
The Role of Nuclear Medicine in the Diagnosis, Differentiation, Management, and Potential Cure of Alzheimer's Disease

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This paper presents an overview of the various studies, techniques, and contributions made in the field of nuclear medicine toward the diagnosis, differentiation, management, and potential cure of Alzheimer's disease. The definitions, history, clinical symptoms, personal, social, and financial impacts are discussed first. Information on research into the causes and risk factors of the disease is presented, along with medically defined levels of disease prevention as they specifically relate to Alzheimer's disease. Finally, studies and their results, employing a number of nuclear medicine techniques are presented (including nuclear medicine techniques combined with other imaging modalities, i.e., magnetic resonance imaging), in order to illustrate the progress being made in the association of nuclear medicine with Alzheimer's disease.

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Alzheimer's disease (AD) is often humorously referred to as "old-timer's disease" or "old geezer's disease." In 1981, Lewis Thomas called Alzheimer's disease the disease of the century (1). In 1985, the personal and financial impact on patients, families, and society was reflected by the \$20 billion (half of the money spent on nursing care in the United States) spent on treatment of AD and other dementias and the \$50 million that is spent each year on research of dementias in the U.S.

Millions of dollars per year have been spent on psychometric and clinical testing, with limited success at diagnosing and staging AD (2). Other statistics, from a 1981 study, show dementia as an underlying cause of death in 70,000 to 100,000 U.S. residents each year, making dementia the fourth or fifth highest cause of death in the late 1970s (3).

To date, there are very few, if any, personal or group health care plans that cover nursing home care for patients with AD. With 1991 nursing home charges running from approximately \$2400-8000 per month, the financial impact on the family of an AD patient can be astronomical.

In recent years, nuclear medicine has been showing promise in the diagnosis, differentiation, management, and poten-

tial cure of Alzheimer's disease through research and experience obtained in the development of a number of imaging and nonimaging techniques. The objective of this paper will be to present these developments in nuclear medicine in a more or less historical sequence. The conclusions to be drawn from the information presented are that (1) there are overwhelming personal, financial, and social reasons for continued contributions from nuclear medicine to the problems of AD, (2) nuclear medicine is, indeed, making a solid contribution, and (3) to date, the most promising nuclear medicine modalities appear to be single-photon emission computed tomography (SPECT) and positron emission tomography (PET).

DEFINING ALZHEIMER'S DISEASE

In the medical field, dementia is defined as a loss or impairment of mental powers. Dementia originated from two Latin words, which mean away and mind. The word crazy is not a part of the definition of dementia (4).

In 1907, Alzheimer's disease was first described by, and consequently named for, a German physician, Alois Alzheimer. Alzheimer was describing a disease observed in a woman in her fifties, originally called presenile dementia. Today, it is believed that dementia occurring in the elderly is the same as or similar to the presenile condition and is often called senile dementia of the Alzheimer's type (SDAT) (4). For the purposes of this paper, all references to Alzheimer's disease (AD) will be considered to be the same as (SDAT).

AD patients usually die within 7 to 10 yr, with some dying more quickly (3 to 4 yr) and some more slowly (up to 15 yr) (4).

AD presents with a gradual but relentless onset. Clinical features include disorientation, confabulations, loss of recent memory, and retrogressive loss of remote memories. Over the course of the disease, concentration, handwriting, speech, and reasoning ability deteriorate so that in the latter stages, patients may exist in a vegetative state (5). In the early stages of AD, patients who are aware of their diagnosis, or who become aware of the progression of their symptoms, frequently are anxious, depressed, and tearful. The emotional devastation experienced not only by the patient, but by those who love and care for him or her, cannot be

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fully appreciated by persons who have no first-hand knowledge of the disease.

Brain biopsies and autopsies of patients with AD show the presence of neurofibrillary tangles and senile plaques, which may also be seen in other conditions including trauma and normal aging (6).

Irreversible dementia in adults appears most frequently as AD. The primary cause of the disease is still unknown and, at this time, there is no way to either halt or cure AD (4). Severe memory loss should never be accepted as a normal part of the aging process, and suspected dementia in a patient should always be evaluated. An evaluation can give information on how best to care for and manage the symptoms of the patient. It helps the caregiver or family to prepare for the future and comforts the family to know that all avenues have been followed and that the patient has received the best medical treatment available.

