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REPLY: We thank Drs. Staudenhertz and Leitha for their comments and note their concern over our finding of a positive relationship between oxyphil cell content of parathyroid lesions and the positive uptake during the late phase of dual-phase ^{99m}Tc-sestamibi (MIBI) (*1*). We initiated our retrospective study after observing positive uptake during the first phase of the scan but not during the late phase in a patient with parathyroid adenoma in whom no oxyphil cells could be found (*2*). Admittedly, our study had some limitations, such as its retrospective design and the small number of patients included. However, we carefully performed the interpretation in a blind fashion for both the scintigraphic and the pathologic findings and assessed the late phase of ^{99m}Tc-MIBI independently from the early phase. This had not been done by other investigators (*3,4*).

The discrepancy noted by Staudenhertz and Leitha between the results of their study (*3*) and ours (*1*) is not entirely clear. In their study, no independent relationship was found between the positivity of the scan and the parathyroid oxyphil cell content using multivariate analysis that included laboratory parameters, age, sex and volume of the parathyroid adenoma. However, they did not differentiate in their analysis between positivity during the early phase versus the late phase. Although their study included more patients than ours, it is likely that it had insufficient power to allow the detection of an independent relationship with oxyphil cell content using a multivariate analysis model. In our study, the calcium levels were almost identical between patients with and without positive late-phase uptake, which is in contrast to the higher calcium levels of those patients who had a positive scan during the early phase. It is therefore unlikely that calcium levels play a role in the late retention of ^{99m}Tc-MIBI in parathyroid lesions. There is a wider concern to us as to the biologic plausibility of prolonged cellular retention of MIBI in parathyroid lesions. Currently, the presence of mitochondria-rich oxyphil cells appears to be the most plausible hypothesis, although more research must be done on this topic.

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Regarding Sentinel Lymph Node Localization in Early Breast Cancer

TO THE EDITOR: In their recent article, Gulec et al. (*1*) state that the ideal radiocolloid for sentinel lymph node biopsy (SLNB) should migrate in a reasonable time frame (0.5–1 h) in sufficient quantities to be detected by a gamma detecting probe. They also state that radiocolloid retention in sentinel lymph nodes and delay of pass-through to nonSNs should be sufficiently long to permit SLNB to be performed over a wide range of time intervals (0.5–8 h) after injection of the colloid. While we understand the desire to embrace such a definition, we have to disagree with it. Logically, the ideal radiocolloid for SLNB is one that most accurately maps physiological lymphatic drainage from the primary tumor site to draining sentinel nodes (SNs). The ideal radiocolloid will thus be one with a particle size that allows it ready entry into the lymphatic system under physiological conditions.

These "ideal" radiocolloids would have particle sizes in the 5–75 nm range. Particles > 75 nm will have only limited entry into lymphatics under physiological conditions and migrate more slowly through the lymphatic vessels. Most particles in filtered ^{99m}Tc-sulfur colloid are >75 nm in diameter; when using this tracer, there are fewer particles in the lymphatic vessels. These vessels usually are not visualized during dynamic imaging, whereas they are routinely seen using radiocolloids such as antimony sulfide or nanocolloid of albumin, both of which have the majority of their particles in the desirable size range. Visualization of the lymphatic vessels is important, because the channels can be seen draining directly into SNs. More accurate identification of SNs is thus obtained, and, therefore, small-particle radiocolloids are preferred for any lymphatic mapping procedure, including SLNB.

With smaller-particle-size colloids, more tracer might be expected to pass through SNs and lodge in second-tier nodes; however, this is not determined solely by particle size and certainly does not occur in all patients. Using ^{99m}Tc-antimony sulfide colloid, the appearance of tracer in second-tier lymph nodes correlates with the speed of movement of the tracer through the lymphatics (*2*). The higher the flow rate, the greater the likelihood that activity will be seen in second-tier nodes. Nevertheless, in many patients, antimony sulfide colloid passes to the SN and remains in this node, with no movement whatsoever to second-tier nodes over several hours.

Some second-tier activity will occur in certain circumstances with any radiocolloid, including microfiltered ^{99m}Tc-sulfur colloid,

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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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.