242. Huh MM, Friedhoff AJ. Multiple molecular forms of catechol-O-methyltransferase. *J Biol Chem* 1979;254:299–308.
243. Kastner A, Anglade P, Bounaix C, et al. Immunohistochemical study of catechol-O-methyltransferase in the human mesostriatal system. *Neurosci* 1994;62:449–457.
244. Andersen PH, Gronvald FC, Hohlweg R, et al. NNC-112, NNC-687 and NNC-756: new, selective and highly potent dopamine D1-receptor antagonists. *Eur J Pharmacol* 1992;219:45–52.
245. Inoue O, Kobayashi K, Sakiyama Y, Suzuki T. The effect of benzodiazepines on the binding of [^{3}H]SCH 23390 in vivo. *Neuropharmacol* 1992;31:115–121.
246. Farde L, Ehrin E, Eriksson L, et al. Substituted benzamides as ligands for visualization of dopamine receptor binding in the human brain by positron emission tomography. *Proc Natl Acad Sci USA* 1985;82:3863–3867.
247. Inoue O, Kobayashi K, Tsukada H, et al. Differences in in vivo receptor binding between [^{3}H]N-methylspiperone and [^{3}H]raclopride in reserpine-treated mouse brain. *J Neural Transm* 1991;85:1–10.
248. Kung HF, Pan S, Kung MP, et al. In vitro and in vivo evaluation of [^{123}I]IBZM: a potential CNS D2-dopamine receptor imaging agent. *J Nucl Med* 1989;30:88–92.
249. Kessler RM, Ansari MS, Schmidt DE, et al. High-affinity dopamine D2 receptor radioligands. 2. [^{123}I]epidepride, a potent and specific radioligand for the characterization of striatal and extrastriatal dopamine D2 receptors. *Life Sci* 1991;49:617–628.
250. Pellevoisin C, Chalon S, Zouakia A, et al. Comparison of two radioiodinated ligands of dopamine D2 receptors in animal models: iodobenzamide and iodoethylspiperone. *Life Sci* 1993;52:1851–1860.
251. Laruelle M, Wallace E, Seibyl JP, et al. Graphical, kinetic and equilibrium analyses of in vivo [^{123}I]β-CIT binding to dopamine transporters in healthy human subjects. *J Cereb Blood Flow Metab* 1994;14:982–994.
252. Gatley SJ, Ding Y-S, Volkow ND, et al. Binding of d-threo-[^{11}C]methylphenidate to the dopamine transporter in vivo: insensitivity to synaptic dopamine. *Eur J Pharmacol* 1995;281:141–149.
253. Volkow ND, Fowler JS, Wolf AP, et al. Distribution and kinetics of carbon-11-cocaine in the human body measured with PET. *J Nucl Med* 1992;33:521–525.
254. Scheffel U, Boja JW, Kuhar MJ. Cocaine receptors: in vivo labeling with ^{3}H-(−)cocaine, ^{3}H-WIN 35,065-2 and ^{3}H-WIN 35,428. *Synapse* 1989;4:390–392.

Ethical Clinical Practice of Functional Brain Imaging

Society of Nuclear Medicine Brain Imaging Council
Reston, Virginia

The development and evolution of functional brain imaging technologies and their broad application to a wide range of neurological and psychiatric disorders have led to their scientifically sound use in specific clinical situations. In addition, there is a growing diversity of empirical new applications where there is little previous research or clinical experience. Therefore, a committee of the Brain Imaging Council of the Society of Nuclear Medicine was formed to address the need for specific guidelines regarding scan interpretation and reporting. This committee considered the wide range of current and potential uses of PET and SPECT, including its growing role in forensics. A set of basic guidelines for the reporting and interpretation of brain imaging studies applicable to all clinical situations, including forensics, was formulated. These guidelines were composed in a manner sensitive to the need for standards that are scientifically defensible now, and which will continue to be valid as the field evolves. It is the intent of the committee and this summary document to positively influence the clinical use of brain SPECT and PET by offering guidance concerning the elements essential to a complete and useful clinical report, defining standards to differentiate well-established clinical applications from research uses and providing a framework in which to consider the appropriateness of functional brain imaging used in the forensic arena.

