Single-Photon Emission Computed Tomography in Human Immunodeficiency Virus Encephalopathy: A Preliminary Report

Joseph C. Masdeu, Anthony Yudd, Ronald L. Van Heertum, Michael Grundman, Emmanuel Hriso, Ralph A. O'Connell, Dana Luck, Ugur Camli, and Lambert N. King

Departments of Neurology, Nuclear Medicine, Psychiatry and Medicine, St. Vincent's Medical Center of New York, and New York Medical College, New York

Depression or psychosis in a previously asymptomatic individual infected with the human immunodeficiency virus (HIV) may be psychogenic, related to brain involvement by the HIV or both. Although prognosis and treatment differ depending on etiology, computed tomography (CT) and magnetic resonance imaging (MRI) are usually unrevealing in early HIV encephalopathy and therefore cannot differentiate it from psychogenic conditions. Thirty of 32 patients (94%) with HIV encephalopathy had single-photon emission computed tomography (SPECT) findings that differed from the findings in 15 patients with non-HIV psychoses and 6 controls. SPECT showed multifocal cortical and subcortical areas of hypoperfusion. In 4 cases, cognitive improvement after 6–8 weeks of zidovudine (AZT) therapy was reflected in amelioration of SPECT findings. CT remained unchanged. SPECT may be a useful technique for the evaluation of HIV encephalopathy.

J Nucl Med 1991; 32:1471–1475

Initial manifestations of AIDS dementia complex or HIV encephalopathy are usually subtle, such as mental fatigue and difficulty reading (*1–6*). Increasing apathy along with mental slowing may be mistaken for depression, and paranoid ideation mimicking a psychosis occasionally heralds the presence of the disorder. The differentiation between a functional depression or psychosis and an early manifestation of HIV encephalopathy is not easy to make clinically and yet it has important implications for treatment. Neuroleptics, used for the treatment of psychosis, are more likely to cause serious extrapyramidal symptoms in patients with AIDS (*7*). Early documentation of HIV encephalopathy is important because zidovudine (AZT) has been shown to ameliorate cognitive dysfunction, albeit often temporarily (*8*). Alternate doses of AZT, or more effective forms of therapy may be needed to effect lasting improvement. However, given the complications of AZT therapy at the dose shown to be effective for encephalopathy, the indiscriminate use of high-dose AZT in HIV-positive subjects with psychiatric manifestations cannot be recommended (*9,10*). Given the prognostic and therapeutic differences between HIV encephalopathy and psychogenic changes in mentation, it becomes important to have a tool that can help differentiate these two entities. CT or MR are useful insofar as they rule out other brain processes that could be responsible for cognitive changes, such as toxoplasmosis or lymphoma (*11*). Unfortunately, these tests show nonspecific findings in HIV encephalopathy and early in the course of the disease both MR and CT are typically normal (*4,12*). Nonspecific, subtle electroencephalographic changes in background rhythm occur early in HIV encephalopathy, but their interpretation becomes clear only by comparing tracings performed months apart (*13*).

Positron emission tomography (PET) is more sensitive than CT or MR to the early changes of HIV encephalopathy (*14*). PET has been recently used to document improvement of HIV encephalopathy in patients treated with AZT (*15,16*). SPECT, like PET, provides information on regional brain perfusion, closely linked to cerebral metabolism. SPECT may be superior to either CT or MR for the diagnosis of HIV encephalopathy and, unlike PET, is inexpensive and widely available. In addition SPECT is easier to obtain than PET in patients who are poorly cooperative.

This preliminary study was designed to determine whether SPECT can help differentiate HIV encephalopathy from psychiatric disorders and whether improvement in clinical status with medication is reflected in normalization of SPECT pattern.

