Taking Brain SPECT Seriously: Reflections on Recent Clinical Reports in *The Journal of Nuclear Medicine*

Jack E. Juni

Department of Nuclear Medicine, William Beaumont Hospital, Royal Oak, Michigan

J Nucl Med 1994; 35:1891–1895

Nuclear neurology is exploding. The brain, always the most secretive of body systems, has been revealing itself to nuclear medicine physicians at a hitherto unimagined rate. The unique perspective offered by nuclear medicine—through pharmacologic interventions; noninvasive, in vivo biochemistry; computer analysis—is bringing new tools to the assessment of brain disease. The tools and technology of nuclear medicine are likewise being enriched in return. The literature is replete with applications of SPECT in stroke and cerebrovascular disease, dementia, seizure disorders, traumatic brain injury, drug abuse, AIDS and psychiatric disorders (*1*). Although the great majority of nuclear medicine facilities now perform brain SPECT, most scan only trivial numbers of patients when compared to the large number treated for neurologic disorders. Clinical neurologists, neurosurgeons and psychiatrists do not yet take brain SPECT seriously. *Why not?*

VARIABILITY IN TECHNIQUE

Comparing the images in the medical literature to those produced by their local nuclear practitioner, our clinical colleagues often notice substantial differences. Resolution, filtration and slice orientation often vary greatly. Is the patient preparation and imaging environment local comparable to that in the relevant literature? If not, will scans obtained locally have the same meaning as those in the journals? Most radiologic imaging procedures have been standardized due to longevity of the technique and the actions of specialty societies. Nuclear medicine in general and brain SPECT in particular have lagged behind. The recent paper by Fletcher et al. (*2*) breaks ground in defining a methodology for establishing consensus among experts for performing brain SPECT. They used a modified Delphi technique in which a panel of experts generated and iteratively rated a number of statements regarding tracer preparation and optimal imaging technique. The resulting data provide a framework for production of guidelines, including a quantitative rating of recommendations and a measure of the agreement between experts regarding each statement. While this falls one step short of producing formal practice guidelines, it is an important beginning. The Delphi technique is a creative and practical method for rapid consensus building. As a professional group, the Society of Nuclear Medicine should take the next step of producing formal guidelines and recommendations.

SUBJECTIVITY IN INTERPRETATION

Most clinical nuclear medicine today is qualitative rather than quantitative. The high level of complexity and normal variability in brain structure and functional interrelationships combine to make brain SPECT images among the most difficult to interpret with the unaided eye. The neurologist who receives a report describing ten different defects in a patient he/she knows to be clinically normal will quickly lose confidence in the procedure. What is the sensitivity and specificity of brain SPECT? To be truthful, nobody knows. Although several studies have looked at the ability of SPECT to differentiate selected populations with a single disease from normals (*3,4*), there is virtually no published data on the ability of SPECT to distinguish normal individuals from a group of neurologically impaired "unknowns." Such studies must be done.

What Is Normal?

A clear and unequivocal knowledge of what represents normal brain perfusion is an absolute prerequisite to objective interpretation of scans and assessment of the accuracy of such interpretations. The extent of anatomic variability must be recognized and accounted for. Normal perfusion and the acceptable limits of variability at each region must be mapped and recognized. Acquiring such a knowledge base is the key task of a nuclear medicine trainee. The appreciation of normal patterns and variability is the accumulated result of observations from a large number of

Received July 5, 1994; revision accepted Sept. 7, 1994.
For correspondence or reprints contact: Jack E. Juni, MD, Department of Nuclear Medicine, William Beaumont Hospital, 3601 West 13 Mile Rd., Royal Oak, MI 48073-6769.

"normal" scans. How do we know such scans are truly normal? We usually do not. In clinical practice, few of us even see normal scans. Patients are not imaged unless they have signs or symptoms of neuropathology. Even patients with no apparent scan defects cannot be considered truly normal in that they had some sort of symptoms. In the actual training experience, we do not have the opportunity of viewing normal scans. Rather, we attempt to learn from the *most normal* areas of abnormal scans and to assemble from these pieces a mental prototype of what is actually normal.

Several research centers have acquired large series of scans on truly normal individuals, i.e., volunteers without neurologic symptoms who have normal neurologic exams and neuropsychiatric testing and have no history of head trauma, drug abuse, etc. These collections of normal scans represent a true buried treasure, extremely valuable yet almost totally inaccessible. There are two ways to redistribute this wealth: (1) converting the image data to a quantitative form that can be transmitted and clinically applied by computer and (2) making the actual image data available to the nuclear medicine community.

