Re: Lymphoscintigraphy with Tc-99m Labeled Dextran

In their unrestrained enthusiasm over the potential use of Tc-99m dextran for lymphoscintigraphy (*1*), the authors have attributed to me statements that are incorrect and do not appear in the reference quoted (*2*) or in any of my other publications. As stated by the authors, studies with radiocolloid that depend upon particle size and functional status of the RE system and do not reflect lymphatic flow "may account for the reported finding that approximately 50% of normal parasternal lymph nodes failed to trap colloid activity and thus were not distinguishable from lymph nodes with metastases." This statement on page 923 is then repeated on pages 927-928. If this had been my experience with $^{99m}TcSb_2S_3$, on what basis would I have been so confident of the anatomic validity of the internal mammary lymphoscintigram? The observation that internal mammary lymphoscintigraphy data compare so well with results of cadaver dissections, which has been confirmed by others as well (*3,4*), is a clear indication that 100% of normal nodes, not 50%, can be and are visualized with subcostally injected $^{99m}TcSb_2S_3$. I would appreciate it if the authors would indicate from whence this statement attributed to me was derived.

The statement that radiocolloid clearance from the injection site varies from 1%-35% is taken out of context. These values were obtained following subcostal—not epigastric—injection in patients with breast carcinoma—not in the hind feet of healthy mongrels.

It has been shown by others (*5*) that transport of radiocolloid is not entirely macrophage dependent and that small particle colloids do enter the lymphatics at the interstitial injection site.

The lymphoscintigraphic images with Tc-99m dextran convincingly demonstrate lymphatic pathways and intense aggregates without any discrete, distinguishable components. The potential diagnostic value in oncology of information of this character awaits much further work. Limited numbers of patients have been studied, but we are not privy to how many or with what conditions.

Until Tc-99m dextran has been shown to be equal or superior to radiocolloids currently in use for the specific requirements fulfilled by lymphoscintigraphy, let us make a concerted effort to accept the facts as they presently stand.

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Reply

Our paper entitled "Lymphoscintigraphy with Tc-99m Dextran" (*1*) was published as a preliminary note and should be considered as such. It was not our intention to question the usefulness of Tc-99 antimony sulfide colloid for lymphoscintigraphy or the well-known work done by Dr. Ege as also stated in our introductory remarks (*1*). We thank Dr. Ege for her interest in our work, in particular for her comments. In our paper (*1*), there is an unfortunate error regarding Refs. 2 and 3. In the last line on p. 923 as well as on the third line on p. 928, the reference cited should be 3 instead of 2, where erroneously we attributed to Dr. Ege the work of Aspergen et al (*2*). We apologize for this mistake, which, however, does not change the validity of our statements in the introduction or in discussion of the paper (*1*). The work by Aspergen et al (*2*) indicates a serious limitation exists with the use of Tc-99m sulfide colloid for lymphoscintigraphy in patients with breast cancer. These authors (*2*) reported a failure of Tc-99m sulfide colloid to accumulate in normal mammary lymph nodes in seven of 16 patients and concluded that "Since absence of incorporation indicates inflammation or malignant invasion, the use of the present Tc-99m sulfur colloid was a high risk of over diagnosis". Accordingly, these authors considered unethical the future evaluation of patients with breast cancer using Tc-99m sulfide colloid. This high rate of almost 50% false positives is also quoted in a recent paper in this *Journal* by Strand et al. (*3*).

The rate of false-positive tests may be substantially lower with Tc-99m antimony sulfide colloid as suggested by Dr. Ege and others (*3*). We never questioned this finding in our article, however, antimony sulfide colloid is still considered an investigational drug in the U.S. and is thus not available for routine use. In addition, an intensive computer search of the literature did not reveal any study, not even in Dr. Ege's work, documenting that 100% of normal mammary lymph nodes are visualized with Tc-99m antimony sulfide colloid. Neither study cited in Dr. Ege's letter (*4,5*) was designed to examine the efficacy of normal lymph node visualization nor did these studies document a 100% visualization of normal lymph nodes with Tc-99m antimony sulfide colloid.

We do not agree with Dr. Ege's assertion in the second paragraph. The statement in our manuscript was not out of context. In her own paper (*6*), Dr. Ege states on p. 102 that "Considerable individual variability in anatomic, physiologic and pathologic factors contributes to the rate of removal and dispersion of a radiocolloid. Estimates of the quantity of radiocolloid transported from the *interstitial* injection site over the first 24 hr have varied from 1% to 35%". Also, Dr. Ege gives no indication as to how these values were derived. No information is given with respect to whether they were derived after subcostal or epigastric injection or whether they were obtained from animal or human studies. This particular statement was referenced as a personal communication from M. J. Bronskill.

We cannot comment on Dr. Ege's remarks made in her third paragraph since the reference quoted (*7*) will be published in 1983 and was thus not available to us. Yet, we never questioned the possibility of very small particles entering the lymphatics at the interstitial injection site without being transported by macrophages.

