tion, data on the amount of the storage granules of the chromaffin cells or the differentiation cannot be given. Whether certain subgroups of carcinoids and apudoma are candidates for this procedure has to be evaluated further. We did not obtain any false positive image using MIBG so far. As we observed patients with and without hormonally active tumors, with primary tumor only and recurrence of the disease as well as ones with and without cytostatic therapy, it is likely that these parameters are not the key determinants for a positive imaging (*8*) at least in patients suffering from carcinoid or apudoma.

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Iodine-131 MIBG for Locating Pheochromocytoma

TO THE EDITOR: In a recent paper in the Journal, Shapiro et al. (*1*) presented their reasoning for iodine-131 metaiodobenzylguanidine ([^{131}I]MIBG) scintigraphy as the study of choice to locate suspected pheochromocytoma. This is an interesting and most useful review; however, in our opinion, several points need further discussion.

1. As [^{131}I]MIBG is a functional imaging method, we believe kinetic measurements of MIBG should be part of these studies, for the evaluation of further therapy in primary tumor or metastatic tissue.

2. A significant number of patients (n = 82) were classified as true negative with lesser degree of certainty. In the formula used for sensitivity, specificity, etc. they are classified in the real "true negatives." A receiver operating characteristic analysis would be helpful for medical decision making. We would also like to have seen a comment on the low negative predictive accuracy of 17% in malignant pheochromocytoma.

3. The published scintigraphy (particularly Fig. 1B) with the corresponding confirmation of the endocrine active tumor is less convincing, compared with the figures of Sone et al. (*3*) in the same issue of the Journal, and from our own routine clincial work. We agree with Mahlstedt (*2*) that a standardization of the imaging procedure is needed.

4. Although the role of computed tomography (CT) and angiography is thoroughly discussed, other noninvasive methods, e.g., ultrasound and bone scan are not considered.

In conclusion, the conformity of this overall "Michigan" and the "Combined German" (*2*) experience concerning sensitivity, specificity, and negative and positive predictive accuracy is promising of a major role for MIBG scintigraphy in the investigation of neuroendocrine tumors. Our strategy in the diagnostic workup of pheochromocytoma is: 1. history and physical examination; 2. clinical laboratory studies; 3. ultrasound examination; 4. [^{131}I]MIBG scintigraphy and CT scan; and 5. angiography followed by surgical intervention.

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REPLY: We thank Drs. Schober et al. for their interest in our recent publication (*1*). In response to the points raised in their letter we wish to point out that:

1. The paper addressed the ability of iodine-131 metaiodobenzylguanidine ([^{131}I]MIBG) scintigraphy, a functional imaging modality, to locate pheochromocytoma deposits. Kinetic data is obtained over a period of 7 days to permit the calculation of radiation dosimetry to those lesions which might benefit from therapeutic MIBG administration of MIBG, but this lay outside the scope of the paper.

2. The patients classified as negative with a lower level of certainty were subjected to a separate analysis but both reviewers and the editor felt this confused the issue and suggested their inclusion with the high certainty patients. The criteria are clearly defined in the paper and most fall into this category due to the presence of minor (nondiagnostic) elevations of catecholamines, and with up to 4½ years follow-up, not one

has yet been shown to harbor a pheochromocytoma. The low predictive accuracy in malignant pheochromocytoma is a consequence of the population studied; there were very few patients in which malignant pheochromocytoma was suspected and in which a true-negative scan was obtained.

3. Figure 1 merely documents the definitions of what constitutes grades 0–3 intensity of [^{131}I]MIBG uptake and is not meant to "convince" anyone of the presence of a tumor or not. As stated in the classification criteria, the vast majority of tumors have grade 3, intense uptake (as shown in Fig. 1C). Figure 1B shows minimal uptake which might occur in some normal individuals [but which occurs with higher frequency in MEN patients with adrenal hyperplasia (*2*)] when imaged with the protocol as defined; namely, 0.5 mCi/1.7 m^2 [^{131}I] MIBG, imaging 24, 48, and 72 hr after injection with large field-of-view camera, high-energy collimator, and an image obtained for at least 100,000 cts or 20 min (*1,2*).