SUBJECTS AND METHODS

The study was performed by retrospective review of the clinical history, CT, and SPECT studies of 32 HIV-positive individuals and 21 individuals with no risk factors for HIV infection or

Received Jul. 23, 1990; revision accepted Jan. 9, 1991
For reprints contact: Joseph C. Masdeu, MD, Department of Neurology, St. Vincent's Medical Center, 153 West 11th St., New York, NY 10011.

neurologic disorders (15 with non-AIDS psychoses and 6 normal controls). A final diagnosis was reached after considering clinical presentation, laboratory data including HIV serology for the HIV-positive subjects, response to medication and clinical outcome. HIV-positive individuals who had a prior history of psychiatric disorder or any focal brain lesion on CT were excluded. Risk factors for HIV infection were homosexuality (28 cases) and intravenous drug abuse in the past (5 cases). At the time of performance of the first SPECT study, the distribution of patients according to the stages of HIV infection (CDC classification) was as follows: 4 in Stages II and III; 5 in Stage IV; and 23 had AIDS. Demographic characteristics of the patients and controls are indicated in Table 1.

Clinical chart review was performed by two neurologists. Cognitive status was estimated from the neurological examination and other information available in the clinical record. Cognitive impairment was rated, using a modification of the criteria given by Navia et al. (*4*), as 0 (normal cognition), 1 (mild attentional deficit or difficulty with forward planning), 2 (moderate attentional deficit and/or mild memory loss, with ability to perform activities of daily living) or 3 (severe impairment in multiple areas of cognition, precluding performance of activities of daily living). None of the patients had lateralized motor findings, but five had gait impairment and spasticity or paratonia in the lower extremities. Motor function was graded as 0 (normal), 1 (increased tone, reflexes or present Babinski sign in the absence of functional impairment), 2 (mild functional impairment not interfering with activities of daily living), or 3 (functional impairment interfering with activities of daily living). A clinical severity score was defined as the sum of the cognitive and motor scores.

SPECT studies were performed with [^{123}I]iodoamphetamine as previously described (*17*). In brief, after informed consent was obtained, all patients received potassium iodine (Lugol's Solution, one drop three times per day prior to and for three days after the study) and 111-185 MBq of [^{123}I]iodoamphetamine. Thirty minutes later the patients were scanned with a General Electric (Milwaukee, WI) 400 ACT cutoff head gamma camera connected to a Star II computer system. Using low-energy, all-purpose collimators, the data were collected in 128 projections of a circular orbit (maximum radius of rotation 14.5 cm) perpendicular to Reid's baseline for 20 sec per projection, with a hardware zoom magnification factor of 1.6 into a 64 × 64 matrix. The data were then uniformity corrected, Butterworth filtered (frequency parameter 0.40–0.43 cycles/cm, power factor 10) and then attenuation corrected ($\mu = 0.12$ per cm). The data were then filtered backprojected to obtain transaxial slices, with subsequent reoriented coronal and sagittal planes obtained. The final data were presented in a two-pixel width format.

CT and SPECT studies were evaluated independently by two nuclear medicine physicians unaware of the clinical picture and clinical group classification. Based on our previous experience, SPECT studies were assigned to one of three groups: **HIV** (heterogeneous cortical uptake, with or without focal defects; multifocal subcortical defects; decreased uptake in the subcortical white matter), **non-AIDS psychosis** (homogeneous uptake throughout the cortex; possible decreased uptake in the frontal lobe and increased focal temporal activity; increased uptake in the caudate nuclei), or **normal**. Subsequently, SPECT studies of HIV-positive individuals were qualitatively evaluated by two nuclear medicine physicians blinded to the clinical status of the patients. The scans were scored according to abnormalities of the cortex and white matter. The cortical pattern was scored as 0 (normal), 1 (mild inhomogeneity or thinning), 2 (inhomogeneous and thinned), or 3 (segmental defects) as shown in Figure 1. The white matter grading was performed in conjunction with CT scans in order to exclude ventricular dilation as a cause of decreased activity in the SPECT images. The white matter pattern was scored as 0 (normal), 1 (mildly enlarged area of periventricular hypoperfusion), or 2 (markedly enlarged area of periventricular hypoperfusion) as shown in Figure 2.