An evaluation can also serve to rule out dementias that are caused by diseases other than AD, which, many times, can be treated and reversed. A dementia caused by thyroid disease, for example, can often be reversed by correction of the thyroid abnormality. If a reversible dementia is not found due to the lack of an evaluation, the patient and family may suffer needlessly. Many reversible dementias will become irreversible if they are not treated promptly. Other forms of dementia include multiinfarct dementia; mixed forms of primary degenerative and multiinfarct dementia; and secondary dementias, such as multiple sclerosis. Some of these secondary dementias may be reversible, i.e., dementia caused by pernicious anemia (5).

RISK FACTORS

The established and potential contributions of nuclear medicine to the diagnosis, differentiation, and management of AD, and to, perhaps, eventually cure AD, take on a great importance when the disease is viewed from the standpoint of emotional tragedy and financial impact on patients, families, society, and the medical field. To fully determine the role of nuclear medicine in AD, three levels of prevention, (primary, secondary, and tertiary) are often discussed.

Primary prevention is defined as intervention before a disease process begins. Primary prevention in AD, then, requires that cause and risk factors be identified (5).

The primary risk factor that has been identified for AD is age. Gender is another risk factor. Many studies show women to be the gender at greater risk for AD. Genetics may be a factor; Down's syndrome is believed to be a risk factor for development of AD and sporadic cases have been documented showing an inherited autosomal dominant pattern (5).

A triploid sequence of DNA on chromosome 21, appearing to be related to AD, has been found and verified in studies by Schweber and by Delabar and associates. Both researchers found this triplication in groups of AD patients, including some postmortem confirmation of AD by neuropathologic

examination. Control groups were shown to be lacking this triplication (5).

Although not well studied, geography has been considered as a possible risk factor with the theory that varying exposure to some geographically limited environmental factors, such as dietary intake of calcium and aluminum, may play a role. Race is also under consideration as a mild risk factor. Some studies in the United States have demonstrated, in a specific population, controlled for age and gender, that blacks have a higher prevalence of AD than do whites (5).

Among potential environmental factors, aluminum exposure has been considered a possible risk. While there is some association between dialysis dementia and aluminum content in the dialysis water supply, and there is a higher concentration of aluminum in neurofibrillary tangles in patients with AD, a causal link has not been established. Aluminum exposure is not currently considered a risk factor for AD (5).

As shown above, primary prevention is not feasible in AD. It is hoped that primary prevention (a cure) will be realized through work being done in medical specialties, such as nuclear medicine, by means of secondary and tertiary prevention (diagnosis, differentiation, and management).

In secondary prevention, the main focus is the diagnosis of a disease that has already begun. The goal is for a prompt, correct diagnosis in order to provide early treatment, which will have a positive effect on the disease process. In the patient with dementia, once symptoms have appeared, prompt and accurate diagnosis is important in order to find reversible causes of dementia and to aid in the management of the AD patient (5).

Tertiary prevention is taking action to ameliorate an incurable condition or delay the clinical progression of a disease process in a compassionate fashion. Primary and secondary prevention of concomitant diseases, which may exacerbate the original disease process, is important. In AD, the goal of tertiary prevention is to recognize and control other conditions that may affect the quality of life during the patient's few remaining years (5).

According to Volicer et al., "Neither loss in cognitive functioning nor decline in the activities of daily living progresses inexorably regardless of treatment. Loss of brain substance and the associated decline in testable cognitive functioning will become more manifest if anemia is permitted to develop, if nutrition is neglected, and if fecal impactions are missed. While in the end the patient with senile dementia will die, the same is true of the clinician. The object of care is not only to influence when the patient will die, but mainly to preserve comfort, a sense of dignity, and a maximum level of functioning for as long as possible (5).

ROLE OF NUCLEAR MEDICINE

It appears that nuclear medicine has, and will continue to have, an important role in the diagnosis, differentiation, and management of, and in the potential discovery of a cure for AD. In the early 1970s, investigators observed that cerebral

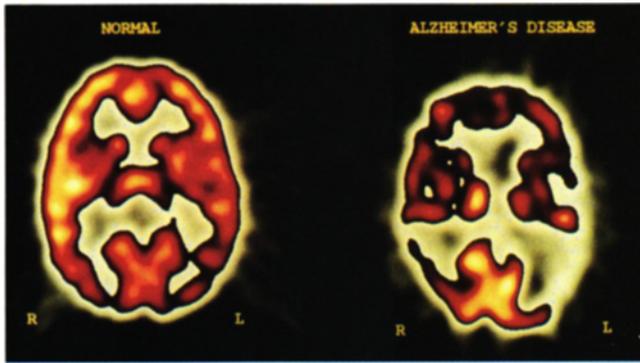


FIG. 1. PET image of a normal patient and a patient with Alzheimer's disease.