Key Words: PET; SPECT; clinical applications; forensics; guidelines

J Nucl Med 1996; 37:1256–1259

The use of SPECT and PET in the management of patients with stroke, epilepsy, brain tumors and dementia, and in some cases, movement disorders and moderate-to-severe head trauma is now well recognized (*1–9*). Scan abnormalities have also been identified in patients with certain psychiatric diagnoses, including depression, obsessive compulsive and panic disorders, schizophrenia and substance abuse (*10–19*), but consistent patterns for these disorders have not been confirmed. Sensitivity and specificity are often unknown and in many cases, group patterns may actually be too subtle to detect in individual patients.

More elusive or less well-characterized behavioral syndromes have also been studied (*20–29*). In many cases, the patterns are variable and not easily interpreted as being causally related to a particular disease entity (e.g., mild head injury, AIDS, chronic fatigue syndrome, toxic exposures, foreign-body reactions, autoimmune disorders, substance abuse, violence and others) (*30,31*). Furthermore, while specific PET and SPECT defects appear useful to confirm a certain disease diagnosis or to support the localization of a particular clinical finding (*32–35*), there is only limited evidence that specific diseases or neurological, psychiatric or behavioral deficits can be predicted from specific scan patterns (*36,37*). While these types of studies remain extremely important for identifying previously unrecognized brain abnormalities and potential disease mechanisms in a variety of neuropsychiatric illness, their utility in the management of individual patients is still far from clear.

As SPECT and PET become more widely available, enthusiasm tempered by a cautious attitude seems appropriate regarding their use in brain disorders as a whole, given clear evidence that functional patterns are highly dependent on a large number of technical, analytical and physiological variables. The purpose of this document is to provide recommendations and basic guidelines for brain SPECT and PET acquisition, interpretation and reporting, with particular attention to recognized and generally accepted clinical indications, and to urge caution regarding applications in unstudied behavioral disorders.

BASIC METHODOLOGICAL ISSUES

The Society of Nuclear Medicine has recently published technical guidelines on brain SPECT acquisition and image reconstruction (*38,39*). However, even with adherence to these recommendations, the quality of the study will vary from institution to institution and is dependent on several factors, including instrumentation, collimation, filters, behavioral state of the subject during tracer uptake, timing of the scan relative to tracer injection, scan duration, patient movement, attenuation, reconstruction and analytical methods, as well as quality control.

In general, disease patterns are established using specific instruments, physiological measurements and methods of analysis. However, for some situations, the imaging technology available at a particular site may not be sufficient for diagnostic purposes. Accordingly, the degree to which subsequent studies

Received Mar. 12, 1996; accepted Mar. 20, 1996.
For correspondence or reprints contact: Joanna Wilson, Council Coordinator, Society of Nuclear Medicine, 1850 Samuel Morse Dr., Reston, VA 22090.

of similar disease states can be reliably interpreted must be related to published and generally accepted standards. That is, not only should scan interpretation be based on published literature describing a given pattern, but additionally, the physical performance of the instrument on which studies are performed must typically be at or better than that of instruments used to establish that specific application for the technique. For example, a low-resolution instrument appropriate for identifying a large stroke may not be appropriate for localizing or lateralizing a temporal lobe seizure focus, where high resolution is required. Older scanners may at times produce low-resolution, low count rate images which could lead to artifacts in the final image presented for interpretation. Thus, the "certainty" of interpretations (vis-a-vis the literature) should be qualified based on the limitations of the instrument used to generate the image, and so stated in the final report.