Effect of Medication

In four instances, serial SPECT was performed before and twice while the patient was being treated with AZT. Clinical scores were compared with SPECT scores in a blinded fashion. In one case, serial scores on the Mattis Dementia Rating Scale (*18*) were available.

Statistical Analysis

The agreement between readers with respect to SPECT scan diagnosis was evaluated by calculating the kappa index. Since the underlying distributions of the clinical and SPECT parameters were unknown, no distributional assumptions were made. Accordingly, statistical comparisons of clinical status and SPECT variables were performed using nonparametric statistics (*19*). In order to reduce the probability of Type I errors in multiple comparisons, the overall significance level ($\alpha = 0.1$) was divided by the number of prespecified comparisons ($\kappa = 6$) to yield an adjusted significance level (α/κ) of $p < 0.02$ (Bonferroni's method) (*20,21*). All p values reported are two-tailed.

RESULTS

SPECT Identification of HIV Encephalopathy Versus non-HIV Psychosis and Controls

The interobserver reliability was found to be excellent as indicated by a kappa index of 0.90. Within the 32 HIV-positive patients both readers correctly diagnosed HIV in 30 (94%) of the patients (Table 2). In the remaining two HIV-positive patients both readers diagnosed non-AIDS psychosis in one case but differed in their SPECT scan diagnoses in the other case (with one reader diagnosing HIV and the other reader diagnosing non-AIDS psychosis).

TABLE 1
Study Subjects

Subject group	Number (male/female)	Age mean ± s.d.
HIV-positive	32 (29/3)	38 ± 10
Non-AIDS psychosis	15 (13/2)	33 ± 9
Normal controls	6 (5/1)	41 ± 9

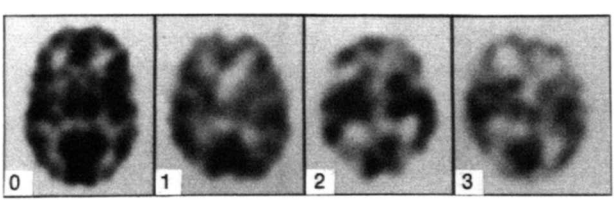

FIGURE 1. Axial SPECT studies illustrating the cortical score from normal (0) to most abnormal (3).

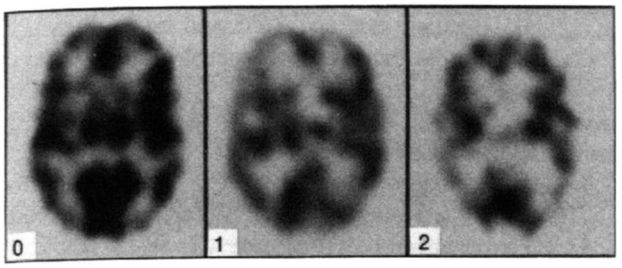

FIGURE 2. Axial SPECT studies illustrating the white matter score, from normal (0) to most abnormal (2).

In the non-AIDS, non-encephalopathy psychosis group, both readers agreed on a diagnosis of non-AIDS psychosis in 12 of 15 patients. Of the remaining three patients with non-AIDS psychosis, both readers diagnosed the scans as normal in two patients, while differing in the third case (with one reader diagnosing the scan as normal and the other diagnosing non-AIDS psychosis). Within the normal control group, both readers diagnosed the scans as normal in all six cases.

In seven of nine HIV-positive individuals with normal cognition, SPECT was read as corresponding to the HIV-positive group by both readers.

