

THE BATTLE AGAINST ALZHEIMER'S DISEASE

In spite of progress in understanding dementia and other memory disorders, Alzheimer's disease is on the rise. Cedars-Sinai's scientists are searching for early markers of the disease and pioneering advanced research that could delay its onset.

BY ELEANOR FOA DIENSTAG

THERE IS NO GENTLE WAY TO TELL THE STORY: the number of people with Alzheimer's disease (AD) is skyrocketing. At this moment, it afflicts more than 4.5 million people in the United States alone. As baby boomers age, those numbers will swell to somewhere between 11 million and 16 million men and women.

"In many ways, the brain is like a black box, an enigma," says Dr. Robert N. Pechnick, associate director of Psychiatry Research at Cedars-Sinai. "There are no biochemical tests for diagnosing most neuropsychiatric disorders or for predicting treatment response. We know genes are important. We know environment is important. We have a cluster of well-defined symptoms, but that leaves a lot unexplained."

Alzheimer's disease is a progressive brain disorder that gradually destroys a person's memory and ability to learn,

reason, make judgments, communicate, and carry out daily activities. As Alzheimer's progresses, individuals may also experience changes in personality and behavior, such as anxiety, suspiciousness, or agitation, as well as delusions or hallucinations. It is the most common form of dementia, yet it manifests itself differently in each patient. It is primarily an age-related disease: one in 10 individuals over 65 and nearly half over 85 have AD or a related memory disorder.

Dr. Pechnick's "black box" view of the brain is particularly apt with Alzheimer's disease. In an autopsy, two important—but, until then, hidden—characteristics of the disease become visible: "plaques" and "tangles," shorthand for protein deposits in or around the neurons. Scientists don't yet know why plaques and tangles are present in excess amounts, but they are beginning

to understand the pathways that produce these two different types of proteins. This, in turn, is leading to new treatments to block their accumulation.

Among researchers there is a "spirited debate," says Dr. Robert Cohen, director of Cedars-Sinai's Psychiatric Research Program, chief of research for Memory Disorders, and holder of the Steven C. Gordon Family Foundation Endowed Chair in Memory Disorders. "Which is the real bad guy: plaques or tangles? Some believe that if you get rid of the plaques you have taken care of the problem; others think plaques are only a part of the problem." Dr. Cohen has not taken sides in the debate, but his studies of cerebral spinal fluid suggest that plaque deposits occur earlier than tangles. "Until we can get rid of amyloid plaques in humans, we won't know which treatment approach will really work."



The Integrated Memory Disorders Program will serve as liaison between patients, families, and a range of inside and outside community services. Best of all, it will combine state-of-the-art clinical care with cutting-edge translational research.

Given that plaques and tangles are impossible to see in living subjects, the holy grail for AD researchers is to find early biomarkers of the disorder. This would allow physicians to detect the disease through a simple test. “Since most of us will get Alzheimer’s if we live long enough,” Dr. Cohen points out, “the question is not so much who is going to get it, but rather can we predict at what age an individual is likely to develop it?”

Since the seeds of AD may be planted as early as our late teenage years, the potential inherent in early diagnosis is immense. Electromagnetic differences in the brain tell us that individuals in their twenties with a particular gene (APOE- ϵ 4) activate their brain differently in response to memory tasks—perhaps less efficiently—than those who do not have the gene. “This means that there are differences in the brain well before aging,” notes Dr. Cohen. He is preparing a developmental study of people with the APOE to further pursue this tantalizing clue to early signs of vulnerability to AD.

DR. COHEN’S PASSION FOR UNDERSTANDING Alzheimer’s disease is both professional and deeply personal. In the mid-1990s, he was a scientist with the National Institute of Mental Health (NIMH). For over a decade, much of his research had been focused on Alzheimer’s disease. Ten years into his pioneering work, Dr. Cohen made a devastating discovery: His father was developing the disease.

“I was the first one to notice the memory problem,” he recalls. In common with so many families of those who have the disease, he encountered physicians who failed to make the diagnosis and, when informed, failed to treat him appropriately. “I would say, you have a problem here, you should do x, y and z, and they would say, well, he’s 75 years old. Do you expect him to live forever?”

During his father’s 10-year decline, Dr. Cohen and his family dealt with a maze of specialists and healthcare providers who did not talk or consult

with one another. “I learned what it’s like to deal with fragmented treatment systems and, in general, how poor care is for older people.”

