



# Painting a Picture of Alzheimer's Disease

It has been said many times that a picture is worth a thousand words, and in the diagnosis of Alzheimer's disease that saying rings especially true. PET images of the brain's function can indicate a diagnosis of this progressive disease earlier and more reliably than any other method.

*By Joanna B. Downer, Ph.D.*

Until recently, Alzheimer's disease was barely diagnosed at all – some cognitive tests, done by the right people, could suggest someone was suffering from Alzheimer's disease, but the only surefire diagnostic criteria were the presence of beta-amyloid plaques and neurofibrillary tangles in the brain at autopsy.

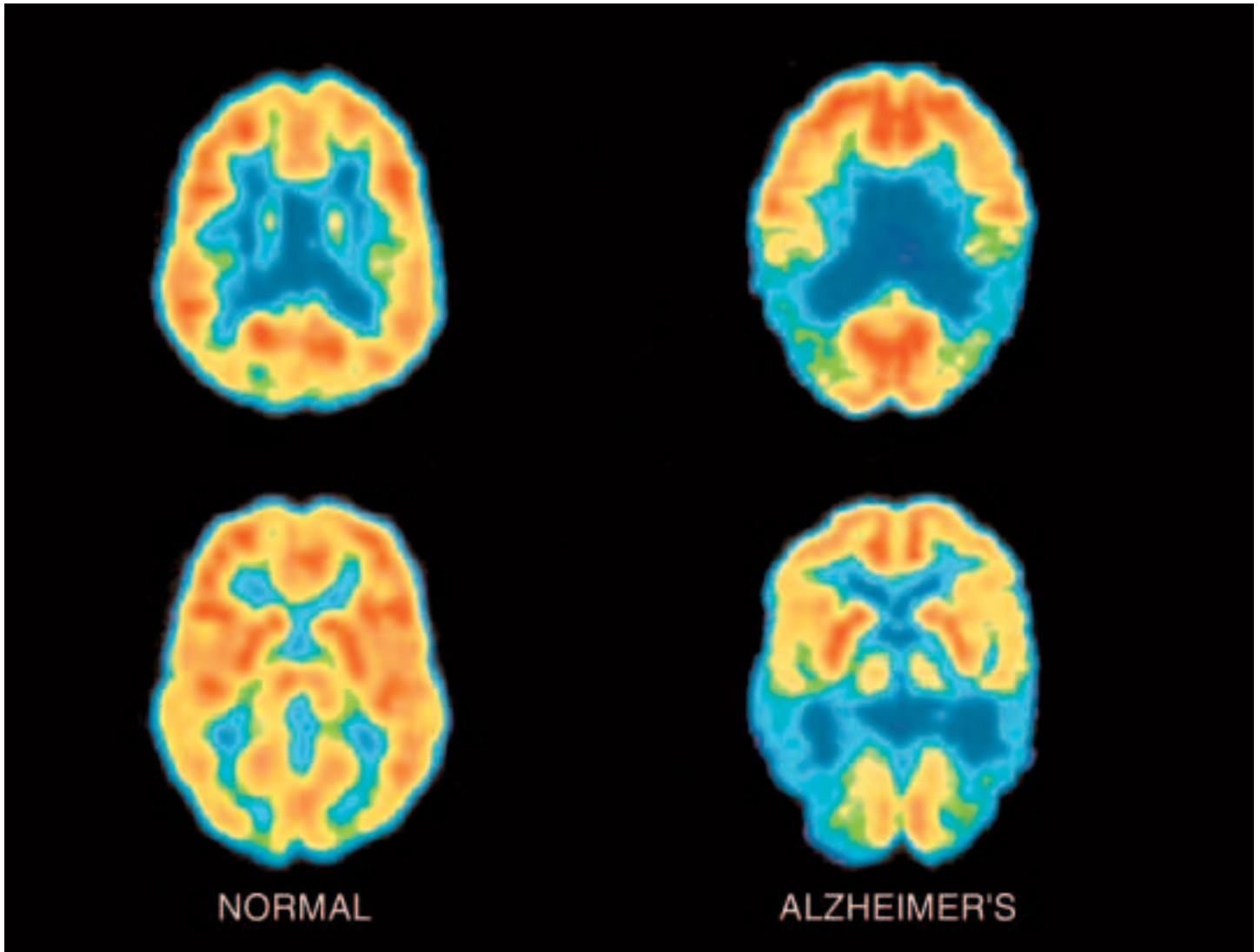
But now, ever more commonly, images provided by Positron Emission Tomography (PET) of the brain's uptake of F-18 fluorodeoxyglucose (FDG) are being used to reveal metabolic changes characteristic of Alzheimer's disease even before clinical symptoms become significant. Images showing low metabolic activity in the posterior parietal and posterior temporal lobes can indicate that mild cognitive impairment is in fact early Alzheimer's, also known as prodromal Alzheimer's.