SOURCES OF INTERPRETIVE ERROR

There is little debate that classical methods of scan interpretation are subjective, and as such may vary from institution to institution or from individual to individual, due to differences in interpretative experience, general level of expertise (intra- and interobserver variability) or a particular clinical bias. Results can also be influenced by:

- Differences in patient behavioral conditions during the acquisition.
- Processing and display variations.
- Nonstandardized definitions of normal and abnormal.
- Availability of scanner-specific or archived normative databases.
- Nonuniform use of quantitative analyses in conjunction with descriptive readings.
- Availability of few published standards defining the criteria for disease pattern identification.
- Lack of published determinations of sensitivity and specificity for scans to identify specific diseases and syndromes before their routine clinical use.

The concepts of "normality" and "abnormality" as they pertain to scan interpretation need unambiguous definition. In the absence of society-wide recommendations, standards or published norms, laboratories should establish a clear definition of "normal" for their own setting. Studies of normal controls should be performed using a consistent, reproducible but practical behavioral state. Use of confidence intervals and normalization to global or a reference region's counts should be considered in making quantitative judgements about the significance of findings in single patients, and in comparing results across laboratories.

Arguments can also be made for developing "normal" databases. However, data collected on instruments of varying resolutions with standardized acquisition and reconstruction protocols will be required to determine if normal variability is dependent on variables such as age, sex and handedness, as well as educational level, socio-economic status and ethnic or cultural background. That is, comparing an individual subject's data to a normal database may require a large number of individuals in the normative pool so that a false-positive rate can be established (i.e., how frequently a normal is flagged as abnormal). For diseases where no well-defined metabolic or flow "signature" has been identified or where different subjects may have variable patterns of abnormalities (such as head trauma, neurotoxic exposures, AIDS, multi-infarct disease, substance abuse, chronic fatigue, immunological disorders), determining the frequency of false-positive scans will be especially critical (*23,40*).

In reporting clinical results, practitioners should specifically state the criteria used to classify a study as abnormal. The written report should articulate whether the determination was made solely on the basis of a "qualitative reading" of the given images or included the use of a normative database, published reference ranges, regions of interest or statistical analyses.

CAUSATION

While SPECT and PET can clearly be used to delineate functional abnormalities of the brain regardless of the cause (given that normal and abnormal are clearly defined as discussed above), it is only after careful study, as has occurred to date with cerebrovascular disease, dementia and epilepsy, that any cause-and-effect or prognostic associations can be made. The sensitivity and specificity of a measurement are central to this issue. While many diagnostic techniques are known to be highly sensitive, the specificity or causation of a finding may not yet be known and in some cases, cannot be determined. Therefore, a statement should be made whether the degree of certainty of a clinical interpretation is substantiated by published studies, particularly if opinions of causation are offered.

If the relation between an observed image pattern and a clinical problem is uncertain, a statement as to the ability or inability to assign causation should be made based on peer-reviewed, published and generally accepted data. Specific diagnoses based on unpublished, limited or unreplicated studies should, if used at all, be interpreted with extreme caution and the limits of interpretation directly stated. This is particularly critical when the abnormal imaging pattern is nonspecific and cannot be readily ascribed to a single disease entity. For example, while research SPECT and PET studies in patients with mild traumatic brain injury, substance abuse, infectious disease states (such as HIV-related encephalopathies), neurotoxic exposures, environmental illness and foreign-body reactions show promise, there is not, as of this writing, adequate evidence to support the use of SPECT or PET in these instances to establish cause-and-effect relationships.

FORENSICS

The use of functional neuroimaging in forensic situations including criminal, personal injury, product liability, medical malpractice, worker's compensation and "toxic torts," remains especially controversial. When there are few controlled experimental studies and no available sensitivity and specificity rates, the forensic application of nonreplicated, unpublished or anecdotal SPECT or PET observations is inappropriate and has ominous implications. This can lead to unsupportable conclusions if introduced as "objective evidence" linking neurophysiological parameters (such as blood flow or metabolism) to a defendant's judgment, insight or motives associated with the commission of a crime, or as an "offer of proof" of a traumatically caused or substance-induced illness or injury (*31*). With increasing frequency, the courts have rejected the use of scans when performed for less than well-established clinical indications.

