NEUROSCIENCE

Possible New Test Found for Alzheimer's Disease

As the population ages, physicians more and more frequently find themselves facing the diagnostic dilemma posed by an elderly patient who has begun showing memory loss and declining mental function. Is this due to Alzheimer's disease, which is currently untreatable? Or is it due to some other condition, such as depression, vitamin deficiency, or overmedication, for which effective therapies are available? It can be a difficult call for the average physician—and that dilemma has fueled the search for a simple and reliable test for Alzheimer's disease. On page 1051, a research team led by Leonard Scinto and Huntington Potter of Harvard Medical School proposes a promising candidate: an eye test that distinguishes Alzheimer's patients from normal subjects.

But as hopeful as the early results seem, previous failures of a series of highly touted potential diagnostic tests have made Alzheimer's researchers more than usually cautious. If the new test works, "it would be marvelous," says Leon Thal, who studies Alzheimer's at the University of California, San Diego. But, he adds, "this is a very early and very preliminary study." Caution aside, one reason for excitement over the current test is the hope that it may be able to identify Alzheimer's before symptoms become apparent—which would be a boon should effective treatments become available.

At present, the only definitive way of confirming a diagnosis of Alzheimer's is at autopsy. But there is also a relatively reliable, albeit expensive, method for diagnosing the disease in a living patient, using a complex battery of neurological and psychological exams. And recently researchers at Albert Einstein College of Medicine in the Bronx announced a psychological test that can tell whether a person is *unlikely* to develop Alzheimer's in the next 4 years. But despite these advances, the search goes on for an even cheaper and simpler diagnostic tool, "something on the level of a pregnancy test," says Alzheimer's researcher Peter Davies of Albert Einstein. The eye test, if it proves reliable, could possibly be such a test, says John Trojanowski, who directs the Alzheimer's research center at the University of Pennsylvania School of Medicine: "It has a lot of appeal because of its simplicity and low cost."

Potter came up with the idea for the eye test by scouring the literature on patients with Down's syndrome. He chose that literature because people with Down's who reach middle age invariably develop a condition whose neuropathology is identical to that of Alzheimer's. Potter was looking for a so-called "peripheral marker" of Down's—a characteristic that can be easily measured without brain scans or psychological tests—that might also be present in Alzheimer's patients and could be used as a diagnostic indicator.

PHOTOS BY JIM HARRISON

Do the eyes have it? Pupils of a patient with Alzheimer's disease *(right)* dilate in response to a dilute solution of an acetylcholine-blocking drug. Those of a normal subject *(above)* show a much smaller response.

Potter's search was productive: He found a marker that seemed promising. Several studies found that Down's patients are hypersensitive to drugs that block the effects of the neurotransmitter acetylcholine. The next step was to see whether Alzheimer's patients show a similar effect, and if so, whether it is specifically associated with the disease. To answer these questions, Potter joined forces in 1991 with clinician Marsel Mesulam, neuroscientist Scinto, and their colleagues, then at Beth Israel Hospital in Boston. Together, they developed a simple assay for the hypersensitivity that measures pupil dilation in response to a very dilute solution of the acetylcholine-blocking drug, tropicamide, which is routinely used during eye exams.

The Harvard team found that the eyes of normal subjects barely respond to tropicamide when it is diluted to one hundredth of the standard concentration. But 18 out of 19 patients with probable Alzheimer's disease, as determined by neurological and psychological tests, were hypersensitive to the drug, their pupils dilating 13% or more. "You get this very dramatic separation between patients with clinical diagnosis of Alzheimer's and nondemented, healthy individuals," says Scinto.

Even more intriguing, Potter and Scinto suggest that their test may be able to predict who will get Alzheimer's even before symptoms develop. In two patients, one of whom is described in the current paper, the pupil test was positive in the year before the first Alzheimer's symptoms developed, Scinto says. If drugs can be found that halt the neuronal degeneration in Alzheimer's, a predictive test would be very valuable. "The biggest bang for your buck with a therapy may come in a patient who is in a predementia state," before the damage to the brain is too extensive, says Penn's Trojanowski.

The current test is intriguing to some researchers who say that it makes biological sense, as acetylcholine-producing (cholinergic) neurons of the brain are among the major neuron groups that degenerate in Alzheimer's. If the loss of cholinergic neurons were to extend outside the brain as well, Thal says, "that could very well explain the supersensitivity to cholinergic agents in the eye."

But given the dismal record of other proposed Alzheimer's tests (there have been various skin-punch tests, blood tests, and brain scans that initially looked good, then failed in larger trials), everyone agrees caution must be maintained until the eye test is validated in trials that go far beyond the present total of 58 subjects and controls. "We need [to test] 10 to 100 times the number [of subjects] in that paper," says Einstein's Davies. "Let's make sure it is [tried] in people without dementia, with dementia, and with eye disorders [that could affect pupil dilation]. ... We need to know what might limit the utility of this test."

Potter and Scinto agree that their test needs confirmation in larger trials. "We hope our colleagues all over the country will try their patients," says Potter. And they are getting their wish. Trojanowski says the Alzheimer's center at Penn is setting up to test the eye exam, and he expects other research centers to follow suit.

But that doesn't mean answers will emerge soon, says Trojanowski, as definitive confirmation of the test's diagnostic value will depend on following a certain number of trial subjects through to death and autopsy. If those longer trials confirm the initial results, though, says Alzheimer's researcher John Blass of Cornell University Medical College, "then they have given us a wonderful adjunct for diagnosis."

–Marcia Barinaga