blood flow was reduced in AD. Studies at several PET facilities found the changes in metabolism and flow to be focal and most widely evident in the parietal areas of the brain. Figure 1 is an example of PET images obtained from a normal patient and from a patient with AD. SPECT imaging has also been used to study the brain perfusion patterns in patients with dementia (6). The use of brain perfusion imaging in nuclear medicine for AD patients has raised a number of questions that are currently under research. These questions, as outlined below, need to be answered in order to determine the accuracy of brain perfusion imaging with radiopharmaceuticals in the diagnosis of AD.

Can PET or SPECT imaging be used as a tool in the early detection of AD? Their accuracy in the early diagnosis of AD

is important as both an early warning system for the impending progression of AD and also as a means of providing reassurance to the patient with reversible dementia. Using SPECT, a study of 13 patients, whose clinical workup met the standard criteria for AD and who were in the early phase of the disease, showed that 10 of the 13 had decreased perfusion to the parietal cortex (6).

Can PET or SPECT be used in the differentiation of AD from other dementias? In many cases, depression, which is reversible, can mimic the symptoms of AD. Studies have shown that most patients with depression have a normal perfusion pattern. SPECT imaging of brain perfusion can be used to differentiate depression from AD by comparison of the depressive's normal perfusion pattern and the bilateral parietal perfusion abnormalities seen in patients with AD (6).

SPECT has also shown other dementias to have different perfusion patterns from AD. In Huntington's dementia, which causes choreiform movements and atrophy of the caudate nuclei, the pattern is one of decreased perfusion to the basal ganglia. Progressive supranuclear palsy shows a perfusion pattern, using iodine-123 iodoamphetamine ^{123}I IMP and SPECT, of decreased tracer uptake in the basal ganglia, less symmetrically than with Huntington's disease. A study of a patient with Jacob-Creutzfeldt disease, verified by biopsy, showed IMP uptake markedly reduced uniformly throughout the cortex, and parietal areas affected to the same extent as the rest of the brain. Korsakoff's psychosis shows a patchy perfusion pattern with no focal defects (6).

