Continuing Education

Current Status of Cerebral Perfusion Radiopharmaceuticals

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This is the first of a four-part Continuing Education series describing current trends in radiopharmaceutical research and development. After reading and studying this article the reader should be able to: 1) discuss the updated approach to brain scintigraphy, 2) discuss characteristics of cerebral perfusion radiopharmaceuticals, and 3) be aware of the prospects of cerebral perfusion imaging in nuclear medicine.

This article describes the development of agents for imaging regional cerebral perfusion and thus regional brain function. The agents that have significant clinical utility and potential commercial availability are iodine-123 (^{123}I)-labeled monoamine N-isopropyl p-iodoamphetamine (IMP), ^{123}I-HIPDM, technetium-99m (^{99m}Tc)-HM-PAO, and thallium-201 (^{201}Tl)-DDC. The current search for alternative agents with similar biologic properties, but improved physical characteristics, is also described.

A great deal of nuclear medicine's history has revolved around scintigraphic images of the brain. Between 1965 and 1975, with the advent of readily available ^{99m}Tc and prior to the commercial explosion of computed tomography (CT), brain scanning accounted for a substantial portion of a department's procedure volume. Because CT yields more specific anatomic information, and in many cases, better lesion detection than with scintillation camera scintigraphy, conventional radionuclide brain scintigraphy almost disappeared from the scene.

Conventional brain scanning has always been misnamed. It is really non-brain imaging, using radiopharmaceuticals that do not penetrate into the normal brain, but will cross a damaged blood brain barrier and appear as focal areas of increased activity (*1*). While this indirect method of imaging brain pathology has declined in popularity, one specialized branch of nuclear medicine (PET) has remained relatively immune from the neurologic sweep of CT. Positron emission tomography (PET) uses radiopharmaceuticals that readily cross the blood brain barrier by one of several active pathways, and for this reason has remained at the forefront of neurophysiology and neurochemistry research. But PET requirements of costly on-site cyclotrons to produce positron emitting radionuclides, and technical support, have limited this technology to a few clinical sites, making it out of reach to the general clinical population.

In the past few years, a number of single photon emitting radiopharmaceuticals that cross the normal blood brain barrier have made their way into the clinical environment. These agents are being used to obtain clinical information in patients with central nervous disorders ranging from cerebrovascular disease to dementia, using standard Anger camera technology, and standard clinical nuclear medicine technology. This review will discuss some current investigative brain radiopharmaceuticals, their physical and biologic properties, technical imaging considerations, and clinical diagnostic potential.

CEREBRAL ANATOMY

Twin cerebral hemispheres make up the bulk of the brain, and are divided into four lobes: frontal, temporal, parietal, and occipital (Fig. 1). The posterior portion of the frontal lobe, the motor cortex or strip, controls discreet voluntary movements of skeletal muscles. The temporal lobe is responsible for hearing and language organization, whereas the occipital lobe's function is dedicated to vision. The parietal lobe receives somatic sensory messages, and sensations of stereoperception. Located separately from the cerebrum, in the posterior fossa of the skull, is the cerebellum, which controls individual orientation in space.

Situated deep within the cerebral hemispheres are masses of gray matter called the basal ganglia, which influence motor responses in addition to relaying messages to the cerebral cortex. Also within the cerebral hemispheres are the thalamus and hypothalamus. The thalamus is a large ovoid of gray matter, and is involved in sensory functions, whereas the hypothalamus serves as one partner in the hypothalamus-pituitary-thyroid axis (*2*).

BLOOD BRAIN BARRIER

The concept of the blood brain barrier (BBB) centers on the structural and functional characteristics of brain capillaries, which inhibit the distribution of a number of small molecules to the extracellular fluid of the brain. The typical systemic

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capillary will pass small molecules between plasma flowing within its lumen and adjacent stationary extracellular fluid, predominantly through clefts between the capillary endothelial cells. Cerebral capillaries, however, are composed of cells whose clefts are sealed shut, thus requiring molecular exchange to occur through the cells themselves.