The Computerized Normal Database

A series of papers appearing recently in the *Journal* have addressed the first of these options. Minoshima et al. (*5*) have defined an atlas of normal structures on FDG PET images which may be used with SPECT images as well. This set of high-quality images defines normal structures and correlates them with the widely recognized Talairach and Tournoux stereotactic neurosurgical atlas (*6*). However, only a single patient is represented. A reasonable approach to producing a computerized normal database would seem to be to align and superimpose a number of normal scans and average corresponding points together. Prior to such analysis, each individual image must be scaled and reoriented in three dimensions so that like regions are overlayed (*7*). The alignment of multiple studies for comparison is a major problem. The Pelizzari technique (*7*) and its many derivatives iteratively rotate two brain image sets and look for correlation of surface contours. Various positions are evaluated until the one providing the best correlation is found. Other researchers (*8–11*) have aligned internal structures such as the anterior commissure-posterior commissure line. Such methods combined with statistical analysis of differences between the clinical image and the reference image have proven quite effective, particularly in PET imaging (*12–14*).

In the May issue of the *Journal*, Crosson et al. (*15*) outlined their system using external fiducial markers to align individual SPECT and MRI slices. The MRI scan was then used for initial placement of ions of interest (ROIs). Unlike other methods, however, ROI placement was further refined by iteratively moving the region across the cortex on the SPECT image to locate the peak of activity in the cortical ribbon. Using this method, they compared SPECT scans obtained during visual activation to those obtained in the same patient under baseline conditions, thus using each patient as their own normal. Use of these finely adjusted ROIs resulted in significantly better ability to detect subtle changes in brain perfusion between two studies than did region placement by MRI alone. Presumably, use of a similar technique would enable better correlation between regional activity in a given patient study and that in a synthesized normal image.

To avoid subjectivity, alignment of scans is typically performed by an automated computer algorithm, yet no computer can replace the expertise of a trained human observer in recognizing and compensating for technical peculiarities, anatomic variability and the functional alterations of disease. Pietrzyk et al. (*16,17*) have developed a set of digital tools strictly for visual co-registration of image sets and have shown it to have an accuracy and consistency comparable to the automated methods. These tools include a variety of approaches to edge enhancement and data display designed to provide rapid interactive feedback while real-time adjustments to scan rotation, translation, etc. are made. Although it remains to be seen whether automated or manual methodologies will become more popular, the ability to combine large numbers of scans into smaller, comprehensible datasets is clearly important.

Simply scaling brain images to the same size and rotating them to the best fit does not result in a perfect alignment. The shape of individual heads differs. The location of each sulcus and gyrus differs slightly from person to person. Since the cortical ribbon is quite thin, averaging data together from different brains results in substantial image degradation. Minoshima et al. (*18*) developed an important technique for avoiding this problem. They first scale and rotate the image sets for best alignment. Following this, however, they perform an additional nonlinear warping of the images. This means that one portion of the image is stretched more than other parts to provide an optimum match. Minoshima has defined "stretching centers" in order to assure that the stretching is done in an anatomically and developmentally reasonable manner. By performing this additional correction for anatomic differences between individuals, this group was able to produce a marked reduction in the apparent normal variability between subjects, thus indicating that much of this variability was in fact due to differences in brain shape rather than differences in function. Using this technique to derive a database of true normals should result in a substantial reduction in the measured limits of normal variability and thus improve sensitivity for detecting subtle lesions. Not surprisingly, Minoshima and colleagues found that use of this nonlinear warping technique improved their ability to detect activation foci and improved their ability to separate a group of Alzheimer's disease patients from normals.

Detecting Variations from Normal

The above-mentioned work provides us with a strong technical foundation for defining normal in a quantitative sense. A key test of computer-based techniques will be

their ability to reliably detect lesions at low thresholds without loss of specificity. Stapleton et al. (*19*) assess the level at which trained human observers deemed single focal count asymmetries to be clinically significant. They found that a rather severe defect (5%–10%) was required for detection. If such severe deficits were required in clinical practice, the sensitivity of scanning in mild disease would be quite poor. One way skilled observers can lower their diagnostic thresholds while maintaining specificity is to look for patterns in images. Although count reductions in individual regions of brain may differ only marginally from normal, recognition of a typical clinical pattern of deficits can result in a confident diagnosis.

