detected cutaneous hot spot. In the rare event that a single axillary lymph node is identified as the first of two or more to image, the surgeon working with a GDP may be unable to distinguish this node from other radiolabeled nodes.

In discussing attributes of the ideal radiocolloid, Uren et al. do not acknowledge that radiocolloids that are optimal for external gamma camera LS may be suboptimal for SLNB using a GDP. This point was briefly addressed in our article (*1*).

Currently available GDPs are highly sensitive, directional, radiation-detecting devices that permit the surgeon to detect radiolabeled lymph nodes despite the proximity (and often large size) of injection site radioactivity in breast cancer patients. In a study of 115 patients, Linehan et al. (*5*) showed that the operative GDP localizes SLNs more often than external imaging (88% versus 66% with uTcSC and 66% versus 41% with fTcSC; $P = 0.01$) and uTcSC gives superior SLN localization compared with fTcSC (88% versus 66%; $P = 0.01$). Krag et al. (*2*) also found that uTcSC gave the highest SLN localization rate among several radiolabeling agents, including fTcSC. That this should be true, even though the fraction of radiocolloid migrating to lymph nodes is lowest for uTcSC among tested radiocolloids (*6*), attests both to the exquisite sensitivity and directionality of surgical GDPs and the fact that uTcSC is most avidly retained in SLNs, with little or no pass-through to nonsentinel nodes.

From the surgeon's standpoint, it is important that the radiocolloid not pass through to second or third echelon nodes for a minimum of several hours after injection. Radiolabeling of multiple nonsentinel nodes would confound the surgeon's ability to find the SLN(s). At present, it appears that radiocolloids with large particle size are well suited for SLNB (*2,3*), whereas smaller colloids give more elegant LS imaging (*7,8*). A recent analysis of a larger series of patients from our institution demonstrates that uTcSC, having migrated to the SLN(s), does not pass through to more distal nodes for at least the first 6 h after injection (unpublished data).

It is also important that the radiocolloid migrate to SLNs within a short period of time. In our experience in a large-animal model in which isosulfan blue and uTcSC are simultaneously injected intradermally, the SLNs become radioactive much faster than they become blue stained. This colloid appears to migrate rapidly; cutaneous hot spots may be detected by the GDP within 15 min of injecting the radiocolloid into the breast, in our clinical experience.

In their series of 34 breast cancer patients, Uren et al. (*4*) reported that LS using antimony sulfide colloid demonstrated drainage to internal mammary and supraclavicular SLNs in 39% and 13% of patients, respectively. They contend that our finding of nonaxillary SLNs in only 9% of our patients (*1*) is evidence of the inadequacy of uTcSC to completely delineate lymphatic drainage. The multicenter University of Vermont validation trial of SLNB in early breast cancer (*3*) demonstrated nonaxillary SLNs in 8% of the 413 patients in whom SLNs were localized. We agree that the discrepancy between this observation and that of Uren et al. (*4*) is probably a function of the different radiocolloid particle sizes. Whether this disparity in nonaxillary SLN localization is caused by incomplete mapping by uTcSC, spurious delineation of clinically insignificant or irrelevant lymphatic pathways by antimony sulfide colloid or a bit of both remains unclear.

Finally, Uren et al. contend that injection of radiocolloid in larger volumes of fluid is nonphysiological and therefore prone to labeling nonsentinel nodes. This assertion is speculation on their part that is refuted by evidence that increasing the volume of injectate simply opens the lymphatic vessel patent junctions, increasing the rate of ingress of radiocolloid into the lymphatic luminal space (*8,9*), without affecting direction of flow. That direction of flow is not altered is supported by clinical data from institutions in which blue dye, radiocolloid or both were injected in volumes of 4 mL or more in breast cancer patients with low false-negative SLNB rates (*3,10,11*). Moreover, larger volumes do not seem to increase the number of labeled nodes (*2*).

Much remains to be done to refine SLNB techniques to reduce intersurgeon variability (*3*) and shorten the surgical learning curve. For example, minimization of the radiocolloid diffusion zone at the injection site would be helpful for surgeons and nuclear medicine physicians alike. A recent report (*12*) suggests that intradermal injection of the labeling agent directly over the breast carcinoma may give as accurate an SLN localization as intraparenchymal injection. If these findings can be reproduced, a marked reduction in injection site interference could be realized.

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Seza A. Gulec
Frederick L. Moffat, Jr.
University of Miami School of Medicine
Miami, Florida

David N. Krag
University of Vermont College of Medicine
Burlington, Vermont