Another difference exists between systemic capillary cells and those of the brain. An ill-defined membranous aperture composes the general capillary wall but is not present in brain capillaries. As a result, substances that exchange between plasma and brain tissue must pass through both inner and outer cell membranes to penetrate into the extracellular fluid of the brain. This series of membrane obstacles provides a filter type function that might be said to be selectively permeable. Thus, substances such as sucrose remain virtually locked out by the BBB, whereas nicotine crosses this barrier freely. The blood brain barrier therefore is not impermeable, but simply selective (*3*).

This barrier system exists for some very practical purposes. The extracellular fluid of the brain has no lymphatics. If plasma proteins enter this fluid, there is no method of absorbing them, with resultant edema. In addition, toxic and other undesirable substances are restricted from the brain parenchyma. This barrier also prevents rapid changes in brain concentration of ions and other substances. For some lipid-soluble substances, such as ethyl alcohol, caffeine, nicotine, heroin, and methadone, a passive diffusion unaffected by barrier mechanisms results in a high penetration rate from the blood into the brain (*1*).

The basic principle behind conventional ^{99m}Tc brain imaging allows polar gamma emitting agents to leak through the capillaries as a result of a breakdown of the blood brain barrier. Intact brain tissue maintains the integrity of the BBB by an ongoing physiologic process. In pathologic abnormalities, the BBB may be lost, with the capillaries reverting to the permeability of capillaries elsewhere in the body. Thus, accumulation of the radiopharmaceutical occurs at the clinical foci as a result of the increased permeability. Our ability to visualize this increased collection of activity is not so much due to tissue avidity, as it is to the extremely high target-to-background ratio created by the low tracer level in surrounding normal brain tissue.

A large number of neurologic abnormalities do not break down the BBB, and imaging these patients with ^{99m}Tc pertechnetate or any of its chelating derivatives may result in normal images. Until recently, BBB permeability necessary to demonstrate abnormal perfusion patterns in functional abnormalities has been limited to cyclotron produced positron emitting radionuclides such as carbon, oxygen, nitrogen, and fluorine. A number of radiopharmaceuticals that meet three requirements for direct Anger camera brain imaging—1) BBB permeability, 2) retention in the brain parenchyma, and 3) single photon physical characteristics—can be labeled with ^{99m}Tc and ^{123}I (*1,4–6*).

RADIOLABELED AMINES

Amines are important chemical mediators of brain function. They affect the transport and uptake of brain metabolites, rates of synthesis, and metabolism. It is likely that many neurologic diseases, including some that are currently labeled as functional disorders, may manifest altered amine kinetics and function. A number of labeled amines that cross the blood brain barrier and remained fixed in the brain for sufficient time to permit tomographic imaging recently have been synthesized and evaluated clinically.

Two radiopharmaceuticals have already received a great deal of clinical attention in direct brain imaging. The ^{123}I-labeled monoamine N-isopropyl p-iodoamphetamine (IMP) and ^{123}I-diamine N,N,N′-trimethyl-N′-[2-hydroxyl-3-methyl-5-iodobenzyl]-1,3-propanediamine (HIPDM) (Fig. 2) have both seen widespread clinical applications, both behaving similarly in humans. There are some differences, however, that may affect the choice of agent for brain perfusion imaging in specific instances or neurologic diseases (*7*).

After intravenous injection, both radiopharmaceuticals accumulate initially in the lungs. Two minutes after injection, brain activity is approximately 75% of peak activity for ^{123}I-HIPDM, but less than 50% for ^{123}I-IMP. While both tracers maintain a steady state in the brain from 30 to 60 min post administration, the peak brain activity is substantially greater for ^{123}I-IMP. Because ^{123}I-IMP is taken up more avidly by the brain, it may be more attractive for tomographic imaging due to the limited sensitivity of rotating gamma cameras.