Computer-assisted image interpretation in nuclear medicine has tended to follow three paths—compare activity in one part of an image to another and look for a certain ratio, compare activity in a region or regions to a normal database or generate kinetic data. These are not the only approaches available and may, in fact, not be optimal in all circumstances. In the January issue of the *Journal*, Kippenhan et al. (*20*) further pursue their initial explorations of the neural network approach to automated computer pattern recognition. Those of us in the business of reading scans will recognize much of what we do in the actions of a neural network algorithm. One of the key advantages of this approach is that the computer attempts to identify what is most important in making a diagnosis. Given one set of images from a normal population and another from patients with Alzheimer's disease, the network will find the best means of differentiating these two image patterns from each other. The computer works with virtually no preconceived notions and has neither the benefit nor the burden of pathophysiologic knowledge of the disease process in question. It is therefore possible to use this approach to see whether quantitative data adds anything to the question at hand. In the simple classification of normals and patients with Alzheimer's disease, absolute levels of regional metabolism proved not to be helpful. What was most important was the relative activity in some regions when compared to others or to the entire brain. The neural network algorithm proved effective at recognizing the pattern of Alzheimer's disease; something more than just a measure of parietal uptake or an asymmetry index. This is something with which the average nuclear medicine practitioner can identify. An image is reviewed for patterns; not a single finding, but rather a constellation of findings, nonspecific when taken individually, but diagnostic when taken together. This is the way the human mind works, the way we train our residents to read and the way we must get our computers to function if they are to provide us with a significant level of diagnostic assistance.

In the May issue of the *Journal*, Chan et al. (*21*) extend the work of Kippenhan et al. (*20*) by teaching the network to recognize two different disease patterns: Alzheimer's dementia and polydrug abuse. Unfortunately, they did not investigate the ability of the network to differentiate between those two disease states. Nonetheless, the success of these authors in early work with this easily generalizable technique warrants further investigation.

Houston et al. (*22*) have devised a method using principal component analysis which allows the computer to coalesce a large series of normal scans into a relatively compact digital database. When presented with a new clinical image for interpretation, their algorithm uses the normal data to reconstruct a "nearest normal equivalent" scan, which can then be compared to the clinical image in question. In a sense, the computer is saying, "I once saw a similar case. . . ." The differences between this nearest normal equivalent image and the clinical image are displayed in an error image, which can be analyzed for statistical significance of the differences. Houston found that this technique resulted in substantially higher accuracy in the diagnosis of Alzheimer's disease and cerebrovascular disease, as defined by the area under an ROC curve, than an alternate method in which a prototypical normal image was created using the mean activity from each image in the original normal database.

As methods for registration and simultaneous viewing of multiple datasets proliferate, practical display issues have clinical significance. In the November issue, Rehm et al. (*23*) explore various options for displaying merged MRI and functional brain images on the 8-bit displays routinely used in nuclear medicine. These displays limit the number of gray or color levels available and pose particular limitations when two images are to be displayed simultaneously. A variety of creative approaches to overcoming these limitations are proposed.

All normals are not alike. There are clear age-related changes in cortical perfusion that must be recognized in clinical scan interpretation. Interestingly, there has never been a meaningful study comparing cerebral perfusion in men and women. In a remarkable article, Levin et al. (*24*) describe a dramatic difference in the incidence of perfusion deficits in otherwise healthy male versus female cocaine users. Twelve of thirteen drug-abusing men had abnormal scans as opposed to only five of thirteen women. Most abnormalities occurred in the frontal and temporal lobes and the basal ganglia. When users of drugs other than cocaine were excluded, eight of nine male users had perfusion defects compared to only one of nine females. The female group of exclusive cocaine users was virtually indistinguishable from a matched group of normal women. The mechanism for this dramatic gender-related difference in cocaine effect is unclear. Levin discusses the possible contributions of differing levels of estrogens, amount of body fat and incidence of atherosclerosis. Although various psychiatric disorders are associated with perfusion deficits and may differ in incidence between genders, the patients in this study had no evidence of major affective disorders. The potential implications of this study for drug abuse treatment and prevention are great. Measurement of subtler differences between groups will be enhanced by the methods described above.

