Lesion Detection in Neuroblastoma with Iodine-131-MIBG

TO THE EDITOR: Like Dr. Shulkin and his group, we too have found better lesion detection in neuroblastoma patients with ^{131}I-MIBG compared to ^{99m}Tc-MDP bone scans (*1–3*). Although the comparative sensitivity of these two techniques has been debated in the literature, Shulkin's estimates of both total, osseus and soft-tissue lesions resulting from a comparison of the two techniques were the same as ours (*2,3*). Our series utilized both ^{131}I and ^{123}I. Iodine-123-MIBG was a little better than ^{131}I-MIBG, but much better than ^{99m}Tc-MDP (*2,3*).

The prognosis and treatment strategy of neuroblastoma is strongly dependent on its stage, tumor volume and metastatic lesion location. Therefore, the test that best provides this information optimizes these children's outcome. Since lesion detection even with MIBG is highly dependent on the dose of MIBG administered, MDP bone scans substantially underestimate tumor burden in neuroblastoma patients (*4*). MIBG is tumor specific, thus false-positives are significantly reduced as well. Clearly, from our studies and those of Dr. Shulkin, MIBG is the best agent.

We also found that MIBG scans are easier to interpret than MDP scans for the relatively inexperienced which should extend the improved diagnostic quality of MIBG compared to MDP to community hospitals (*3*). Listening to all this, we wonder why Shulkin continues to teach, "nonetheless, bone scintigraphy remains valuable in the routine evaluation of neuroblastoma . . . "(*1*).

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REPLY: The comments of Drs. Hattner and Parisi are well (but lightly) taken. The following is meant neither to endorse nor justify the routine use of bone scanning for neuroblastoma, but to restate the findings. In fact, any response to the inquiry runs the risk of overstating our enthusiasm for bone scanning in neuroblastoma. Those reservations considered, both of our studies show that MIBG scintigraphy is superior to bone scanning for the detection of skeletal foci from neuroblastoma. We also agree that MIBG better depicts the overall tumor burden. We demonstrated that in each of 77 patients, the two techniques were concordant for the presence or absence of skeletal disease. Although many more lesions were found using MIBG, in no case was staging altered (two patients had abnormal MDP scans in sites of prior surgery or bone marrow biopsy). For staging purposes, a single bone metastasis assigns the patient to the same Stage 4 as multiple lesions and within Stage 4 (with the exception of 4s), there are no subclassifications. So the finding of more bone metastases than a single one neither influences staging nor prognosis.

In addition, approximately 10% of neuroblastomas fail to accumulate MIBG and in these cases bone scanning remains the "gold standard" for evaluating bone involvement. Thus, we agree that MIBG scintigraphy is superior to skeletal scintigraphy for lesion detection; skeletal scintigraphy is somewhat of a "has been" when matched against the current champion, MIBG. Let us not forget, however, that even a "has been" wins when the champion defaults.

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Functional Imaging of Peripheral Vascular Disease

TO THE EDITOR: I read with great interest the paper by Dr. Segall et al. on functional imaging of peripheral vascular disease by whole-body thallium scintigraphy (*1*). If this method seems to be useful in the evaluation of known peripheral arterial disease, its diagnostic performances should be known for two reasons. First, the method has never been used as a diagnostic test in populations where the prevalence of peripheral vascular disease is less than 100%. Second, the diagnostic criteria seem to be rather imperfect because they have been estimated based on a very small group of patients (12 patients in Reference 1) with large confidence intervals. I think this is a real problem not only in clinical practice, but also in other fields of potential applications, such as epidemiological research or prognostic evaluation of multifocal atherosclerosis. Interextremity asymmetry seems to be the most reliable sign in favor of peripheral vascular disease rather than regional uptake in the legs during exercise. Peripheral vascular function is a multifactorial process which depends not only on gender and age, but also on physical training, type and level of exercise. This has been well demonstrated by venous occlusion plethysmography (*2*) in healthy subjects, with regard to age, gender and physical training. In a previous work (*3*), Segall et al. also found that regional thallium activity in the legs decreased in older patients (14 males, 12 females) without clinically patent peripheral vascular disease. Our own