4. Ultrasound, in skilled hands, may be helpful in locating certain abdominal pheochromocytomas (intra- and extra-adrenal) but does not permit screening of the entire body (e.g., intra-thoracic and cervical lesions) nor does it lend itself to the location of metastatic deposits. The radionuclide bone scan may be useful in locating skeletal metastases (the commonest site of metastases) but will not reveal soft-tissue tumor deposits. However, a bone scan probably should be obtained in all patients with pheochromocytoma as part of the staging procedure (there being about a 10% chance of malignancy).

5. In general, we fully concur with the sentiments expressed in the final paragraph of Dr. Schober et al.'s letter. We must emphasize again that [^{131}I]MIBG scintigraphy is *not* a technique for the diagnosis of pheochromocytoma. Diagnosis should rest on the clinical and biochemical investigations. The location of the suspected lesion is the next step and should initially be by a noninvasive technique (e.g., [^{131}I]MIBG scintigraphy). Ultrasound may have a role if the skills are locally available, but does suffer from the limitations listed above.

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Technetium-99m DMSA Uptake by Metastatic Carcinoma of the Prostate

TO THE EDITOR: In a recent report, Lamki and Shearer (*1*) observed the visualization of bone metastases from carcinoma of the prostate after technetium-99m (^{99m}Tc) DMSA injection. They discussed some of the possible explanations for their finding such as non specific binding, the similarity between the cytosol proteins in some of malignant tumors and those found in renocortical tubules, and the metallothionein content of the tumor.

The aim of our report is to propose another possible explanation, which is the presence in the [^{99m}Tc]DMSA injected by these authors, of DMSA labeled by ^{99m}Tc of another valence. Indeed, since Lin et al. (*2*) labeled DMSA with ^{99m}Tc, many authors (*3–5*) have studied this radiomolecule and they have concluded that a mixture of various technetiated complexes could appear depending on factors such as the pH, ^{99}Tc carrier, relative concentration of the reagents, delay between the labeling and the analysis (*6*). When the DMSA is labeled with ^{99m}Tc at an alkaline pH and low concentration of $SnCl_2$, it is postulated (*7*) that the radiotracer obtained holds a pentavalent Tc core and is different from the well-known renal scanning agent. The accumulation of this tracer has been observed in some tumors (*8–11*).

Actually, we are evaluating the clinical value of this last tracer for the detection of neoplasic lesions. So far, we studied three patients with carcinoma of the prostate and we found that bone metastases visualized by [^{99m}Tc]methylene diphosphonate (Mallinckrodt Diagnostica) bone scintigraphy showed an increased uptake of [^{99m}Tc] 5 DMSA (Fig. 1).

The hypothesis that the [^{99m}Tc]DMSA used in the above-referred report contained an aliquot of [^{99m}Tc] 5 DMSA is supported by the chromatographic analysis. The thin layer chromatography (Merck Silicagel 60 in n-butanol, acetic acid,

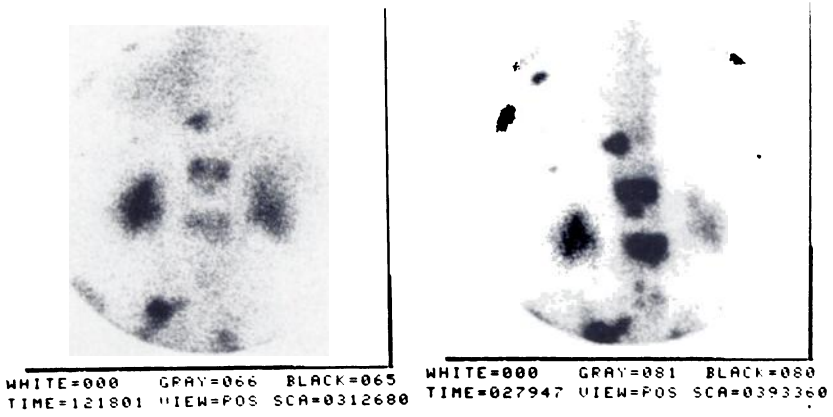

FIGURE 1
Posterior image of lumbar spine taken at 2 hr. Accumulation of [^{99m}Tc] 5 DMSA (left) in areas coinciding with [^{99m}Tc]MDP (right) skeletal lesions