Labeled amines such as IMP and HIPDM are lipophilic, moving across the blood brain barrier with almost complete extraction during a single passage through the cerebral circulation. Once inside the brain, these ^{123}I-labeled amines are either bound to nonspecific receptors or metabolized to nonlipophilic compounds. As a result, there is no redistribution of the tracer within the brain for at least an hour after injection. Steady state brain activity thus is maintained so tomographic imaging of regional cerebral perfusion can be performed before any appreciable redistribution of the compound has occurred (*8*).

Iodine-123-labeled compounds have a considerably challenging technical problem that has discouraged a number of potential advocates. These tracers are usually labeled with ^{123}I produced by the direct method [^{124}Te(p,2n)→^{123}I]. The bulk of ^{123}I currently made in the United States is produced by this method because it is inexpensive, requiring a lower energy proton than the alternative indirect method of production. Unfortunately, the ^{123}I produced by the less expensive direct method, (p,2n) reaction on ^{124}Te, has a small (2%–4%) amount of ^{124}I. The fraction of this impurity increases with time because ^{123}I ($T_{½}$ = 13 hr) decays more rapidly than ^{124}I ($T_{½}$ = 100 hr). This impurity creates three problems. First, image degradation occurs because ^{124}I emits several abundant high energy photons (603 keV to 3.0 MeV) that increase the number of scattered photons detected within the 159 keV photopeak of ^{123}I. Second, patient radiation exposure results from the presence of ^{124}I, thus limiting the amount of tracer that may be injected to 5 mCi or less. Finally, the long physical half-life of the ^{124}I may increase the time interval necessary between sequential studies.

There are two potential solutions to the ^{124}I contamination problem. The most expensive technique is ^{123}I production from

