

## Brain changes may foretell Alzheimer's

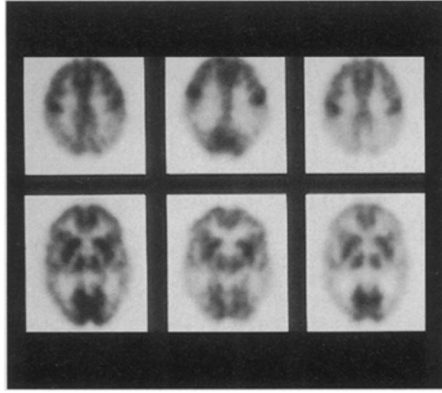
Subtle alterations in brain function may foreshadow the onset of Alzheimer's disease in genetically at-risk middle-aged people, according to a new report.

"The findings suggest there are changes going on years before the disease can be confirmed clinically," says lead researcher Gary W. Small of the University of California, Los Angeles, School of Medicine.

Small and his colleagues recruited 31 men and women age 50 or older from families with a history of Alzheimer's disease. These high-risk volunteers all had mild memory complaints, such as misplacing familiar objects. However, they all performed normally on tests of cognitive function. The researchers wondered if they could identify those who would go on to develop Alzheimer's disease, which causes severe memory loss.

All of the subjects underwent a scanning procedure called positron emission tomography (PET). This test allows researchers to gauge the brain's use of glucose, a sugar that provides nourishment for nerve cells.

Small's team knew that PET scans of people with Alzheimer's disease reveal a decreased ability to utilize glucose, a deficit that starts initially in the parietal cortex (see photo). This brain region is



*This photo shows the progressive change in brain function of a person suffering from Alzheimer's disease. The whitish areas of the PET scan represent patches of nerve cells that aren't functioning properly. As the dementia worsens, the lighter areas become more pronounced.*

associated with memory, language, and other functions impaired by the disease process.

Yet those scans had never been shown to flag otherwise healthy people who later succumbed to Alzheimer's disease. So the researchers decided to add a genetic assessment to their study design.

They knew that a team at Duke University Medical Center in Durham, N.C., had previously linked a gene known as apolipoprotein E-IV to Alzheimer's disease (SN: 1/1/94, p.8). This prompted

Small's group to collect blood samples from its recruits. Twelve of the 31 had inherited this risky gene.

The group then combined the brain scan and genetic testing results. The 12 volunteers who carried apo E-IV displayed significantly reduced glucose utilization in the parietal region, compared to the 19 who did not inherit this gene. The researchers report their results in the March 22-29 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION.

The reduction in glucose metabolism suggests that the neurons in the parietal region either aren't working well or have died, points out Zaven S. Khachaturian, an Alzheimer's researcher at the National Institute on Aging in Bethesda, Md. For people without dementia, such slight changes may be the first step in a decline leading many years later to full-blown disease, he says.

If researchers can identify such people, they may be able to test experimental drugs aimed at preventing the nerve cell death that underlies Alzheimer's disease.

The ultimate goal is "not only to identify these people early, but to have an intervention so that you can actually stop the [disease] process in its tracks," says Sheryl L. Williams of the Chicago-based Alzheimer's Association.

Still, the researchers emphasize that other groups must verify their results. "These are preliminary findings," Small says.

— K. Fackelmann

## Schizophrenia drugs: A case for tapering

About 40 years after neuroleptic drugs gained renown for their ability to quell hallucinations and other symptoms of psychosis, psychiatrists face a vexing dilemma in deciding how to use these substances to treat schizophrenia. Prolonged use of neuroleptics, also known as antipsychotic drugs, causes severe movement disorders in a substantial minority of those whose mental condition improves. Yet taking patients off the drugs can trigger the return of schizophrenia in an intensified form.

Either way, physicians may face a lawsuit. And recently, researchers studying how people with schizophrenia react to the withdrawal of neuroleptics drew a federal reprimand after several patients suffered severe relapses and one committed suicide (SN: 3/19/94, p.188).

A new review of all such withdrawal studies concludes that schizophrenia often remains under control after a gradual lowering of the drug dosage to levels much less likely to cause movement disorders, such as the uncontrollable tics and jerks known as tardive dyskinesia. This approach, as opposed to rapid withdrawal, best prevents relapses, the review's authors argue.

"The optimal solution in many cases is to slowly taper neuroleptic therapy, once a patient's condition has become stable, to a substantially lower dose that still controls symptoms of schizophrenia," asserts study director Dilip V. Jeste, a psychiatrist at the University of California, San Diego. "For some patients, it may be possible to stop neuroleptic therapy."

In their review of 66 studies conducted between 1958 and 1993, Jeste and his colleagues find that nearly half of all patients diagnosed with schizophrenia remained largely symptomfree for at least 10 months after they stopped taking neuroleptics. A total of 4,365 people with schizophrenia participated in these investigations.

About 53 percent of those taken off neuroleptics had a return or worsening of schizophrenia symptoms within 10 months, compared to 16 percent of those kept on the drugs.

Repeated drug "holidays" lasting several months at a time do not prevent — and may indeed worsen — tardive dyskinesia, Jeste and his colleagues contend in the March ARCHIVES OF GENERAL PSYCHIATRY. Moreover, continuous

antipsychotic treatment controls schizophrenia much better than intermittent treatment instituted only when psychotic symptoms flare up, they argue.

It usually takes a year or more to find the particular type and amount of neuroleptic that best controls a person's schizophrenia. At that point, gradual tapering of the dosage should be tried, Jeste holds.

Patients respond best to reduced dosages if they have access to programs that teach social skills, an option that is often unavailable or unaffordable, Jeste notes.

Studies to date have not identified any characteristics of schizophrenia sufferers that mark some as more likely to suffer a relapse following neuroleptic withdrawal, he says.

In comments accompanying the new report, several psychiatrists support frequent neuroleptic tapering. Some note that a new class of medication may replace neuroleptics as a safer alternative in schizophrenia treatment, although the long-term effects of these drugs remain unclear (SN: 6/18/94, p.398). Other clinicians argue that finding the lowest effective neuroleptic dose is often difficult and not worth the risk of a relapse.

— B. Bower