"You have to diagnose Alzheimer's in the early stages because that's when you can do the most good with today's drugs," says Marie Carlisle, M.D., Ph.D., and comedical director of the Northern California PET Imaging Center (NCPIC) in Sacramento, California. "PET has far superior sensitivity and specific-

ity at these stages than other methods." PET with FDG has a sensitivity of about 96 percent and a specificity of 100 percent when patients have questionable results on clinical diagnostic criteria, Carlisle says, although single-baseline PET has been reported to have a specificity of roughly 73 to 78 percent. In contrast, clinical diagnosis via cognitive testing and related methods is reported to have a sensitivity of 83 to 85 percent and a specificity of only 50 to 55 percent. And it's nearly impossible for clinical or neuropsychological testing alone to determine whose mild cognitive impairment is really prodromal Alzheimer's and whose is not – information critical for proper application of drugs to fight Alzheimer's.

## A Picture of Progress

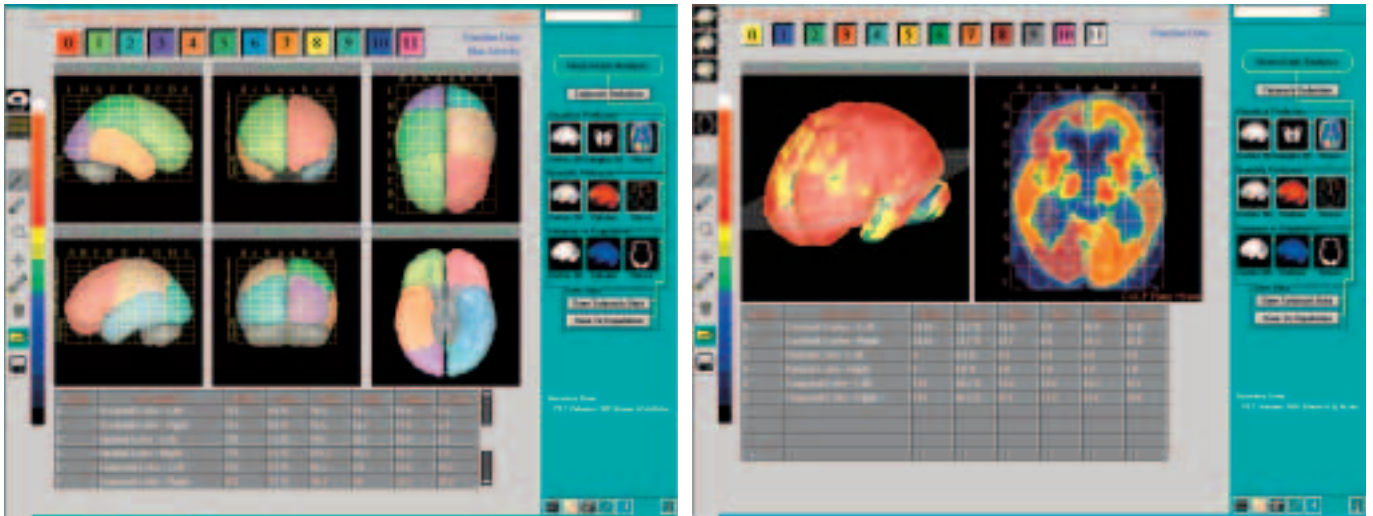
PET for Alzheimer's diagnosis has been available in certain circles for ten to twelve years. For example, the NCPIC's eightieth patient, imaged on a Siemens PET scanner twelve years ago, had Alzheimer's and a strikingly abnormal FDG image. But only very recently has FDG-PET been accepted as a tool for



IMAGES SHOWING low metabolic activity in the posterior parietal and posterior temporal lobes.

diagnosing Alzheimer's disease in the United States. Insurance companies' coverage is increasing. The federal government has recently adopted limited coverage guidelines for Medicare, the health care reimbursement program that benefits Americans over the age of 65. In September 2004, the Centers for Medicare and Medicaid Services approved Medicare coverage of FDG-PET for selected patients whose cognitive and neuropsychological tests point to a possible, but inconclusive, Alzheimer's diagnosis. While it's a critical development, the federal reimbursement program isn't taking advan-

tage of everything PET can provide for Alzheimer's diagnosis – especially seeing that four million Americans are affected by Alzheimer's now, but if prevention doesn't improve, the Alzheimer's Association says 7.7 million Americans will likely have Alzheimer's by 2030 as the "baby boomers" surpass age 65. As it stands, Medicare will reimburse for patients whose symptoms are not the usual battery of memory and cognitive problems, but that instead overlap with those more typical of front-temporal dementia. Medicare reimbursement of FDG-PET for Alzheimer's, then, would generally



QUANTITATIVE tools to evaluate brain function.

apply to patients whose symptoms are primarily behavioral rather than cognitive.