In the last paragraph, Dr. Ege almost literally quotes our conclusion (*1*). We emphasized that "the potential value of this new radiopharmaceutical [Tc-99m dextran] for diagnosis and follow-up of patients with cancer, lymphoma and primary lymphatic disease awaits clinical trials" (*1*). We do not believe that such a statement can be interpreted as "unrestrained enthusiasm" or as intended "to distort the facts as they presently stand", an opinion that was shared by the reviewers as well as the author of the teaching editorial (*8*).

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8. DWORKIN HJ: Potential for lymphoscintigraphy. *J Nucl Med* 23:936-938, 1982

Re: Teaching Editorial. Potential for Lymphoscintigraphy

As a Teaching Editorial, I find this article somethat confusing with regard to the subject of lymph node imaging by a variety of modalities (*1*). The first paragraph is unsettling for the critical reader. For example, in radiocontrast lymphangiography (RCL) if water soluble medium is used to examine lymphatics of the upper and lower limbs whereas oily contrast media are used for groin, pelvic, abdominal and axillary lymph nodes, how does one deliver the oily media to these respective lymph node groups without introducing it into the relevant lower and upper limbs for which water soluble contrast media are indicated? Such a contradictory statement deserves further elaboration.

The properties, qualities, and applications of $^{99m}TcSb_2S_3$ have been underestimated. This agent has been used in our institution for ten years in over 9,000 studies and is currently in use in multiple centers in the U.S.A., Europe, Australia, New Zealand and South Africa. The clinical applications have not been as narrow as implied, and this agent has found a use *not* in the therapy of metastatic breast carcinoma but in the assessment, treatment planning and follow-up of patients with all stages of breast cancer as well as in patients with pelvic neoplasms and malignant melanoma. If the market for $^{99m}TcSb_2S_3$, compared with other pharmaceuticals has been limited, this reflects the prevalence of malignancy compared with the broad range of other pathological conditions investigated in our departments.

The experience of those personally involved in carrying out lymphoscintigraphy on a regular basis does not support the assertions of problems associated with particle size or reagent instability and batch-to-batch variability.

The objective of lymphoscintigraphy as it has developed over the past decade has been to assess the status of lymph nodes at risk from neoplastic infiltration and not specifically to establish the temporal interval for lymphatic visualization. Individual discrete lymph nodes can be distinguished with radiocolloid, comparison between different lymph nodes is possible, and patterns indicative of abnormality can be recognized. The same cannot be said currently about images obtained with Tc-99m dextran (*2*), where lymph node groups appear coalesced and individual features obscured.

Comparison of Tc-99m dextran with RCL and TCT for sensitivity and specificity would be unproductive for many anatomic sites. Under no clinical circumstance has RCL and only in the detection of appreciably enlarged lymph nodes has TCT had any application to investigation of the internal mammary lymphatics. Radiocolloid lymphoscintigraphy surpasses both these techniques in sensitivity and specificity.

Finally, the potential for lymphoscintigraphy rests with the astute, sound, critical, and informed judgment of individuals—not in reagents.

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Reply

I thank Dr. Ege for her carefully considered, clarifying response to the referenced Teaching Editorial—"Potential for Lymphoscintigraphy" (*1*). I trust that the critical reader to whom she refers will be knowledgeable enough to know that contrast media for visualization of efferent and afferent channels of the lymphatic system is delivered in the usual manner, as explained in the next paragraph in the editorial. In the first paragraph, there is no stated or implied alternate route of administration. A similar misinterpretation is displayed later in Dr. Ege's letter, where she comments that, ". . . . , and this agent has found a use *not* in the therapy of metastic breast carcinoma. . ." At no point is it implied that any of the agents mentioned in the initial portion of that paragraph are used for therapy, and, in fact, it is stated quite plainly that these tracer colloids are used for radionuclide lymphoscintigraphy (RNL). The next sentence in the editorial amplifies this point by offering the ultimate compliment to Dr. Ege's work using antimony colloid by stating that, "A high correlation has been shown between internal mammary RNL and the clinical stage of disease and prognosis." Out of context a quote is misleading, for I quite agree with Dr. Ege's statement that the agent is used in the assessment, treatment planning, and follow-up of patients with breast cancer and malignant melanoma.

When compared with all the diseases of the lymphatic system that might be studied, one is struck by the fact that antimony sulfur colloid has had application only in patients who have breast cancer and malignant melanoma. This finding supports the observation reported in the teaching editorial that the application is narrow, compared with the number of diseases that might be studied. To claim that antimony sulfide colloid has had wide application requires very selective vision. Knowledgeable sources at the Food and Drug Administration in the United States have informed me that fewer than 12 investigators in the United States have ever sought investigational new drug (IND) applications for the use of antimony sulfide colloid for radionuclide lymphoscintigraphy. Under these INDs, approximately 90 hospitals and institutions have been supplied with the material, although most of these users order the material on a sporadic basis only. Apparently, the agent was used by so few investigators in the United States that it was