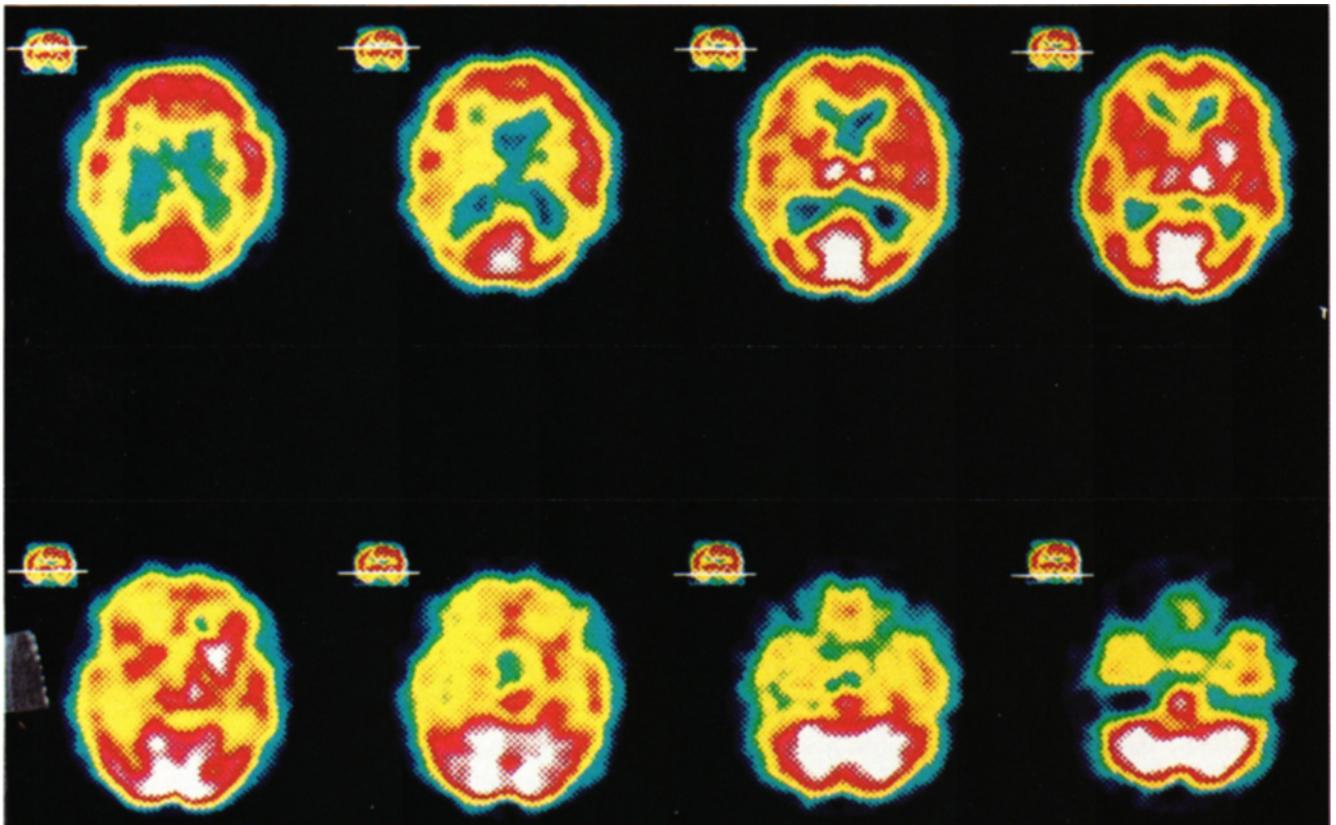


FIG. 2. SPECT images, using $^{99\text{m}}\text{Tc}$ -HMPAO, of a patient with Alzheimer's disease.

Thus, perfusion imaging may be useful in the differential diagnosis and staging of the dementias.

Other questions that must be answered are how the underlying mechanisms of AD can be determined and what can be done to detect the disease before it becomes symptomatic. It is currently believed that perfusion changes seen in the posterior temporoparietal and posterior frontal lobes of the brain may be secondary and indirect consequences of AD. Studies have shown a profound decrease in the neurotransmitter acetylcholine in the basal forebrain; this probably results from degeneration of the acetylcholine-containing cells originating in the medial septum and basal nucleus of Meynert. Radiotracer techniques are being developed, using high specific activity radioisotope-labeled neurotransmitter antagonists and emission tomography, to measure receptor binding in living patients. Muscarinic acetylcholine receptor binding in a normal subject and dopamine receptor binding studies have been reported (6).

The question of what radiotracers are to be used in perfusion imaging is an ongoing one. A large amount of experience has been obtained with [^{123}I]IMP. Agents labeled with technetium 99m ($^{99\text{m}}\text{Tc}$) are gaining favor due to the physical characteristics, cost, and availability of $^{99\text{m}}\text{Tc}$. Biologic characteristics of the tracer are also important. Radiotracers must have high first-pass extraction and rapid blood clearance, along with slow metabolism and back-flux into the blood. Their distribution must also reflect regional cerebral perfusion from time of injection until completion of the study (6). While diagnostic procedures such as computed tomography (CT) and magnetic resonance imaging (MRI) give anatomic information, physiologic information, such as cerebral blood flow and cerebral metabolism, are obtained from PET and SPECT.

Technetium-99m hexamethyl propyleneamine oxime ($^{99\text{m}}\text{Tc}$ -HMPAO) is a radiotracer whose biological characteristics allow it to cross the blood-brain barrier. It thus becomes trapped inside functional cells and proportionally reflects regional cerebral blood flow (7). Figure 2 is a SPECT image with $^{99\text{m}}\text{Tc}$ -HMPAO in a patient with AD, while Figure 3 is an MRI image of the same patient.

A more in-depth look at the work being done in PET, SPECT, and combinations with other modalities is necessary to emphasize the important contributions of nuclear medicine to AD. PET imaging with fluorine-18 fluorodeoxyglucose ([^{18}F]FDG) and oxygen-15 (^{15}O) has been shown to be the first imaging procedure to provide accurate diagnoses of AD and multiinfarct dementia (MID) (8).

