The thyroglobulin ELISA (*10–13*) is about 20-fold more sensitive than conventional thyroglobulin assays and can measure serum thyroglobulin reliably and simply in the follow-up of treated DTC patients without exogenous or endogenous TSH stimulation. Serial measurements of low levels of thyroglobulin by ELISA enable detection of recurrence 6–12 mo earlier than would be possible using a conventional thyroglobulin IRMA. A prospective study is now needed to extend these initial observations.

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**REPLY:** We greatly appreciate the comments of Dr. Zöphel et al. concerning the sensitivity of enzyme-linked immunosorbent assay (ELISA), the occurrence of high-dose hook effects, and recovery testing for serum thyroglobulin measurement. They noted that the high-dose hook effects in 2-step ELISA for thyroglobulin assays occurred theoretically but not in daily routine (*1*), as was supported by the report that the high-dose hook effects occurred in only 1 of 356 consecutive differentiated thyroid carcinoma (DTC) patients in the whole study population (*2*). Furthermore, they speculated that recovery testing could reveal a falsely low thyroglobulin concentration leading to a false sense of safety in patient management. Generally, we agree with their comments. No current thyroglobulin method is perfect. There can be a 4-fold between-method variability that precludes the use of different thyroglobulin methods for serial monitoring of DTC patients (*3*). Therefore, the functional sensitivity of thyroglobulin methods, including ELISA, is reported differently. We also acknowledge that the retrospective study by Zöphel et al. ($n$ = 126) suggests that serial measurements of low levels of thyroglobulin by ELISA in treated patients with DTC enable detection of recurrence (without using thyroid-stimulating hormone stimulation) 6−12 mo earlier than would be possible using a conventional thyroglobulin immunoradiometric assay (*4*). However, as the authors put it, a prospective study is now needed to confirm their observations. According to the abstract of the paper by Görges et al. (*5*), we cannot identify the immunoenzymatic assay as ELISA. As for recovery testing for serum thyroglobulin measurement, recently it was reported that the potential for thyroglobulin autoantibody (TgAb) interference is only weakly related to the TgAb concentration, and even low levels have the potential to interfere (*6–8*). Therefore, guideline 46 of the National Academy of Clinical Biochemistry states that "recovery tests do not reliably detect TgAb and should be discouraged and eliminated" (*6*). Although TgAb interference with serum thyroglobulin measurements, especially when made by immunometric assay methodology, is likely to remain a problem for the foreseeable future, serial TgAb concentrations are, fortunately, a useful surrogate tumor marker test for monitoring the disease status of TgAb-positive DTC patients (*9*).

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## Diffuse Tracer Uptake in Scintimammography: Not as Nonspecific or Benign as Originally Believed?

**TO THE EDITOR:** We read with interest the recent article by Dr. Mathieu et al. (*1*) regarding the role of scintimammography in initial breast cancer diagnosis, detection of recurrence, and evaluation of tumor extent when the results from a protocol encompassing mammography, ultrasound, and fine-needle aspiration biopsy are inconclusive. Prompted by the results and discussion arising from this work, we feel the need to underline the significance of the interpretation of a diffuse radiotracer uptake pattern that is often observed in many scintimammography studies. According to the authors (*1*), faint, diffuse radiopharmaceutical uptake was shown to correspond to lobular or in situ breast carcinoma and therefore should not be systematically classified as nonspecific or benign.

We certainly agree with this observation and the notion that any diffuse uptake pattern in scintimammography should not be considered as a nonspecific or false-positive finding but should draw attention and be further investigated. In a previous series of ours (*2*), we enrolled patients with suggestive breast lesions (on physical examination or mammography) that were scintimammographically evaluated (planar imaging) with $^{99m}$Tc-sestamibi or $^{99m}$Tc-labeled dimercaptosuccinic acid [$^{99m}$Tc-(V)DMSA]. The occurrence of a diffuse, widespread pattern of radiotracer uptake was consistently associated with the presence of histologically confirmed preinvasive breast lesions. In particular, a locally diffuse, heterogeneous (patchy), poorly circumscribed increased uptake—predominantly with $^{99m}$Tc-(V)DMSA and to a lesser degree but more specifically with $^{99m}$Tc-sestamibi—was associated with in situ carcinoma, both ductal and lobular. This uptake was independent of the presence of suggestive microcalcifications on mammography, because it occurred in several lesions mammographically classified as class 3 or even class 2 in some cases, according to the Breast Imaging Reporting and Data System (*3*). A similar diffuse uptake pattern, although not patchy but more homogeneous, was observed in some benign but highly proliferative and potentially premalignant cases of usual-type or atypical-type breast hyperplasia, but never in the benign lesions of fibrosis, adenosis, or ductal dilatation (*2*).

Furthermore, the intensity of diffuse $^{99m}$Tc-(V)DMSA uptake in both ductal and lobular carcinoma in situ and hyperplastic breast lesions was found to be related to their proliferative activity, as immunohistologically demonstrated by Ki-67 expression (*2*); that is, preinvasive—in situ or hyperplastic—breast lesions at high risk of evolving to invasive malignancy are associated with this particular $^{99m}$Tc-(V)DMSA uptake pattern. This finding is in accordance with in vivo (*4*) and in vitro (*5*) reports that associate $^{99m}$Tc-(V)DMSA uptake with cellular proliferation activity in invasive breast cancer. With regard to $^{99m}$Tc-sestamibi, although it appears to be less sensitive in displaying this diffuse distribution in ductal or lobular carcinoma in situ (probably because its cellular uptake is not stringently associated with proliferative activity (*4,6,7*), it maintains a higher specificity than $^{99m}$Tc-(V)DMSA in imaging in situ carcinoma, because its degree and intensity of uptake by nonmalignant breast hyperplasia are considerably lower (*2*).

It might therefore be useful if the reading of both planar and tomographic (SPECT) scintimammography studies incorporated not only the typically pathologic sites of focal tracer accumulation but also regions of diffuse uptake suggestive of preinvasive abnormalities. A scoring system for scintimammography that would classify the scintigraphic findings in proportion to their likelihood for malignancy in mammography, in a way similar to that in which the Breast Imaging Reporting and Data System classifies mammographic findings (*3*), might prove useful in increasing the diagnostic accuracy of scintimammography to detect invasive and preinvasive breast carcinoma, both at initial presentation and at suspected relapse after treatment. In such a diagnostic approach, any focally increased radiotracer uptake (with or without a coexistent diffuse uptake pattern) could be characterized as highly suggestive of invasive malignancy, with or without a preinvasive component (class 4); a diffuse inhomogeneous radiotracer distribution could be characterized as suggestive of a preinvasive lesion (class 3); a diffuse homogeneous uptake could be characterized as probably benign (epithelial hyperplasia) (class 2); and a study without any increased uptake could be characterized as negative (class 1). Hence, a class 3 patient, despite lacking the typical diagnostic criterion of focally increased uptake corresponding to invasive cancer, may be subject to a closer follow-up and possibly a breast biopsy, because it might reveal an underlying in situ or diffuse lobular breast carcinoma.

Conclusively, because scintimammography is an important complement to mammography in patients with suspected breast cancer (*1*) and may also reveal suggestive findings even in mammographically nonsuggestive cases (*2*), we propound that such a scoring system for scintimammography studies deserves to be prospectively evaluated with regard to its reliability in establishing an early and accurate diagnosis as well as in influencing patient management and therapeutic decision making.

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