It is acknowledged that virtually all diagnostic procedures in medicine will eventually find their way into the courtroom, and it is not the intention of this guideline to recommend that all functional imaging studies should be summarily excluded as evidence in legal proceedings. However, it is important to clarify the court's expectation of physicians who find themselves in these situations. "Experts" are called upon to provide definitive answers with "reasonable medical certainty or prob-

ability." Therefore, the appropriateness of findings and conclusions offered in the form of expert testimony, based on PET or SPECT studies, in any but the few generally accepted clinical situations is difficult and often impossible to substantiate based on the current level of scientific and clinical knowledge (*41*).

Clinical ethics and legal procedure demand the rigid application of "evidentiary tests," as articulated in the Kelly-Frye (*42*) and Daubert (*43*) decisions, in determining admissibility of imaging studies on a case-by-case basis. These Supreme Court rulings have defined specific "rules of evidence" for the determination of admissibility in both Federal and State jurisdictions.

In considering the admissibility of scientific evidence in any legal proceeding, it is necessary to determine whether a given scientific or clinical method is technically adequate, whether a clear distinction can be made between what is termed to be "normal" versus "abnormal," whether sufficient scientific reliability and validity have been established and whether or not there has been demonstrated an accepted efficacy for a specific scientific or clinical application of the tool, technique or method that is to be introduced to the court as evidence (*41,43*). As a part of this determination, expert testimony must be able to adequately demonstrate to the court that the method has been adequately tested in the index situation (or present circumstance) based on substantial peer-review and publications that form the scientific basis for its admissibility. Furthermore, the potential rate of error for the method, as well as the existence and maintenance of standards for controlling its use for clinical applications, must be demonstrated. Similar demands are made for other laboratory procedures applied in forensic situations such as DNA testing, blood typing, electrophysiological measures (EEG) and psychometric tests.

OPERATIONAL PROCEDURES

In view of the above considerations, the Committee has developed operational procedures which serve as basic guidelines for scan interpretation and reporting. The following statements are offered for initiating a practical and consistent mechanism for interpreting and reporting clinical brain SPECT and PET studies.

Each clinical report should include the following:

1. Indications for the study (brief synopsis).
2. Assessment of the technical quality of the scan (good, adequate, poor, including presence of patient movement, deviations from usual lab protocol, etc., if relevant).
3. Description of abnormalities (including criteria for definition of abnormal, i.e., visual inspection criteria, regions of interest, comparison to lab database, reference paper, etc.).
4. Interpretation and conclusions
   A. Explicitly state that the scan interpretation is or is not based on peer-reviewed and generally accepted disease-specific patterns.
   B. Explicitly state whether or not the instrument and methodology used in an individual patient is significantly different than that used to define the disease-specific pattern as defined in (A).
   C. If possible, provide a full differential diagnosis based on (A).
   D. Qualify the scan interpretation in the context of all known clinical history, associated co-morbid conditions, medications and other diagnostic studies (CT, MRI, EEG). Alternatively, state the limitations of the offered differential diagnosis if relevant clinical data are not available, and recommend additional tests, as indicated.

If a study does not conform to the above criteria, the clinical report should include one or more of the following statements, where relevant:

1. The abnormal pattern of increased or decreased activity [in the anatomical area] is a pattern not proven by well-accepted, peer-reviewed published studies to be related to a specific disease entity.
2. The accumulation or reduction of activity [in the anatomical area] could be interpreted as an artifact associated with insufficient resolution or statistical variations.
3. Although abnormalities are present in this study, there are no established cause and effect relationships between these observed abnormalities and the patient's clinical history or behavior in question.

CONCLUSION

This position statement represents the voluntary efforts of a multidisciplinary group of physicians, technologists, neuropsychologists and neuroscience researchers. It is anticipated that these recommendations and guidelines will evolve and change over time as technical, research and clinical advancements continue in the nuclear medicine and general medical communities. We believe this current position reflects a realistic standard for the ethical use of brain SPECT and PET imaging in the clinical and forensic arenas.