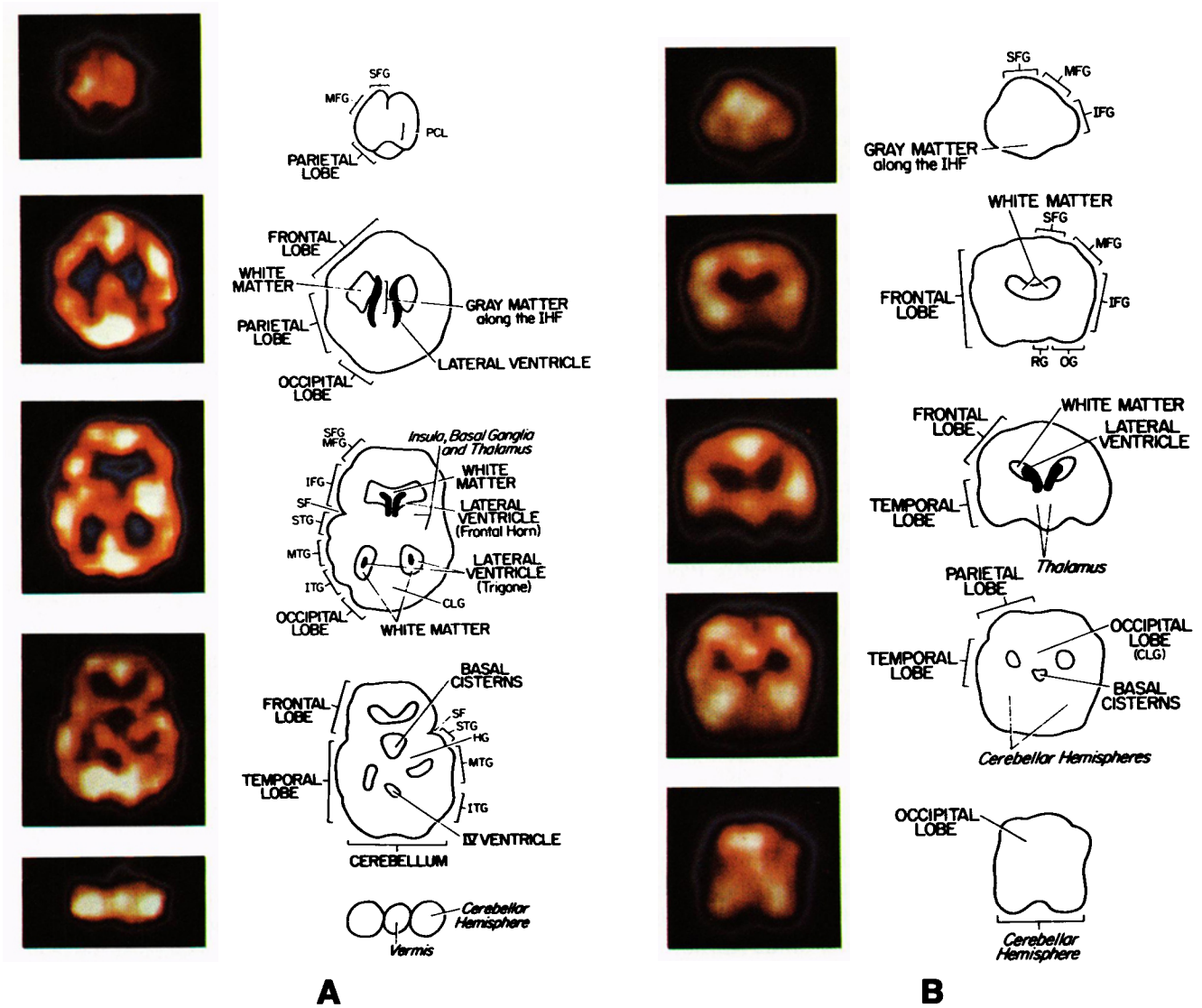

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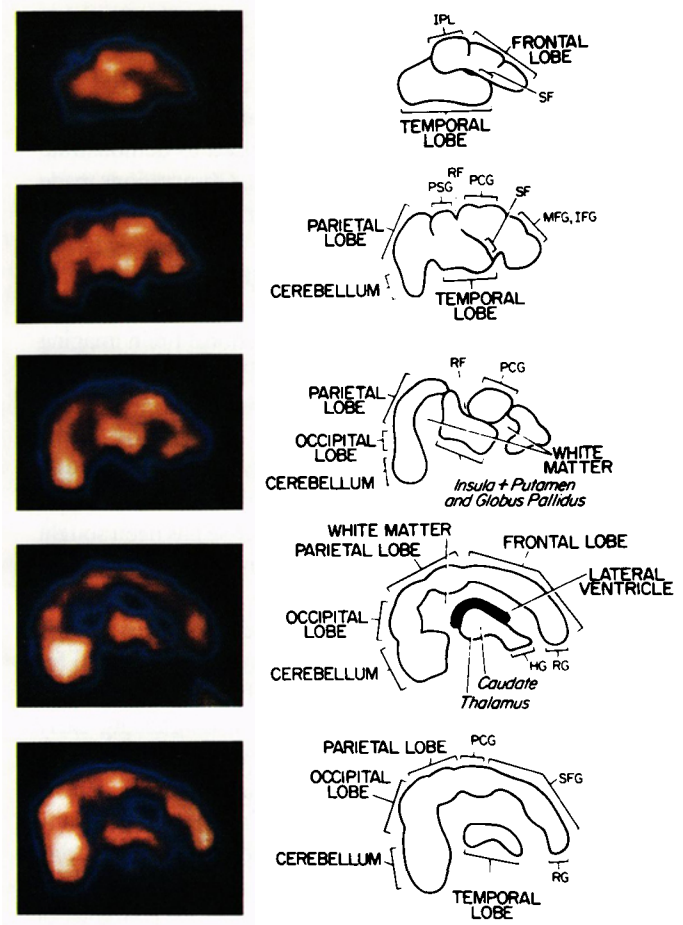
FIG. 1. SPECT images of ^{123}I-IMP, demonstrating normal anatomic landmarks. (A) Transaxial; (B) coronal; (C) sagittal. This figure is reprinted from *Applied Radiology* 1984;13(6):4–27, with the permission of the authors, B.L. Holman and T.C. Hill, and Brentwood Publishing Corp., a Prentice-Hall/Simon & Schuster unit of Gulf + Western, Inc.