REDISTRIBUTION OF WEALTH

As important as it is to develop objective means of comparing clinical images to each other and to a normal database, it is even more important that the nuclear medicine community have access to this database. As mentioned previously, it is impractical for most nuclear medicine clinicians to obtain their own large series of normals. For this reason, the Brain Imaging Council of the Society of Nuclear Medicine has recently undertaken to put together a collection of normal data derived from multiple institutions and obtained on several makes of equipment. These data will be collected and distributed in electronic form as raw, unprocessed projection data, which will permit an individual user to process the data in a manner identical to that of their clinical practice. Patient data will be accepted from all willing institutions and must be accompanied by a thorough description of the patient's screening and identification process as well as appropriate demographic information (age, sex, right or left handedness, etc.). A similar project has been started in Europe to create a cardiac database (*25*). The Council hopes that in addition to providing a resource for individual clinicians and investigators, the brain SPECT database will free commercial equipment vendors from the expensive and difficult process of developing their own normal databases to accompany image quantitation software. Commercial support for this project is being sought. It is anticipated that separate databases will be acquired for ^{99m}Tc-HMPAO and ^{99m}Tc-bicisate. Data will also be segregated initially according to equipment manufacturer. Readers interested in participating in this effort should contact the author.

DOES BRAIN SPECT PROVIDE ADDITIONAL INFORMATION TO THAT PROVIDED BY EXISTING METHODS?

Unless it does, we are unlikely to gain a real foothold in clinical practice. A number of studies in trauma have shown that brain perfusion SPECT reveals lesions that are larger and more numerous than on CT (*26–29*). Is this clinically relevant? The recent paper by Jacobs et al. (*30*) provides evidence that it is. This group evaluated patients following mild to moderate acute head trauma and found that SPECT imaging had a high negative predictive value for clinical outcome. That is, when the initial SPECT scan was negative, 32/33 (97%) patients had resolution of all clinical symptoms 3 mo postinjury. In their series, 95% of patients with clinical symptoms at 3 mo had a positive scan. These findings may have important implications in triage of patients to rehabilitation therapy, prediction of patients' ability to return to work, and may have significant medicolegal liability implications (*31,32*).

Ichise et al. (*33*) take the important step of correlating neuropsychological testing with brain imaging. In their evaluation of patients with chronic traumatic brain injury, the presence of abnormalities on brain SPECT correlated with performance on a number of neuropsychological tests. In particular, they found that the ratio of anterior activity to posterior activity predicted the degree of neuropsychological deficit. In contrast, a morphologic parameter associated with traumatic brain injury, the ventricle-to-brain ratio, correlated poorly with neuropsychological testing. A recent contrasting study by Goldenberg et al. (*34*) revealed a much looser correlation between SPECT and neuropsychological testing. Studies such as these, correlating the functional outcome with SPECT findings are crucial to determine the ultimate role of brain SPECT in traumatic brain injury patients.

Despite the relative lack of specificity of many brain perfusion patterns, functional neuroimaging is garnering an ever increasing role in litigation. Documenting the presence or absence of brain injury, whatever the cause, is critical to many liability lawsuits. Although behavioral and neuropsychological testing is routinely used for this purpose, it is expensive, time-consuming, and lacks the objectivity desired when large sums of money are in dispute. Increasingly, practitioners of nuclear neurology have found themselves sought out by the legal profession to testify to the presence, extent and cause of brain injury. We can make a great contribution to some of these questions but very little to others. As we have discussed, defining the presence and extent of brain abnormalities is a challenging endeavor. Ascribing these abnormalities to a particular etiology or disease entity is often much more difficult. When viewing a scan showing bifrontal perfusion deficits in a patient with a history of head trauma, is it appropriate to state that the scan reveals "traumatic injury"? Mayberg et al. (*35*) recently reported a very similar pattern in unipolar depression. Goldenberg et al. (*34*) have reported thalamic hypoperfusion in trauma. Lill et al. (*36*) reported an identical pattern in manganese toxicity. AIDS encephalopathy, chronic fatigue syndrome and drug abuse can produce multiple focal defects similar to those described in many of the reports of trauma (*37,38*). Some clinicians have claimed that exposure to chemicals such as pesticides, glues and solvents result in specific, identifiable patterns on brain SPECT (*39*). Others strongly dispute this.