ACKNOWLEDGMENTS

Committee Members: Helen S. Mayberg, MD, Chairman, University of Texas Health Science Center, San Antonio, TX; Abass Alavi, MD, University of Pennsylvania, Philadelphia, PA; Frederick J. Bonte, MD, University of Texas Southwestern Medical Center, Dallas, TX; Nicholas Borys, MD, Amersham Healthcare, Chicago, IL; Thomas Budinger, MD, PhD, Lawrence Berkeley Laboratory, University of California, Berkeley, CA; Durval Costa, MD, PhD, Middlesex Hosp, Institute of Nuclear Medicine, London, U.K.; Michael D. Devous, Sr, PhD, Nuclear Medicine Center, University of Texas Southwestern Medical Center, Dallas, TX; Michael M. Graham, PhD, MD, University of Washington, Seattle, WA; Jack E. Juni, MD, William Beaumont Hospital, Royal Oak, MI; Thomas C. Hill, MD, New England Deaconess Hospital, Boston, MA; Jeffrey Schaeffer, PhD, University of California, Los Angeles, CA; Eileen O. Smith, CNMT, MBA, Yale University, New Haven, CT; Ronald S. Tikofsky, PhD, Harlem Hospital/Columbia University, New York, NY; Alan D. Waxman, MD, Cedars Sinai Medical Center, University of California, Los Angeles, CA; Ronald L. Van Heertum, MD, Columbia Presbyterian Med Center, New York, NY.

REFERENCES

1. Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: positron emission tomography. *Neurology* 1991;41:163–167.
2. Holman BL, Devous MD. Functional brain SPECT: the emergence of a powerful clinical method. *J Nucl Med* 1992;33:1888–1904.
3. Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment of brain SPECT. *Neurology* 1996;46:278–285.
4. Fisher RS, Frost JJ. Epilepsy. *J Nucl Med* 1991;32:651–659.
5. Coleman RE, Hoffman JM, Hanson MW. Clinical application of PET for the evaluation of brain tumors. *J Nucl Med* 1991;32:616–622.
6. Duara R, ed. *Positron emission tomography in dementia.* Frontiers of Clinical Neuroscience Series, vol. 10. New York: Wiley-Liss; 1990.
7. Baron JC. Positron tomography in cerebral ischemia. *Neuroradiology* 1995;27:509–516.
8. Brooks DJ. Functional imaging of movement disorders. In: Marsden CD, Fahn S, eds. *Movement disorders, 3.* Boston: Butterworth-Heinemann; 1993:65–87.
9. Ichise M, Chung DG, Wang P, Wortzman G, Gray BG, Franks W. Technetium-99m-HMPAO SPECT, CT and MRI in the evaluation of patients with chronic traumatic brain injury: a correlation with neuropsychological performance. *J Nucl Med* 1994; 35:217–226.