the indirect (p,5n) method. This reaction requires a large cyclotron capable of producing protons of 55–70 MeV. Iodine-123 produced by this method is contaminated with ^{125}I, but this impurity has little impact on image quality. Another solution to the ^{124}I problem is to use collimators that exclude the high energy scatter of the ^{124}I. There are currently a number of collimator designs under investigation that produce high quality tomographic images using ^{123}I with rotating gamma cameras (*9–12*).

ADDITIONAL BRAIN IMAGING AGENTS: ^{99m}Tc-HM-PAO AND ^{201}Tl-DDC

The potential for a radiotracer that can be used for three-dimensional imaging of regional cerebral blood flow (rCBF) on a routine basis has been clearly established by a number of investigators (*1,13–15*). However, the expense, availability, and physical characteristics of the radioiodine amines may restrict their potential long-term application. For example, although SPECT and ^{123}I-IMP have been shown superior to CT for the diagnosis of acute stroke (*16,17*) the relatively short physical half-life of ^{123}I limits the availability and use of this agent. Because a number of neurologic conditions seen at the community hospital level may be acute and sudden, the need for a brain agent kit that can be prepared as needed is of the utmost importance.

To date, the most widely used tracer technique to determine rCBF has been xenon-133 (^{133}Xe) (*18*), which suffers from serious radiopharmaceutical and instrumentation technical constraints that restrict its clinical applicability. Xenon rCBF studies are frequently performed observing the rapid transit of ^{133}Xe use probes, which do not produce images. One of the attractions of the amine family of perfusion agents is their retention in the brain parenchyma for periods long enough to enable tomographic image acquisition. The ideal tracer for a brain agent should be readily available, retained in the brain parenchyma for at least an hour, have compatible photons with standard rotating Anger camera technology, and be relatively



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inexpensive. These four conditions have led investigators to develop a number of technetium and thallium compounds.

The most convenient radiopharmaceutical for imaging rCBF would be a ^{99m}Tc compound that is trapped in its first pass through the brain. The first of these, ^{99m}Tc-propyleneamine-oxime (^{99m}Tc-PAO) was described by Volkert et al. (*4*) for possible rCBF measurement. However, the washout rate of the agent is too rapid for SPECT imaging. Fortunately, a derivative of this agent, hexamethylpropyleneamine (^{99m}Tc-HM-PAO) reported by Holmes et al. (*5*) is retained in the brain parenchyma.

The uptake of ^{99m}Tc-HM-PAO in the brain at 20 min post injection has been reported to be in the range of 3.4%–5.7% of the injected activity, with approximately 10% in the liver, and 4% in the kidneys. This agent shows both hepatobiliary and urinary excretion, with some additional soft tissue uptake in the skeletal muscles. High uptake in the gray matter and basal ganglia has been reported, with little surrounding soft tissue uptake (*6*).

An additional alternative to the iodinated amine compounds is ^{201}Tl-diethyldithiocarbamate (DDC). This easy-to-prepare, highly lipophilic complex shows a distribution similar to the radiolabeled amines, with marked uptake in the salivary glands, thyroid, myocardium, muscles, liver, and intestines. Although the energy and physical half-life of ^{201}Tl are not as ideal as ^{99m}Tc, the images obtained with relatively low activity have been reported to be encouraging (*19,20*).

