Preface

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One hundred years ago, Emil Kraepelin built his neuroscience department at the Psychiatric Clinic in Munich, Germany, by recruiting some of the most talented men in medicine. Among those who joined Kraepelin were Franz Nissl and Alois Alzheimer. Kraepelin charged his faculty with uncovering the biological bases of mental illness and dementia. This request was remarkable at the time, and it is still the focus of much of neuroscience research today. No sooner was the challenge issued than Alzheimer, in 1906, took a giant step forward when he described the microscopic neuritic plaques and neurofibrillary tangles in the brain of his patient Auguste D. These features stand today as the cardinal histopathologic abnormalities of what Alzheimer called presenile dementia and that characterize the dementia that Kraepelin was later to call Alzheimer disease (AD). From this humble beginning of a single case report, AD is now recognized as the most common cause of dementia in the world. For many years after Alzheimer's case report, however, this condition was considered a rare disease, seen only in demented individuals younger than 65 years old. The elderly with dementia were diagnosed as having senile dementia, a condition attributed to a variety of pathologic processes including arterial sclerosis. It is now clear that the clinical symptoms and signs of dementia, and the number and distribution of neuritic plaques and neurofibrillary tangles in brain, are similar in affected individuals across all ages, and that AD does not respect the arbitrary boundary of a date on a birth certificate. It is true that increasing age is the single most powerful risk factor

for developing AD, but AD is not the inevitable consequence of aging as the majority of people die without dementia.

In the past 25 years, the pace of research directed toward unraveling the etiology of AD and understanding its pathophysiology has greatly accelerated. Clinical and basic research mutually reinforce each other. Clinicians caring for AD patients have conducted sophisticated epidemiologic, genetic and neuropsychological research and identified central problems in the diagnosis of dementia and its care. These clinical observations, in turn, directed research at the laboratory bench, and focussed efforts designed to uncover the mechanisms whereby causative genetic mutations and genetic risk factors account for the development of AD. These deepening insights into the pathophysiology of AD should guide drug development and give clinicians effective modes of therapy. Working together in this way, contemporary clinicians and investigators seek to provide molecular answers to Kraepelin's original challenge. Much progress has been made, and a brief chronology over the past 25 years would include the following high points.

(1) 1977. Discovery that indices of acetylcholine metabolism are selectively reduced in brains of AD patients.

(2) 1982. Report of severe atrophy of cholinergic neurons in the ventral forebrain nucleus basalis of Meynert and medial septal nucleus in AD brain. This anatomic discovery, coupled with the prior biochemical finding of impaired cholinergic neurotransmission, eventually led

to the successful introduction of acetylcholine esterase inhibitors as drug treatment for AD.

(3) 1984. Purification and characterization of cerebrovascular amyloid protein, which enabled an explosion of information on the molecular biology of the amyloid precursor protein (APP). These studies continue today with an emphasis on APP metabolism and the putative central role of amyloid fragments in the pathophysiology of AD.

(4) 1984. NINCDS-ADRDA clinical criteria for the diagnosis of AD were established.

(5) 1984. Destruction of entorhinal relay neurons in the medial temporal lobe partially disconnects hippocampus from neocortex and accounts for amnesia as the prominent symptom in AD. These and subsequent clinical-pathological correlative studies led to the eventual conclusion that loss of synaptic contacts and actual neuronal loss far exceeds the number of visible neurofibrillary tangles, and are the likely anatomic bases for AD dementia.

(6) 1987. APP is cloned, which led to the subsequent identification of the first demonstrated cause of early-onset familial AD.

(7) 1987. Tau is identified as the major component of neurofibrillary tangles.

(8) 1990. Recognition of dementia with Lewy bodies as a clinical variant of AD.

(9) 1991. Demonstration that the distribution of neuritic plaques and neurofibrillary tangles is not homogeneous throughout the AD brain, but occurs in a hierarchical distribution. This conclusion led to studies characterizing the vulnerable neuronal and synaptic populations in normal aging as well as AD.

(10) 1992. Amyloid- β peptide is found to be normally secreted from all cells; begin of modern secretase research.

(11) 1993. Discovery that the apolipoprotein e4 allele is a risk factor for developing late-onset AD.

(12) 1995. Point mutations in the presenilin 1 and presenilin 2 genes account for many cases of early-onset familial AD, thereby adding support to amyloid deposition as a trigger initiating a cascade of events eventually leading to AD dementia.

(13) 1995. The era of developing and testing transgenic mice that overexpress human amyloid with amyloid deposits in brain similar to that seen in AD begins.

(14) 1997. Identification of α -synuclein being a major protein component of cortical Lewy bodies in dementia with Lewy bodies.

(15) 1998. Discovery that mutations in the tau gene underlie many cases of frontotemporal dementia linked to chromosome 17 provides evidence that dementia can occur without amyloid deposition.

(16) 1999. The seminal demonstration that vaccination of APP overexpressing transgenic mice with A β _{1–42} markedly attenuates or even prevents amyloid deposition in brain. This finding sparked A β vaccination trials in human patients with AD.

(17) 2001. Development of transgenic mice that express human tau and that form neurofibrillary tangles in the brain.

(18) 2002. Report that an amyloid ligand for PET imaging accurately discriminates living patients with AD from non-AD subjects opens a new era in AD diagnostics and offers the prospect of new precision in detecting drug effects in clinical trials.

Despite these advances, as impressive as they are, there is more work to do. Separating AD from other forms of dementia in the differential diagnosis remains imprecise and relies heavily on clinical acumen instead of objective biological measures. There are still major gaps in knowing the cause of AD, especially the most common forms of late-onset AD, and many steps in the cascade of initiating events to the final stages of neuronal dysfunction and death that result in dementia remain unknown. Further, effective treatment remains elusive: the few drugs approved for AD provide only modest symptomatic benefit. Clinicians are just now beginning to speak of drugs for neuroprotection. Prospects for cure are still remote, and the goal of prevention is only a dream. It is in this context, therefore, that DIADEM was formed.

DIADEM was organized by the Verum Foundation in 2001 and coordinated until the end of the project in 2004. Funds came mainly from the European Union and to a lesser part from the Swiss Government and the Verum Foundation. DIADEM brings together 18 prominent investigators in AD research from 9 European countries and 1 from the USA. This research consortium integrates basic neurobiological and biotechnology research into advanced clinical and molecular genetic study protocols. The name, DIADEM, hints at its mission: Early Diagnosis of Alzheimer's Disease and Related Dementia. The ultimate goal and future vision of the DIADEM research consortium for the treatment of dementia is prevention. To provide the scientific basis for developing preventive treatments, DIADEM identified three areas of critical research: animal models to characterize early pathophysiological events that occur long before neurons degenerate; cellular pathophysiology to identify validated pharmaco-

logical targets that can be used for high throughput screening and lead compound identification as an initial step in the design of drugs that slow the disease processes, and biological and genetic markers that will indicate the risk for developing dementia in nondemented healthy subjects. At the formation of DIADEM, the individual laboratories were a loose confederation of investigators in the clinical and basic sciences relevant to dementia. As a result of DIADEM, these scientists have begun to see themselves as collaborating partners and openly exchange ideas, share data, conduct joint projects, and facilitate junior investigator training. The fruits of research conducted in DIADEM-funded laboratories are reported to the scientific community in high-impact peer-reviewed journal publications. The reports of DIADEM research collected for this issue of *Neurodegenerative Diseases*

highlight some of the discoveries made by the consortium and demonstrate the growing impact of European neuroscience research in the field of dementia.

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