Correlation of Clinical Status with SPECT Findings

Of the 32 HIV-positive patients, detailed information on cognitive or motor status enough for comparison with the SPECT data was available in 25 cases. The cortex scores from the two independent readers were concordant in 17 cases, discordant by one grade in 7 cases, and discordant by two grades in one case. The kappa statistic was calculated to be 0.51 denoting a moderate interrater agreement. The results for white matter scoring were concordant in 22 cases and discordant by one grade in three cases. The kappa statistic was calculated to be 0.72, denoting a substantial interrater agreement. Correlation with clinical findings was performed in the 19 cases where both cognitive and motor scores were available. The degree of SPECT abnormalities correlated well with the degree of clinical impairment (Table 3; Figs. 3 and 4). The combined clinical severity score correlated highly with both the cortical (Spearman $r = 0.80$, $p < 0.01$) and the white matter SPECT abnormality scores (Spearman $r = 0.83$, $p < 0.01$).

TABLE 2
SPECT Identification by Independent Readers

Final diagnosis	Number of subjects	SPECT diagnosis	HIV +	Non-AIDS psychosis	Normal controls
HIV +	32	Rater 1	31	1	0
		Rater 2	30	2	0
Non-AIDS psychosis	15	Rater 1	1	12	2
		Rater 2	0	13	2
Normal controls	6	Both raters	0	0	6

TABLE 3
SPECT and Clinical Status (Spearman Correlation Coefficients)

Clinical ratings	SPECT abnormality ratings: Cortex	SPECT abnormality ratings: White matter
Cognitive impairment	0.63	0.79
Motor impairment	0.73	0.51*
Clinical severity score	0.80	0.83

* $p < 0.02$; all others, $p < 0.01$.

SPECT and Improvement with Therapy

In four patients treated with AZT who had serial SPECT, the clinical status correlated with SPECT findings. One of these patients, a 29-yr-old homosexual man, had been HIV-positive for at least 2 yr when he developed increasing attentional disturbances and paraparesis severe enough to prevent ambulation. When evaluated approximately three months after the onset of symptoms he scored 122 on the Mattis Dementia Rating Scale (at the 1 percentile for elderly norms). SPECT at the time showed multiple areas of hypoperfusion in the cortex and basal ganglia bilaterally (Fig. 5, left panels). AZT was given at a dose of 400 mg every 5 hr while awake. In 2 mo the patient improved remarkably. He could ambulate without support and on a repeated Mattis Dementia Rating Scale he scored 141 (70% for elderly norms), showing gains on tasks involving attention, concentration, conceptualization, and memory. SPECT at that time was also improved, with increased perfusion as compared to the one performed 2 mo earlier (Fig. 5, right panels). CT remained unchanged, showing moderate atrophy. In all the other cases clinical

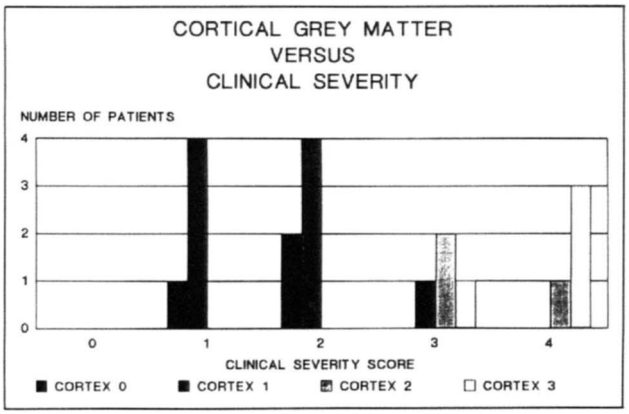

FIGURE 3. Histogram of the distribution of patients with HIV encephalopathy according to clinical severity score, from normal (0) to most abnormal (4) and the degree of cortical perfusion impairment, from normal (0) to most abnormal (3).