As we move forward in the clinical arena, we must be prudent. Overstating the specificity of various diagnostic patterns may transiently "increase business," but in the long run damage the credibility of our technique. It behooves us to remember the meteoric rise and fall of thermography and computerized electroencephalographic brain mapping. Must we, then, hedge all our diagnostic calls? Certainly not. In the appropriate clinical context, many disease entities can be specifically diagnosed with confidence. These include temporal lobe epilepsy, many dementias, cerebrovascular disease and other entities. Often, however, it is most appropriate for us to simply describe the perfusion defects seen and present a list of possible causes. While it may be possible in a given case to state that a particular scan defect is consistent with certain

behavioral abnormalities, it is generally not possible to state with confidence that the two are causally related.

CONCLUSION

In summary, reports in this year's *Journal* have brought us significantly closer to being taken seriously by our clinical colleagues. Important advances have been made in defining normal brain perfusion and condensing such descriptions into usable digital formats. Although we are not yet where we hope to be, significant progress has been made toward standardizing technique, objectifying our findings, identifying the perfusion patterns associated with various disease entities and correlating these patterns with clinical outcome. This is an exciting time to be a nuclear neurologist. We will be taken as seriously as we take ourselves.

REFERENCES

1. Holman BL, Devous MD. Functional brain SPECT: the emergence of a powerful clinical method. *J Nucl Med* 1992;33:1888–1904.
2. Fletcher JW, Woolf SH, Royal HD. A consensus-development method for producing diagnostic procedure guidelines: SPECT brain perfusion imaging with Tc-99m HMPAO. *J Nucl Med* 1994;35:2003–2010.
3. Johnson KA, Holman BL, Rosen TJ, et al. Iofetamine I-123 single-photon emission computed tomography is accurate in the diagnosis of Alzheimer's disease. *Arch Intern Med* 1990;150:752–756.
4. Holman BL, Johnson KA, Garada B, et al. The scintigraphic appearance of Alzheimer's disease: a prospective study using technetium-99m-HMPAO SPECT. *J Nucl Med* 1992;33:181–185.
5. Minoshima S, Koeppe RA, Frey KA, et al. Stereotactic PET atlas of the human brain: aid for visual interpretation of functional brain images. *J Nucl Med* 1994;35:949–954.
6. Talairach J, Tournoux P. *Co-planar stereotaxic atlas of the human brain*. New York: Thieme; 1988.
7. Pelizzari CA, Chen GT, Spelbring DR, et al. Accurate three-dimensional registration of CT, PET, and/or MR images of the brain. *J Comput Assist Tomogr* 1989;13:20–26.
8. Friston KJ, Passingham RE, Nutt JG, et al. Localization in PET images: direct fitting of the intercommissural (AC-PC) line. *J Cereb Blood Flow Metab* 1989;9:690–695.
9. Minoshima S, Berger KL, Lee KS, Mintun MA. An automated method for rotational correction and centering of three-dimensional functional brain images. *J Nucl Med* 1992;33:1579–1585.
10. Junck L, Moen JG, Hutchins GD, et al. Correlation methods for the centering, rotation and alignment of functional brain images. *J Nucl Med* 1990;31:1220–1226.
11. Minoshima S, Koeppe RA, Mintun MA, et al. Automated detection of the intercommissural line for stereotactic localization of functional brain images. *J Nucl Med* 1993;34:322–329.
12. Fox PT, Perlmutter JS, Raichle ME. A stereotactic method of anatomical localization for positron emission tomography. *J Comput Assist Tomogr* 1985;9:141–153.
13. Fox PT, Mintun MA, Reiman EM, Raichle ME. Enhanced detection of focal brain responses using intersubject averaging and change-distribution analysis of subtracted PET images. *J Cereb Blood Flow Metab* 1988;8:642–653.
14. Friston KJ, Frith DC, Liddle PF, Frackowiak RSJ. Comparing functional (PET) images: the assessment of significant change. *J Cereb Blood Flow Metab* 1991;11:690–699.
15. Crosson B, Williamson DJG, Shukla SS, et al. A technique to localize activation in the human brain with technetium-99m-HMPAO SPECT: a validation study using visual stimulation. *J Nucl Med* 1994;35:755–763.