“The pattern of FDG uptake in Alzheimer’s disease is very different from the pattern of uptake in frontal lobe dementia – the reduced uptake in Alzheimer’s is posterior, while that in frontal lobe dementia is anterior,” notes Elma Abella, M.D., comedical director of NCPIC. “So it’s a fairly straightforward distinction,” she adds.

While many clinicians waited for Medicare coverage, researchers have been using FDG-PET to capture in “pictures” the natural history of Alzheimer’s disease and mild cognitive impairment. High-resolution PET scanners, such as those using Siemens LSO HI-REZ detector technology, allow ever more precise localization of FDG and experimental tracers in the brain. Studies have been conducted, for example, at the Duke Evidence-based Practice Center in 2001\*, to determine the effectiveness of PET in the diagnosis and management of Alzheimer’s disease and dementia. The knowledge gained from this and other studies will help researchers begin to address Alzheimer’s – number 7 on the Center for Disease Control and Prevention’s

list of the nation’s top killers – as they’ve addressed the top two causes of death in the United States.

“For cancer and cardiovascular disease, there has been great progress in advancing early diagnosis, offering preventive strategies and developing effective treatments. We were not able to do as much for dementia, and our future is fairly obvious if nothing changes – we’re going to live longer and die demented,” says Jorge R. Barrio, Ph.D., a professor of molecular and medical pharmacology at the University of California in Los Angeles (UCLA). “There are still many things we don’t know about Alzheimer’s, but it can be predicted that a better understanding of food constituents, anti-inflammatory drugs and (future) development of antiaggregation drugs will help us prevent or slow down progression of the disease.”

### A Picture of the Possibilities

And PET isn’t just helping doctors diagnose Alzheimer’s disease, it’s actually helping researchers identify and improve strategies to prevent and treat the disease. In the experimental arena, researchers are testing radiolabeled compounds that actually reveal the presence and number of plaques and tangles in a living person’s brain, offering the chance to identify the disease even before

\* “Use of Positron Emission Tomography and other neuroimaging techniques in the diagnosis and management of Alzheimer’s disease and dementia”, December 14 2001  
Prepared for the Agency for Healthcare Research and Quality by David B. Matchar, M.D.



neurons die, track plaques and tangles as brain function declines, and determine how treatments affect these harbingers of destruction.

So far, the Food and Drug Administration has approved only two classes of drugs for Alzheimer's, and both provide the most benefit when started as early in the course of the disease as possible. Around the world, scientists are evaluating the abilities of new agents, and even existing drugs, to help prevent the buildup of plaques and tangles, "dissolve" them once they are present, or keep them from killing neurons. Experimental PET radiotracers such as F-18 FDDNP, or 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl) amino]-2-naphthyl} ethylidene) malonitrile, both developed at UCLA, can help measure those agents' effects and reveal how they work.

For example, Barrio and his colleagues reported last year that two over-the-counter pain relievers, ibuprofen and Naproxen, bind to plaques at the same active site as FDDNP and showed that all three compounds prevent or reduce aggregation of plaques in laboratory experiments. Their work suggests a potential neuroprotective mechanism of

action for nonsteroidal anti-inflammatories other than their intrinsic anti-inflammatory properties. F-18 FDDNP could eventually provide even earlier diagnoses of Alzheimer's disease in populations at particular risk, too. "We're thinking ahead. We're thinking about being able to identify the very earliest stages of Alzheimer's disease, before pathology can cause neuronal death and well before neuronal death can cause symptoms," says Barrio. "But we studied FDG in Alzheimer's for 25 years and just got Medicare approval, so we expect it will be some time before we really know what role FDDNP and other radiotracers will have in Alzheimer's disease." PET with FDG and perhaps newer tracers will be quite important in evaluating new treatments for a disease whose course can run for decades, which makes prospective, longitudinal studies of a potential drug's effects and benefits daunting. "PET gives you an earlier chance to see what's happening," says Abella of NCPIC. "Are there changes in uptake of FDG after giving the drug? Are the changes taking place because the patient has clinically improved? Is hypometabolism of the posterior parietal or posterior temporal lobe improving, is it changing, is it staying the same? With the medication, does the brain continue to deteriorate, does the deterioration stop, or does it even get better?" Carlisle adds: "There will definitely be more studies using PET as insurance coverage increases and as people become more aware of the value of PET in diagnosing Alzheimer's. A lot of people have heard of PET, mostly for applications in cancer, but we still have a long way to go in educating patients and physicians about the ability of PET to quickly and accurately diagnose Alzheimer's disease."

With PET imaging to diagnose the disease as early as possible and to help develop and evaluate new drugs, the future of Alzheimer's disease is likely to shift from a picture of inevitable decline to one of promise and hope.

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