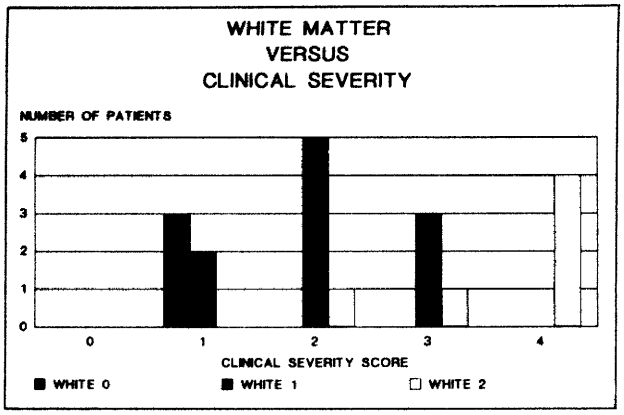

FIGURE 4. Histogram of the distribution of patients with HIV encephalopathy according to clinical severity score, from normal (0) to most abnormal (4) and the degree of white matter abnormality, from normal (0) to most abnormal (3).

amelioration following AZT treatment was reflected by an improvement in the SPECT pattern.

DISCUSSION

Our study shows the usefulness of SPECT as an ancillary technique for the diagnosis of HIV encephalopathy. Using criteria derived from clinical experience, 30 of 32 SPECT studies were correctly classified by both readers. Characteristically, SPECT in HIV encephalopathy shows a heterogeneous pattern of cortical uptake, with or without focal defects, and multifocal subcortical defects. Often there is decreased uptake in the white matter of the hemispheres. SPECT is particularly useful in instances of psychosis or mild attentional impairment or depression in HIV-positive individuals, where the diagnosis of HIV encephalopathy is still unclear.

In a retrospective study with iodoamphetamine-SPECT of 12 HIV-positive patients, Pohl and co-workers (*22*) found unilateral or bilateral lesions in the hemispheres in all their cases. Although comparison with a control group was not performed, they felt that the studies were clearly abnormal in all cases.

Initial reports of abnormal SPECT in clinically normal HIV-seropositive individuals seem to agree with our data (*23*). In seven out of our nine patients without clinically detectable cognitive impairment the SPECT studies were classified by both independent readers as characteristic of HIV encephalopathy. This finding is potentially important for the diagnosis and treatment of this disorder. It must be emphasized, however, that detailed neuropsychologic testing was not performed and subtle impairment may have been missed.

Our study has several methodologic shortcomings. It was not a prospective study. Since uniform neuropsychologic data was not available for most patients, we had to use a simple scale, similarly to other workers in the field (*4,22*). In addition, SPECT data were only semiquantitative. Comparison of regional uptake with cerebellar uptake, a technique that we employed successfully in the study of psychoses, could not be used because HIV frequently involves the cerebellum (*15,24*). It would also be helpful to assess whether similar changes are identified in this disorder with the use of ^{99m}Tc-labeled agents. Further work with a prospective protocol, including neuropsychologic data and SPECT quantitation, is needed to better define the role of SPECT in the diagnosis of HIV encephalopathy.

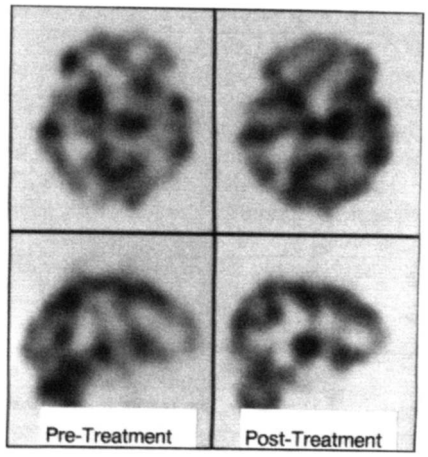

FIGURE 5. Axial (top) and sagittal (bottom) images of the SPECT of a 29-yr-old HIV-positive individual before (left) and after therapy with AZT (right). Neuropsychologic performance and brain perfusion were improved after therapy.

ACKNOWLEDGMENTS

Patient referrals by Drs. Stephen Billick, David Kaufman, and Josh Torgovnick are thankfully acknowledged. We appreciate the contribution of Dr. Mark Nathanson, who psychiatrically evaluated many of the patients.