A study by Jagust, Friedland, and Budinger, using PET and [^{18}F]FDG, was conducted to differentiate normal pressure hydrocephalus (a reversible dementia) from AD (9). Since normal pressure hydrocephalus can only be diagnosed retrospectively by observed improvement following cerebrospinal fluid shunting, a method of excluding patients unlikely to respond to cerebrospinal fluid shunting (such as patients with AD) is needed to ensure higher success rates.

Three patients with normal pressure hydrocephalus, 17 patients with AD, and 7 healthy elderly controls were used.

Findings showed both AD and normal pressure hydrocephalus groups with lower cortical rates of FDG utilization than controls. Metabolic abnormality patterns were distinctly different between the AD group and the normal pressure hydrocephalus group. However, the AD patients showed bilateral temporoparietal hypometabolism while the normal pressure hydrocephalus patients showed globally diminished glucose use.

The findings in the AD subjects were in agreement with other studies of cerebral metabolism; focal or multifocal abnormalities and hypometabolism were most evident in the temporoparietal and frontal association cortex (9). To date, PET imaging is limited by a lack of available centers, cost, and its requirements for a large, highly trained staff.

SPECT imaging with a variety of gamma cameras and collimators is also being considered as an accurate testing technique in the differential diagnosis of dementia. It is much more widely available than PET. In a study by Cohen, Graham, Lake, et al., SPECT imaging was done using a scintillation camera, a rotating slant-hole collimator, and IMP labeled with high purity ^{123}I (8). Subjects were six normal volunteers, five AD patients, and three MID patients. All subjects received electroencephalograms, computer-aided tomography scans, and appropriate laboratory evaluations to rule out other dementias. AD patients were diagnosed based on the criteria of McKhann et al., and MID patients were clinically diagnosed with a high score on the Hachinski scale. Image slices were reconstructed using commercially available software.

In evaluation by four physicians, five of the six normal subjects were correctly identified by all physicians. The sixth subject was correctly identified by three of the four physicians. All three MID patients were correctly identified by all four physicians. Two of the five AD patients were correctly identified by all four physicians. A third AD patient was correctly identified by three of the four physicians and was misidentified as an MID patient by the other physician. A fourth AD patient (considered early AD) was identified as normal by two physicians and as an AD patient by the other two. A fifth AD patient (considered advanced AD) was incorrectly identified as an MID patient by all four physicians. While the sensitivity and specificity for AD using this SPECT system was not impressive, its use in ruling out the normal subjects and MID patients for AD was demonstrated.

In another study of perfusion SPECT using [^{123}I]IMP (6), cortical to cerebellar ratios (radiotracer activities in the parietal, frontal, temporal, and striate cortex compared with activity in the cerebellum), were significantly lower in AD patients for most regions of the cortex, compared to the controls. Uptake was decreased in posterior parietal, frontal, lateral, medial, and posterior temporal cortex. The uptake in the posterior parietal cortex in AD patients was decreased in 13 of 15 subjects. Ten of fifteen AD patients showed decreased frontal temporal cortex activity, and six of the fifteen showed decreased lateral temporal cortex activity.

In a study by Burns, Philpot, Costa, et al. (7), SPECT imaging with $^{99\text{m}}\text{Tc}$ -HMPAO was performed to quantify the

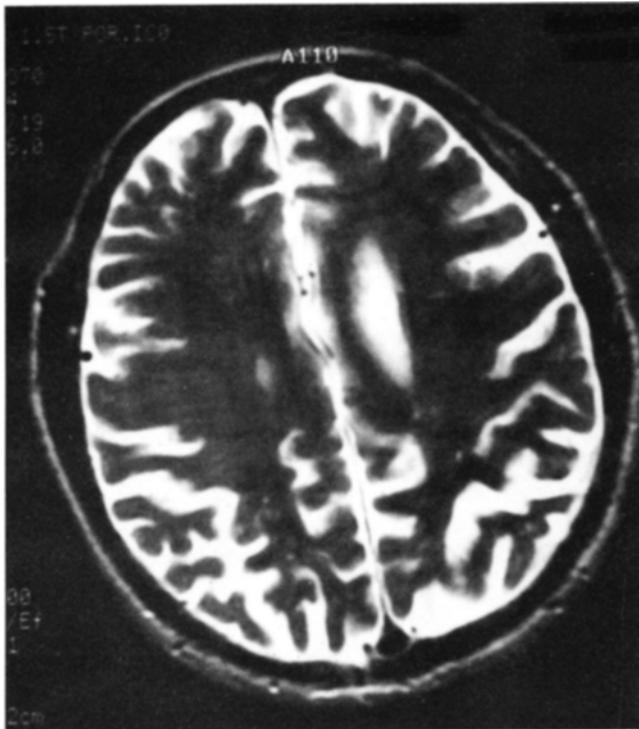


FIG. 3. Magnetic resonance image of the patient with Alzheimer's disease in Figure 2.