results confirm this trend on a larger scale (*4*). In 59 apparently healthy male nonsmokers aged 19–73 yr (mean = 49.8 ± 13.5 yr), the regional uptake of thallium in the thighs and calves was found to be negatively correlated with age ($r = -0.40$; $p < 0.001$ and $r = -0.23$; $p < 0.05$). Indexes of asymmetry in the calves only were also weakly but significantly correlated with age ($r = 0.23$; $p < 0.05$). This suggests subclinical peripheral vascular disease in some patients although none of them had coronary artery disease or smoking habits. This study shows how difficult it is to define normal values for indexes of asymmetry, particularly in older male patients who have a relatively high prevalence of subclinical atherosclerosis. Nevertheless, asymmetry seems to be a more specific sign of peripheral arterial disease, although it remains to be quantified at each level of the legs with the buttocks being more asymmetric than the thighs and calves. In another study (*5*), 114 male patients with proven coronary artery disease exercised at levels near their maximum capacity. Whole-body thallium scintigraphy showed an asymptomatic interextremity asymmetry in 54% of the cases. The prevalence of this sign increased with age, from less than 14% for those younger than 45 yr to 65% in patients older than 65 yr. These results were obtained by both the lecture of analogic images and quantitative analysis which confirmed (1) the relatively low prevalence of decreased unilateral or bilateral fractional uptake in the whole population and (2) the lack of correlation between the prevalence of this sign and age.

I believe that whole-body thallium exercise scintigraphy has to play an important and growing role in the noninvasive detection of silent or subocclusive peripheral vascular disease and the evaluation of multifocal atherosclerosis. Normal distribution of thallium during exercise in the legs should be more precisely defined and quantified in larger populations. The performance of such a method clearly depends on this fundamental step, at least in its diagnostic applications.

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REPLY: Dr. Tellier states that asymmetry is a more specific sign of peripheral arterial disease than fractional thallium uptake on whole body imaging. This is true, but experience has taught us that the sensitivity and overall accuracy of the study is improved by adding other quantifiable measures such as fractional uptake. Bilateral disease causing a balanced reduction of flow is not rare and would be overlooked if one relied solely on the presence of asymmetry. I was disturbed by Dr. Tellier's finding that 54% of male patients with coronary artery disease who do not have claudication show interextremity thallium asymmetry. It would be important to know the degree of asymmetry. We have found that an interextremity symmetry ratio of ≤90% is a specific disease marker in asymptomatic older men. I agree with Dr. Tellier that the normal distribution of thallium in the legs following exercise should be studied in larger populations. However, anyone can easily and quickly generate a practice-specific normal data base that can be immediately applied to clinical practice.

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Fluorodeoxyglucose, Myocardial Perfusion and Myocardial Cell Death

TO THE EDITOR: The success of positron emission tomography (PET) in the clinical setting depends upon the credibility factor, i.e., the demonstration that the science behind cardiac PET is sound. Otherwise, PET will be slowed down by uncertainties.

Opie and Camici (*1*) wrote a provocative editorial in the August issue of *JNM* on myocardial blood flow, deoxyglucose uptake (FDG) and myocyte viability in ischemia. Bianco and Wilson also wrote an editorial (*2*) which is pertinent to several sections of the Opie and Camici editorial and is consistent with our experimental findings and with the work of others. I would like to discuss some of the controversial scientific points.

Myocardial Hibernation

This clinical entity, the most important indication for a cardiac PET scan, can be assessed with: PET and FDG, PET and ^{11}C-acetate, the stress/reinjection ^{201}Tl technique or with dobutamine wall motion echocardiography. As Opie and Camici state, and contrary to opinions by others, FDG does not measure the metabolic rate of glucose. In fact, as shown by Lear and Ackermann (*3*), FDG studies underestimate energy production when substrates other than glucose are being metabolized. FDG studies also underestimate energy production when glycolysis occurs. One must note that glucose and FDG may both have differences in affinity for the transmembrane sugar transporter and for hexokinase (*1*). Opie and Camici accurately state that crucial data linking glucose extraction and myocardial blood flow have been missing. Stanley et al. (*4*) showed that after 50 min of myocardial ischemia (blood flow = 40% of control) the rate of glucose uptake in swine did not change, although its extraction was significantly increased, regional blood flow was decreased and delivery of glucose was curtailed. Under these conditions, increased glycolysis is not related to glucose uptake but rather to accelerated glycogen breakdown.

Finally, the data from Bergmann's laboratory (*5*) indicate that FDG activity in reversible as well as in persistently dysfunctional myocardium is markedly variable. Therefore they recommend that ^{11}C-acetate rather than FDG should be used to detect dysfunctional but still viable myocardium in patients likely to benefit from coronary revascularization. The science behind the use of FDG for detecting viability and for predicting improvement after revascularization is in its infancy.