16. Pietrzyk U, Herholz K, Heiss W-D. Three-dimensional alignment of functional and morphological tomograms. *J Comput Assist Tomogr* 1990;14:51–59.
17. Pietrzyk U, Herholz K, Fink G, et al. An interactive technique for three-dimensional image registration: validation for PET, SPECT, MRI and CT brain studies. *J Nucl Med* 1994;35:2011–2019.
18. Minoshima S, Koeppe RH, Frey KA, Kuhl DE. Anatomical standardization: linear scaling and nonlinear warping of functional brain images. *J Nucl Med* 1994;35:1528–1537.
19. Stapleton SJ, Caldwell CB, Leonardt CL, Ehrlich LE, Black SE, Yaffe MJ. Determination of thresholds for detection of cerebellar blood flow deficits in brain SPECT images. *J Nucl Med* 1994;35:1547–1555.
20. Kippenhan JS, Barker WW, Nagel J, Grady C, Duara R. Neural network classification of normal and Alzheimer's disease subjects using high-resolution and low-resolution PET cameras. *J Nucl Med* 1994;35:7–15.
21. Chan KH, Johnson KA, Becker JA, et al. A neural network classifier for cerebral perfusion imaging. *J Nucl Med* 1994;35:771–774.
22. Houston AS, Kemp PM, Macleod MA. A method for assessing the significance of abnormalities in HMPAO brain SPECT images. *J Nucl Med* 1994;35:239–244.
23. Rehm K, Strother SC, Anderson JR, et al. Display of merged multimodality brain images using interleaved pixels with independent color scales. *J Nucl Med* 1994;35:1815–1821.
24. Levin JM, Holman BL, Mendelson JH, et al. Gender differences in cerebral perfusion in cocaine abuse: ^{99m}Tc-HMPAO SPECT study of drug abusing women. *J Nucl Med* 1994;35:1902–1909.
25. Bourguignon MH, Sochor H, Sokole EB. An European nuclear cardiology database [Abstract]. *J Nucl Med* 1994;35(suppl):176P.
26. Abdel-Dayem HM, Sadek SA, Kouris K, et al. Changes in cerebral perfusion after acute head injury: comparison of CT with Tc-99m-HMPAO SPECT. *Radiology* 1987;165:221–226.
27. Roper SN, Mena I, King WA, et al. An analysis of cerebral blood flow in acute closed-head injury using technetium-99m-HMPAO SPECT and computed tomography. *J Nucl Med* 1991;32:1684–1687.
28. Gray B, Ichise M, Chung D-G, et al. Technetium-99m-HMPAO SPECT in the evaluation of patients with a remote history of traumatic head injury: a comparison with x-ray computed tomography. *J Nucl Med* 1992;33:52–58.
29. Newton MR, Greenwood RJ, Britton KE, et al. A study comparing SPECT with CT and MRI after closed head injury. *J Neurol Neurosurg Psych* 1992;55:92–94.
30. Jacobs A, Put E, Ingels M, Bossuyt A. Prospective evaluation of technetium-99m-HMPAO SPECT in mild and moderate traumatic brain injury. *J Nucl Med* 1994;35:942–947.
31. Tikofsky RS. Evaluating traumatic brain injury: correlating perfusion patterns and function [Editorial]. *J Nucl Med* 1994;34:227.
32. Tikofsky RS. Editorial: Predicting outcome in traumatic brain injury: what role for rCBF/SPECT? *J Nucl Med* 1994;35:947–948.
33. Ichise M, Chung DG, Wang P, et al. Technetium-99m-HMPAO SPECT, CT and MRI in the evaluation of patients with chronic traumatic brain injury: a correlation with neuro-psychological performance. *J Nucl Med* 1994;35:217–226.
34. Goldenberg G, Oder W, Spatt J, Podreka I. Cerebral correlates of disturbed executive function and memory in survivors of severe closed head injury: a SPECT study. *J Neurol Neurosurg Psych* 1992;55:362–368.
35. Mayberg HS, Lewis PJ, Regenold W, Wagner HN. Paralimbic hypoperfusion in unipolar depression. *J Nucl Med* 1994;35:929–934.
36. Lill DW, Mountz JM, Darji JT. Technetium-99m-HMPAO brain SPECT evaluation of neurotoxicity due to manganese toxicity. *J Nucl Med* 1994;35:863–866.
37. Holman BL, Garada B, Johnson KA, et al. A comparison of brain perfusion SPECT in cocaine abuse and AIDS dementia complex. *J Nucl Med* 1992;33:1312–1315.
38. Schwartz RB, Komaroff AL, Garada BM, et al. SPECT imaging of the brain: comparison of findings in patients with chronic fatigue syndrome, AIDS dementia complex and major unipolar depression. *AJR* 1994;162:943–951.
39. Heuser G, Mena I, Thomas C, Alamos F. Cerebral blood flow in patients exposed to neurotoxic chemicals [Abstract]. *J Nucl Med* 1994;35(suppl):210P.