Presented in part at the 36th Annual Meeting of the Society of Nuclear Medicine, June 13–16, 1989, St. Louis, MO.

REFERENCES

1. Snider WD, Simpson DM, Nielson S, Gold JWM, Metroka CE, Posner JB. Neurological complications of acquired immune deficiency syndrome: analysis of 50 patients. *Ann Neurol* 1983;14:403–418.
2. Levy RM, Bredesen DE, Rosenblum ML. Neurological manifestations of the acquired immunodeficiency syndrome (AIDS): experience at UCSF and review of the literature. *J Neurosurg* 1985;62:475–495.
3. McArthur JC. Neurologic manifestations of AIDS. *Medicine* 1987;66:407–437.
4. Navia BA, Jordan BD, Price RW. The AIDS dementia complex. I. Clinical features. *Ann Neurol* 1986;19:517–524.
5. Centers for Disease Control. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. *MMWR* 1987;36 (suppl):1–15.
6. Price RW, Brew B, Sidtis J, Rosenblum, Scheck AC, Cleary P. The brain in AIDS: central nervous system HIV-1 infection and AIDS dementia complex. *Science* 1988;239:586–592.
7. Edelstein H, Knight RT. Severe parkinsonism in two AIDS patients taking prochlorperazine. *Lancet* 1987;2:341–342.
8. Schmitt FA, Bigley JW, McKinnis R, Logue PE, Evans RW, Drucker JL, the AZT Collaborative Working Group. Neuropsychological outcome of zidovudine (AZT) treatment of patients with AIDS and AIDS-related complex. *N Engl J Med* 1988;319:1573–1578.

9. Richman DD, Fischl MA, Grieco MH, et al. The toxicity of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. *N Engl J Med* 1987;317:192–197.
10. Volberding PA, Lagakos SW, Koch MA, et al. Zidovudine in asymptomatic human immunodeficiency virus infection. A controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. *N Engl J Med* 1990;322:941–949.
11. Post MJD, Sheldon JJ, Hensley GT, et al. Central nervous system disease in acquired immunodeficiency syndrome: prospective correlation using CT, MR imaging and pathologic studies. *Radiology* 1986;158:141–148.
12. Cahill WT, Brey RL, Marshall DW. Neurophysiologic and radiologic evaluation of human immunodeficiency virus (HIV)-infected patients. *Neurology* 1988;38(suppl 1):337.
13. Norcross-Nechay K, Boruchi MJ, Boruchi SJ, Pollard RJ. Definite EEG background changes occur early in HIV-positive patients. *Neurology* 1989;39(suppl 1):361.
14. Rottenberg DA, Moeller JR, Strother SC, et al. The metabolic pathology of the AIDS dementia complex. *Ann Neurol* 1987;22:700–706.
15. Pizzo PA, Eddy J, Fallon J, et al. Effect of continuous intravenous infusion of zodovudine (AZT) in children with symptomatic HIV infection. *N Engl J Med* 1988;319:889–896.
16. Brunetti A, Berg G, Di Chiro G, et al. Reversal of brain metabolic abnormalities following treatment of AIDS dementia complex with 3′-azido-2′,3′-dideoxythymidine (AZT, zidovudine): a PET-FDG study. *J Nucl Med* 1989;30:581–590.
17. O'Connell RA, Van Heertum RL, Billick SB, et al. Single photon emission computed tomography (SPECT) with [123I]IMP in the differential diagnosis of psychiatric disorders. *J Neuropsychiatry* 1989;1:145–153.
18. Mattis S. Dementia rating scale. In: Bellack R, Karasu B, eds. *Geriatric psychiatry*. New York: Grune and Stratton; 1976:108–121.
19. Zar JH. *Biostatistical analysis*. Englewood Cliffs, NJ: Prentice-Hall; 1984.
20. Godfrey K. Statistics in practice: comparing the means of several groups. *N Engl J Med* 1985;313:1450–1456.
21. Neter J, Wasserman W. *Applied linear statistical methods*. Homewood, IL: R.D. Irwin, 1974:472–482.
22. Pohl P, Vogl G, Fill H, Rössler H, Zangerle R, Gerstenbrand F. Single-photon emission computed tomography in AIDS dementia complex. *J Nucl Med* 1988;29:1382–1386.
23. LaFrance ND, Pearlson G, Schaerf F, et al. SPECT imaging with I-123-isopropyl amphetamine in asymptomatic HIV seropositive persons [Abstract]. *J Nucl Med* 1988;29:42.
24. Michaels J, Sharer LR, Epstein LG. Human immunodeficiency virus type 1 (HIV-1) infection of the nervous system: a review. *Immunodeficiency Rev* 1988;1:71–104.