regional distribution in the brain and to determine how that distribution related to a number of clinical and neuropsychological characteristics in a group of AD patients. Studies before this had focused mainly on describing the scan appearances in different dementias and assessing the researchers' ability to differentiate patients with dementia from age-matched controls. Twenty patients and six controls were scanned.

Table 1 shows results of metabolic activity in the regions of interest (ROIs) in the AD group and control group.

Table 2 shows the clinical differentiation of AD patients into groups with and without aphasia/apraxia. The AD group had significantly lower activity bilaterally in the temporal and posterior parietal lobes. Psychological testing (MMS, CAMCOB-praxis, AMTS, and CAMCOG-memory) showed correlation between posterior parietal lobe activity and apraxia; between temporal lobe activity (mainly left) and memory loss; and between left frontal, left lateral temporal, and left posterior parietal activity and language dysfunction.

Findings of the study showed evidence that amnesia is associated with decreased cerebral blood flow to the temporal lobe, apraxia is associated with decreased cerebral blood flow to the parietal lobe, and aphasia is associated with decreased cerebral blood flow throughout the left hemisphere. An early age of onset in AD was associated with decreased activity in the left posterior parietal lobe (7).

In the search for accurate diagnoses of Alzheimer's disease, several methods for combining modalities and for comparing modalities have been researched. A method for combining SPECT and MRI has recently been studied (10). T₂-weighted axial MRI images and transaxial ^{99m}Tc-HMPAO and thallium-201 (²⁰¹Tl) images, acquired with an annular gamma camera, were merged. Perfusion images of SPECT and anatomical images of MRI were superimposed in an attempt to correlate high tracer uptake and gray matter structures. Five normal volunteers, four AD patients, two patients with recurrent glioblastoma, and three patients with focal lesions (stroke, arachnoid cyst, and head trauma) were imaged.

Results showed excellent correlation between high tracer uptake and gray matter structures in normal subjects. In the three patients with focal lesions, abnormalities on MRI and SPECT superimposed. The two patients with recurrent glioblastoma showed focal areas of increased uptake on SPECT corresponding to areas of tumor recurrence on MRI. The four patients with AD showed perfusion defects in posterior temporal, inferior parietal, and frontal cortices on SPECT.

TABLE 1. Regional Cerebral Activity in Alzheimer's Disease Patients and Control Groups

Cerebral Region	Regional Activity* (mean, s.d.)		Significance of Difference
	Alzheimer's [†]	Control [‡]	
R. Frontal	0.77, 0.04	0.78, 0.03	NS
R. Lateral temporal	0.72, 0.05	0.79, 0.04	p < 0.01
R. Medial temporal	0.69, 0.04	0.77, 0.05	p < 0.01
R. Anterior parietal	0.77, 0.04	0.78, 0.04	NS
R. Posterior parietal	0.72, 0.08	0.80, 0.04	p < 0.01
L. Frontal	0.76, 0.05	0.79, 0.03	NS
L. Lateral temporal	0.70, 0.08	0.79, 0.04	p < 0.01
L. Medial temporal	0.65, 0.08	0.76, 0.05	p < 0.02
L. Anterior parietal	0.76, 0.05	0.79, 0.05	NS
L. Posterior parietal	0.70, 0.08	0.80, 0.04	p < 0.01

*Expressed as a ratio of regional to total cerebellar activity.

[†]N = 20; mean age = 69.5, s.d. = 9.2, NS.

[‡]N = 6; mean age = 67.5, s.d. = 8.7, NS.

NS = not significant at p < 0.05.

All statistics: Mann Whitney "U" test, two-tailed (except age, Student's t-test).