BIODISTRIBUTION

Once ^{123}I-IMP is injected intravenously, the dose is initially deposited in the lungs. Maximal lung uptake is achieved between 1 and 2 min, with fairly rapid washout from the pulmonary compartment. Brain activity is observed 30 sec after injection and is greater than 80% of peak activity by 2 min. Brain activity remains constant from about 20 min to 60 min after injection, with between 6% and 9% of the injected dose deposited within the brain parenchyma. Technetium-99m-HM-PAO and ^{201}Tl-DDC, as previously mentioned, demonstrate similar biologic properties.

Patients without central nervous system disorders demonstrate bilaterally symmetric activity throughout the transaxial tomographic images (Fig. 3). Activity is greatest in a strip of cortex along the convexity of the frontal, temporal, parietal, and occipital lobes corresponding anatomically to cortical gray matter. The region between the basal ganglia and the convexity corresponding anatomically to cortical white matter has less radiopharmaceutical uptake. Activity in the visual cortex of patients injected while exposed to bright light is greater than in patients studied with eyes closed at the time of injection (*13*).

CLINICAL UTILITY

The distribution of radiolabeled perfusion agents imaged with SPECT appears useful in a number of neurologic conditions. Although the clinical assessment of these agents is in its infancy, a number of ongoing studies warrant attention. The application of radiolabeled perfusion agents in the diagnosis

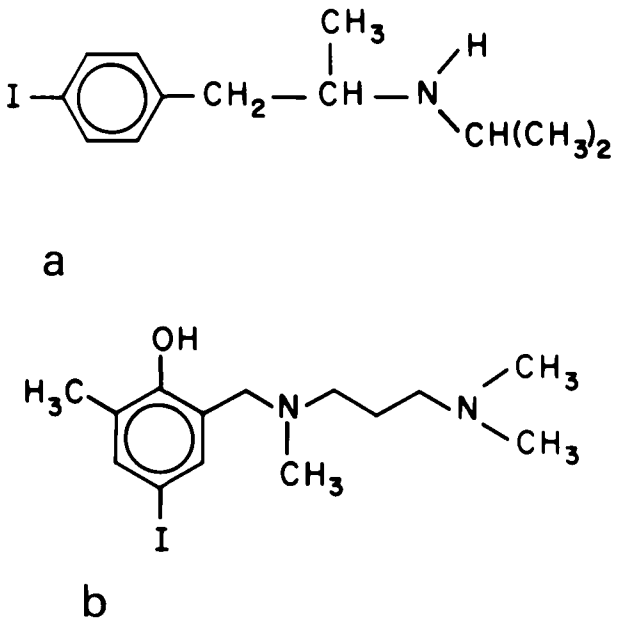

FIG. 2. Chemical structures of a) ^{123}I-IMP and b) ^{123}I-HIPDM.

FIG. 3. Transaxial, mid-brain cut of normal distribution of ^{123}I-IMP.

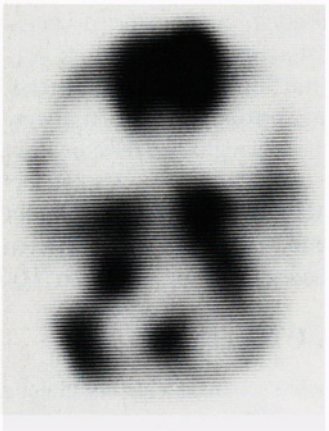

FIG. 4. Transaxial, mid-brain cut of ^{123}I-IMP distribution in patient with severe Alzheimer's disease, demonstrating reduced radiotracer distribution in all portions of the brain except the motor cortex region.