EDITORIAL

HIV Encephalopathy: On The Road to a Useful Diagnostic Test?

Future generations will look back on the AIDS epidemic as one of the most malicious mutations that nature has hurled at the human life form. Yet the course of the disease may play out differently from past plagues. Unless the virulence of HIV-1 takes another malignant turn, the extent of this disaster may be limited by changes in behavior and cultural values. The AIDS epidemic may also be muted by the galaxy of high technologies arrayed against it. If the ravages of AIDS are to be reduced before a vaccine is developed, diagnostic aides and effective therapeutic regimens must be developed. Diagnosis and therapy go hand in hand and it is often the development of the former that leads to meanful progress with the latter.

In an exciting study in this issue of the *Journal*, Masdeu et al. report on the accuracy of SPECT in the retrospective diagnosis of HIV-1 encephalopathy, the most frequent neurologic complication of HIV-1 infection (*1*). They found a high incidence of perfusion abnormalities even in patients with early disease (CDC Groups II and III) using [^{123}I]IMP SPECT. In a prospective study Schielke et al. reported similar results with ^{99m}Tc HMPAO SPECT (*2*). As promising as these studies are, we are only a short way along the road to documenting SPECT's clinical effectiveness.

The validation of any diagnostic test follows a path beginning with invention, standardization and description, leading ultimately to investigations of accuracy, cost effectiveness, and impact on patient outcome (*3*). While it is not possible to leapfrog directly to the multicenter trial or complex outcome studies before standardization, description, and early validation have taken place, it is vital that we not get bogged down on the way to clear answers.

The first reports of a new test typically compare its appearance in diseased patients and normal control subjects. If the test cannot distinguish between these two groups, it is too insensitive and there is no point to further testing. The specificity of a test must also be determined by taking into account other diseases which might mimic the one under study. Masdeu et al. are the first to address the specificity of brain perfusion SPECT for diagnosing HIV encephalopathy by including an abnormal control population. They found a clear separation in brain perfusion between patients with HIV encephalopathy and non-AIDS psychoses. Other confounding and overlapping processes will have to be considered in the future. Approximately 40%–60% of intravenous drug users are seropositive for HIV-1 antibody. Cocaine use among HIV-1 seropositive patients is at least as high as it is in the general population. Chronic polydrug use is associated with widespread focal cortical defects (*4,5*) which may be indistinguishable from the brain perfusion pattern seen in AIDS dementia.

The ultimate subject population for the validation of any diagnostic test must be an accurate replica of the population that will be referred to the test once it has been proved accurate. In the case of AIDS encephalopathy, that population will not include normal subjects and it will not include patients with non-AIDS psychosis. It will be a population made up entirely of HIV-1 seropositive patients. The usefulness of the test will hinge on its ability to distinguish HIV encephalopathy from other neurological complications such as opportunistic infections, metabolic encephalopathies, and vascular disorders and from those

Received Mar. 4, 1991; accepted Mar. 4, 1991.
For reprints contact: B. Leonard Holman, MD, Chairman, Department of Radiology, Brigham and Women's Hospital, 75 Francis St. Boston, MA 02115.