TABLE 2. Comparisons Within the Alzheimer's Group

Cerebral Region	Regional Activity* (mean, s.d.)		Significance of Difference
	Aphasia/Apraxia absent [†]	Aphasia/Apraxia present [‡]	
R. Frontal	0.79, 0.02	0.76, 0.05	NS
R. Lateral temporal	0.75, 0.05	0.70, 0.05	p < 0.05
R. Medial temporal	0.69, 0.04	0.69, 0.04	NS
R. Anterior parietal	0.78, 0.03	0.77, 0.05	NS
R. Posterior parietal	0.76, 0.05	0.69, 0.09	p < 0.05
L. Frontal	0.75, 0.05	0.75, 0.05	NS
L. Lateral temporal	0.75, 0.05	0.66, 0.07	p < 0.01
L. Medial temporal	0.68, 0.08	0.64, 0.07	NS
L. Anterior parietal	0.77, 0.04	0.75, 0.05	NS
L. Posterior parietal	0.77, 0.04	0.66, 0.07	p < 0.01

*Expressed as a ratio of regional to total cerebellar activity.

[†]N = 8; mean age = 72.6, s.d. = 10.3, NS; mean on CAMCOG-language test = 26.8, s.d. = 1.8, p < 0.001; mean on CAMCOG-praxis test = 10.8, s.d. = 1.8, p < 0.003.

[‡]N = 12; mean age = 67.4, s.d. = 8.1, NS; mean on CAMCOG-language test = 11.8, s.d. = 9.4, p < 0.001; mean on CAMCOG-praxis test = 5.7, s.d. = 4.1, p < 0.003.

NS = not significant at p < 0.05.

All statistics: Mann Whitney "U" test, two-tailed (except age, Students t-test).

The MRI images in the AD patients were either normal or showed only generalized atrophy.

In a study by Fazekas, Alavi, Chawluk, et al. (11), a comparison was made of CT, MRI, and PET (using [¹⁸F]FDG) in Alzheimer's disease and normal aging. In both CT and MRI scans, higher grades of cortical and ventricular atrophy were seen in AD patients than in age-matched controls. PET images were ranked as normal in 21 of 25 age-matched controls. Mild metabolic abnormalities were present in three controls, a moderate abnormality was present in one control, and 29 of 30 patients with AD were shown to have significant hypometabolism. The opinion of the authors was that test results "confirm that metabolic dysfunction may be the first indication of a degenerative cortical process in DAT [dementia of the Alzheimer's type], whereas anatomic changes like cortical atrophy, while still associated with hypometabolism, become evident on CT or MR only later in the course of the disease process."

In a 1990 study by Gemmell, Evans, Besson, et al. (12), a comparison of ^{99m}Tc-HMPAO SPECT and carbon-15 (¹⁵C) ²O PET in regional cerebral blood flow imaging was done in an attempt to quantify, in absolute units, the regional cerebral blood flow values found in demented patients (AD and MID). Since therapeutic trials for both AD and MID are beginning to emerge, and the numbers of demented patients are increasing greatly in developed countries, quantitative differentiation between AD and MID would be of great benefit. While the results of the study were disappointing regarding the use of SPECT alone (without comparison to another technique, such as PET) to quantitatively determine regional cerebral blood flow, there was good agreement between the PET images and the equivalent SPECT images.

CONCLUSION

The present and future role of nuclear medicine and its varied applications appears to be that of a major influence in the diagnosis, differentiation, management, and potential cure of AD. Recent statistics indicate that the number of Americans who will be either directly or indirectly effected by the trauma of AD is growing at an astronomical rate. Nuclear medicine can have a positive impact in the diagnosis and prevention of AD for the people whose minds are taken from them prematurely.

Nuclear medicine can help to protect patients, families, and society from the frightful toll that AD is projected to have on the human race. According to a University of South Florida (USF) study, described recently in the *Tampa Times* (13), AD could cause the collapse of America's health care system. This study projects a quadrupling of the nation's number of Alzheimer's patients to 16 million by the year 2040. Eric Pfeiffer, director of USF's Suncoast Gerontology Center, has warned that while only 3% of people aged 65-74-yr-old can expect to suffer from the disease, for those 75-84-yr-old, the rate is 19%, and for those 85-yr-old or older, 47% will succumb. Pfeiffer has said, "We've got a freight train coming toward us." Nuclear medicine not only has the ability, but an obligation to play a significant role in the medical community's effort to slow down the train.

ACKNOWLEDGMENT

This paper is dedicated to my mother, Shirley Alice Ten-Broeck, who was diagnosed with AD at the age of 59 and is today in the final stages of the disease. In her eighth year of the illness, she can no longer walk, talk, or take care of her basic needs, but she can still cry.

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