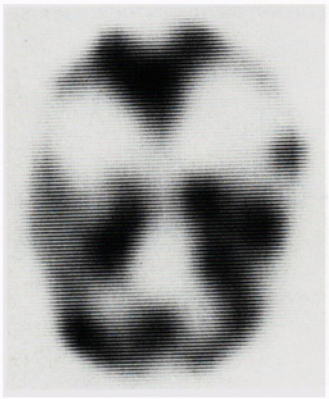

FIG. 5. Transaxial, mid-brain cut of ^{123}I-IMP distribution in patient with early Alzheimer's disease, demonstrating reduced radiotracer perfusion only in the parietal regions of the brain.

of cerebral infarction is extremely promising. In such patients the abnormality on SPECT with ^{123}I-iodoamphetamine is immediately evident, unlike the defect on transmission CT, which does not appear until 3 to 4 days after the onset of symptoms. In patients with acute infarction, early CT examinations demonstrate normal morphology, whereas functional iodoamphetamine images show a perfusion defect in areas that will later develop abnormalities on CT. Although this argument should lead referrals to IMP imaging in cases of stroke, the lack of on-hand availability prevents widespread application of this diagnostic tool. This handicap may be reversed, however, with further development of ^{99m}Tc-HM-PAO and ^{201}Tl-DDC.

A number of in vivo methods to measure regional cerebral blood flow and metabolism have been used to demonstrate variations in flow during epileptic seizures. Observations made with positron emission computed tomography and with fluorine-18 (^{18}F)-labeled deoxyglucose have been repeated with the ^{123}I perfusion agents. Basically both PET and SPECT studies have shown increased blood flow to the regions of the seizure focus. Although this aspect of functional brain imaging has not been fully investigated with SPECT, this imaging modality may be of significant practical importance in monitoring drug treatment and/or managing epilepsy (*13,21*).

Recently, a great deal of attention has been paid to changes in regional cerebral blood flow in dementia (*14,15*). A method for the early diagnosis of Alzheimer's disease has been sought for some time. Alzheimer's disease is a disorder characterized by progressive dementia that occurs in middle or late life, accounting for approximately 50% of dementia cases in the United States (*18*). Computed tomography has been useful for the diagnosis of the treatable causes of dementia (tumors, abscesses, stroke) but is of little value in diagnosing early Alzheimer's disease. SPECT perfusion images reveal a diffusely diminished model of brain activity in severe Alzheimer's patients (Fig. 4), but also an identifiable reduction of activity in the parietal lobes of the less severe patients (Fig. 5), sparing the visual primary motor and sensory cortex seen in severe disease, an observation that correlates with PET studies of early Alzheimer's disease (*22*).

If further investigation with SPECT confirms the usefulness of a scintigraphic signature in the diagnosis of Alzheimer's disease, a valuable tool may now exist for diagnosing and for monitoring treatment of this condition. When Alzheimer's disease becomes clinically apparent, it may be late in its biologic course. Structural alterations (cerebral atrophy, plaques, and tangles) are already present and may be irreversible even if the underlying biochemical abnormalities are corrected. Thus, SPECT perfusion studies may have the potential for detecting physiologic abnormalities if and when treatment at an early stage is possible.

In summary, radiolabeled amines have paved the way for the development of SPECT brain perfusion imaging. Its sensitivity in acute cerebral infarction, and its excellent correlation with PET in patients with stroke or dementia, demonstrate only the tip of the clinical iceberg. However, the physical characteristics and cost of ^{123}I make it a less than optimal radiolabel for everyday applications, leading investigators to develop alternative agents labeled with either technetium or thallium. There is a renewed interest in brain imaging, and the future appears promising for the reintroduction of routine functional brain scintigraphy.

REFERENCES

1. Holman BL, Hill TC, Magistretti PL. Brain imaging with emission computed tomography and radiolabeled amines. *Invest Radiol* 1982;17:206–215.

2. Early PJ, Sodee DB. Principles and practice of nuclear medicine. St.

Louis: C.V. Mosby, 1985:627–631.

3. Oldendorf WH. The quest for an image of brain: a brief historical and technical review of brain imaging techniques. *Neurology* 1978;28:517–533.