10. Baxter LR, Schwartz JM, Phelps ME, et al. Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Arch Gen Psychiatry* 1989;46:243–250.
11. Mayberg HS, Lewis PJ, Regenold W, Wagner HN. Paralimbic hypoperfusion in unipolar depression. *J Nucl Med* 1994;35:929–934.
12. Baxter LR Jr, Schwartz JM, Mazziotta JC, et al. Cerebral glucose metabolic rates in nondepressed patients with obsessive-compulsive disorder. *Am J Psychiatry* 1988;145:1560–1563.
13. Rauch SL, Jenike MA, Alpert NM, et al. Regional cerebral blood flow measured during symptom provocation in obsessive-compulsive disorder using oxygen-15-labeled carbon dioxide and positron emission tomography. *Arch Gen Psychiatry* 1994;51:62–70.
14. Reiman EM, Raichle ME, Butler FK, et al. A focal brain abnormality in panic disorder: a severe form of anxiety. *Nature* 1984;310:683–685.
15. Gur RE, Resnick SM, Gur RC. Laterality and frontality of cerebral blood flow and metabolism in schizophrenia: relationship to symptom specificity. *Psychiatry Res* 1989;27:325–334.
16. Buchsbaum MS. The frontal lobes, basal ganglia and temporal lobes as sites for schizophrenia. *Schizophrenia Bull* 1990;16:379–391.
17. Zametkin AJ, Nordahl TE, Gross M, et al. Cerebral glucose metabolism in adults with hyperactivity of childhood onset. *N Engl J Med* 1990;323:1361–1366.
18. Volkow ND, Hitzemann R, Wang GJ, Wolf AP, Dewey SJ. Decreased brain metabolism in neurologically intact healthy alcoholics. *Am J Psychiatry* 1992;149:1016–1022.
19. Volkow ND, Fowler JS, Wolf AP, Hitzemann R, et al. Changes in brain glucose metabolism in cocaine dependence and withdrawl. *Am J Psychiatry* 1991;148:621–626.
20. Holman BL, Garada B, Johnson KA, Mendelson J, et al. Comparison of brain perfusion SPECT in cocaine abuse and AIDS dementia complex. *J Nucl Med* 1992;33:1312–1315.
21. Ichise M, Salit IE, Abbey SE, et al. Assessment of regional cerebral perfusion by ^{99m}Tc HMPAO SPECT in chronic fatigue syndrome. *Nucl Med Commun* 1992;13:767–772.
22. Goldstein JA, Mena I, Jouanne E, Lesser I. The assessment of vascular abnormalities in late life chronic fatigue syndrome by brain SPECT: comparison with late life major depressive disorder. *J Chronic Fatigue Syndrome* 1995;1:55–79.
23. 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.
24. Callender TJ, Morrow L, Subramanian K, Duhon D, Ristovv M. Three dimensional brain metabolic imaging in patients with toxic encephalopathy. *Environmental Res* 1993;60:295–319.
25. Heuser G, Mena I, Alamos F. NeuroSPECT findings in patients exposed to neurotoxic chemicals. *Toxicol Industrial Health* 1994;10:561–571.
26. Simon TR, Hickey DC, Fincher CE, Johnson AR, Ross GH, Rea WJ. Single-photon emission computed tomography of the brain in patients with chemical sensitivities. *Toxicol Industrial Health* 1994;10:573–577.
27. Volkow ND, Tancredi L. Neural substates of violent behavior: a preliminary study with PET. *Br J Psychiatry* 1987;151:668–673.
28. Volkow ND, Tancredi LR, Grant C, et al. Brain glucose metabolism in violent psychiatric patients: a preliminary study. *Psychiatry Res Neuroimaging* 1995;61:243–253.
29. Raine A, Buchsbaum MS, Stanley J, et al. Selective reductions in prefrontal glucose metabolism in murderers. *Biol Psychiatry* 1994;36:365–373.
30. Mayberg HS. Critique: SPECT studies of multiple chemical sensitivity. *Toxicol Industrial Health* 1994;10:661–666.
31. Mayberg HS. Functional brain scans as evidence in criminal court: an argument for caution. *J Nucl Med* 1992;33:18N–25N.
32. Metter EJ, Kempler D, Jackson CA, et al. Cerebral glucose metabolism in Wernicke's, Brocas's and conduction aphasia. *Arch Neurol* 1989;46:27–34.
33. Pappata S, Mazoyer B, Tran Dinh S, et al. Effects of capsular or thalamic stroke on metabolism in the cortex and cerebellum: a PET study. *Stroke* 1990;21:519–524.
34. Jagust WJ, Reed Br, Seab JP, et al. Clinical-physiological correlates of Alzheimer's disease and frontal lobe dementia. *Am J Physiol Imaging* 1989;4:89–96.
35. Fazio F, Perani D, Gilardi MC, et al. Metabolic impairment in human amnesia: a PET study of memory networks. *J Cereb Blood Flow Metab* 1992;12:353–358.
36. Haxby JV, Duara R, Grady CL, Cutler NR, Rapoport SI. Relations between neuropsych and cerebral metabolic asymmetries in early Alzheimer's disease. *J Cereb Blood Flow Metab* 1985;5:193–200.
37. Grafton ST, Mazziotta JC, Pahl JJ, et al. A comparison of neurological, metabolic, structural and genetic evaluations in persons at risk for Huntington's disease. *Ann Neurol* 1990;28:614–621.
38. Fletcher JW, Woolf SH, Royal HD. Consensus development for producing diagnostic procedure guidelines: SPECT brain perfusion imaging with exametazime. *J Nucl Med* 1994;35:2003–2010.
39. Weber DA, Devous MD, Tikofsky RS. Brain SPECT perfusion imaging: image acquisition, processing, display and interpretation. In: Springfield, VA: National Technical Information Service, 1991; *Proceedings of Workshop Held at Brookhaven National Laboratory*, October 8–9, 1991.
40. Loessner A, Alavi A, Lewandrowski KU, Mozley D, Souder E, Gur RE. Regional cerebral function determined by FDG-PET in healthy volunteers: normal patterns and changes with age. *J Nucl Med* 1995;36:1141–1149.
41. Thornton JI. Courts of law versus courts of science: a forensic scientist's reaction to Daubert. *Shepard's Expert and Scientific Evidence Quarterly* 1994;1:475–486.
42. U.S. Supreme Court. Frye versus United States. 1923;293 F. 1013, 1014.
43. U.S. Supreme Court. Daubert versus Merrell Dow Pharmaceuticals. *113 Supreme Court*. 1993:2786.