The experience motivated Dr. Cohen to envision a better system of clinical care for people with memory disorders. It led him to leave the pure research environment of NIMH for Cedars-Sinai, where patients’ needs drive the research and where research findings translate quickly into patient care. In Dr. Cohen’s words, “Patients should lead us to solutions.”

Dr. Cohen’s early studies helped lay the foundation for effective medications to improve early AD symptoms, and significant progress has been made in the assessment of patients with dementia, as well as in our understanding of the causes of AD.

Dr. Cohen’s work employs neuroimaging and genetic tools to look at atrophy of the hippocampus, a key area of the brain for memory function. Although the size of the hippocampus diminishes as we age, the rate of shrinkage is increased in some subjects. Those with a specific gene (a variety of the APOE gene) have an increased risk of developing Alzheimer’s. “In patients with Alzheimer’s disease, the rate of hippocampal shrinkage is increased,” says Cohen. “We are studying this to see if it is an indicator of the beginning stages of the disease. If so, we could use this measure to determine which individuals are at increased risk before the onset of memory problems. We could also determine the effectiveness of treatments in preventing the onset of dementia.”

Drs. Cohen and Pechnick—two experts who clearly enjoy brainstorming new ideas and approaches—have been working on an innovative research model for Alzheimer’s disease. It is ideal for advancing the development of new vaccines, as well as the impact of stem cells on memory disorders, particularly on the regeneration of brain tissue. They are also working with the Board of Governors Gene Therapeutics Research Institute to devise immune therapies.



TODAY, ALZHEIMER’S PATIENTS AND THEIR families find few experts and modest help. Typically, a family goes to their general practitioner who asks a few questions, says “you may have Alzheimer’s,” prescribes a medication and sends you on your way. There is no full diagnostic workup, little provision of care services, and unclear road maps for patient and family. It is a frightening and disjointed world in which families navigate their way from neurology to psychiatry to skilled nursing, strictly on their own.

Cedars-Sinai is responding to this deficit of patient care options by establishing the Integrated Memory Disorders Program. Its mission: to transform antiquated care models by creating an innovative, donor-supported, multi-depart-

mental program in partnership with the Alzheimer’s Association of Los Angeles (AALA). Spearheaded by Dr. Cohen and the Department of Psychiatry and Behavioral Neurosciences, it will offer comprehensive care for patients and families dealing with memory disorders, including Alzheimer’s, frontotemporal dementias, and vascular dementia. Says Cohen, “Cedars-Sinai was particularly attuned to the need for such a program because many of the patients that were successfully treated for other illnesses at the Medical Center were now succumbing to these disorders.”

Collaboration will take place between the departments of Psychiatry, Imaging, Occupational and Rehabilitation Medicine, Neurosurgery, Medicine, and

the Division of Neurology, as well as the Alzheimer’s Association.

The Integrated Memory Disorders Program will serve as liaison between patients, families, and a range of inside and outside community services. Best of all, it will combine state-of-the-art clinical care with cutting-edge translational research. Physician-scientists, like Dr. Cohen, will identify, through imaging and other techniques, the causes and risk factors of dementias, then apply their knowledge to patients and develop innovative treatments ranging from drugs and immune system therapies to vaccines and the stem cell regeneration of brain tissue.

“We have an opportunity to create something truly special at Cedars-Sinai,” says Dr. Mark Hyman Rapaport, chair of the Department of Psychiatry and Behavioral Neurosciences. “There are a number of different AD programs and scientists in Los Angeles, but they are more focused on research questions than on integrating a comprehensive care program with research.”

Peter Braun, executive director of AALA, points out, “With AD there are two clients: the person with the disease and the caregiver. So there are really over 14 million people impacted by AD.” In Los Angeles County alone, more than 150,000 are affected.

Ironically, just as Alzheimer’s research is on the cusp of dramatic advances, proposed federal funding for AD in fiscal 2007 is being reduced. As reported in the July-August 2006 edition of the *AARP Bulletin*, proposed funding for Alzheimer’s research for 2007 is \$645 million, down from \$652 million in 2006 and \$658 million in 2003. To make the Integrated Memory Disorder Program a reality will require, above all, the generosity of donors. The need is great. The vision is powerful. The potential breakthroughs are hopefully on the horizon. ●