4. Volkert WA, Hoffman TJ, Seger RM, et al. Tc-99m propyleneamine oxine (Tc-99m-PnAO); a potential brain radiopharmaceutical. *Eur J Nucl Med* 1984;9:511–516.

5. Holmes RA, Chaplin SB, Royston KG, et al. Cerebral uptake and retention of ^{99m}Tc hexamethyl propyleneamine oxine (^{99m}Tc-HM-PAO). *Nucl Med Comm* 1985;6:443–447.

6. Sharp PF, Smith FW, Gemmell HG, et al. Technetium-99m HM-PAO stereoisomers as potential agents for imaging regional cerebral blood flow: human volunteer studies. *J Nucl Med* 1986;27:171–177.

7. Holman BL, Lee RG, Hill TC, et al. A comparison of two cerebral perfusion tracers, N-isopropyl I-123 p-iodoamphetamine and I-123 HIPDM, in the human. *J Nucl Med* 1984;25:25–30.

8. Holman BL, Zimmerman RE, Schapiro JR, et al. Biodistribution and dosimetry of N-isopropyl-p-[^{123}I] iodoamphetamine in the primate. *J Nucl Med* 1983;24:922–931.

9. Polak JF, English RJ, Holman BL. Performance of collimators used for tomographic imaging of I-123 contaminated with I-124. *J Nucl Med* 1983;24:1065–1069.

10. Polak JF, Holman BL, Moretti JL, et al. I-123 HIPDM brain imaging using a rotating gamma camera equipped with a slant hole collimator. *J Nucl Med* 1984;25:495–498.

11. English RJ, Brown SE. Single photon emission computed tomography: a primer. New York: The Society of Nuclear Medicine, 1986:54–61.

12. Tsui BMW, Gullberg GT, Edgerton ER, et al. Design and clinical utility of a fan beam collimator for SPECT imaging of the head. *J Nucl Med* 1986;27:810–819.

13. Royal HD, Hill TC, Holman BL. Clinical brain imaging with isopropyl-iodoamphetamine and SPECT. *Sem Nucl Med* 1985;15:357–375.

14. Gemmell PS, Cherryman G, Besson J, et al. Application of iodine-123-labeled isopropyl-amphetamine imaging to study dementia. *J Nucl Med* 1986;27:761–768.

15. Cohen MB, Graham LS, Lake R, et al. Diagnosis of Alzheimer's disease and multiple infarct dementia by tomographic imaging of iodine-123 IMP. *J Nucl Med* 1986;27:769–774.

16. Lee RG, Hill TC, Holman BL, et al. N-isopropyl (I-123) p-iodoamphetamine brain scans with single photon emission tomography: discordance with transmission computed tomography. *Radiology* 1982;145:795–799.

17. English RJ, Summerville D, Polak JF, et al. Brain imaging of cerebrovascular disease with I-123 HIPDM. *J Nucl Med Technol* 1984;12:13–15.

18. Buell U, Moser EA, Schmiedek P, et al. Dynamic SPECT with Xe-133: regional cerebral blood flow in patients with unilateral cerebrovascular disease. *J Nucl Med* 1984;25:441–446.

19. Royen EVA, deBruine JF, Hill TC, et al. Thallium-201 DDC, an alternative to iodine-123 IMP (abstr). *J Nucl Med* 1985;26:828.

20. deBruine JF, Van Royen EA, Vyth A, et al. Thallium-201 diethyldithiocarbamate: an alternative to iodine-123 N-isopropyl-p-iodoamphetamine. *J Nucl Med* 1985;26:925–930.

21. Holman BL, Hill TC, Polak JF, et al. Cerebral perfusion imaging with iodine-123-labeled amines. *Arch Neurol* 1984;41:1060–1063.

22. Holman BL. Perfusion and receptor SPECT in the dementias. *J Nucl Med* 1986;27:855–860.