Brain SPECT and Thrombolysis in Acute Ischemic Stroke: Time for a Clinical Trial

Andrei V. Alexandrov, James C. Grotta, Stephen M. Davis and Niels A. Lassen

Division of Neurology, Sunnybrook Health Science Center, University of Toronto, Canada; Department of Neurology, University of Texas Health Science Center, Houston, TX; Melbourne Neuroscience Center, Royal Melbourne Hospital, University of Melbourne, Australia; Department of Clinical Physiology and Nuclear Medicine, Bispebjerg Hospital, Copenhagen, Denmark

Key Words: brain SPECT; acute stroke; thrombolysis

J Nucl Med 1996; 37:1259–1262

THROMBOLYSIS FOR STROKE

The spirit of resignation in management of patients with acute stroke will likely disappear when measures for brain tissue rescue are proven effective (*1*). The first four randomized placebo-controlled trials showed no benefit from intravenous thrombolysis with streptokinase (SK) and tissue plasminogen activator (tPA) (*2*). This was due to excessive numbers of hemorrhagic transformations (HT) of brain infarction and deaths in the treatment group which exceeded 30% of treated patients in the European and Australian trials (*2*). The only trial so far to demonstrate the therapeutic effect of tPA was the National Institutes of Health-sponsored study in which half of the patients were treated within 90 min of stroke onset (*3*). Yet the incidence of symptomatic HT was at least ten times greater with tPA than in the placebo group: 6.4% versus 0.6% (*3*).

The entry criteria in the thrombolytic trials include: the duration of symptoms, clinimetric assessment of stroke severity and admission CT scan. These tests are inadequate to determine stroke pathogenesis and depth of ischemia, and thus large numbers of patients are required to demonstrate the benefit from treatment, if any, compared to a placebo group (*2,3*). A natural extension of first successful trials would be to determine a time threshold when thrombolytic agents become more harmful than useful, and a target group of patients for safe

Received Apr. 1, 1996; revision accepted Apr. 2, 1996.

For correspondence or reprints contact: A. V. Alexandrov, MD, Division of Neurology, Sunnybrook Health Science Centre, 2075 Bayview Ave., Toronto, Ontario, Canada, M4N 3M5.