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EDITORIAL

The Broad Range of Research in Alzheimer's Disease and Related Dementias

Steven T. DeKosky[1,3,4] · **Ranjan Duara**[2,3,4]

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The modern history of Alzheimer's disease (AD) research and discovery dates to well over 100 years ago, with the discovery of distinctive plaques and neurofibrillary tangles in the brain. However, the contemporary history of research in dementia was initiated in 1963 by Terry [1] and Kidd [2], who performed electron microscopic studies of neuropathological lesions in patients with advanced AD and demonstrated the microstructure of neurofibrillary tangles (NFTs). Subsequently, the landmark studies of Tomlinson et al. [3, 4] demonstrated the quantitative distinction in the pathological features of AD, between demented and non-demented persons, and the neuropathological studies by Davies and Maloney, and White et al., revealing the loss of cholinergic neurons in the brains of AD subjects [5, 6]. The establishment of the National Institute on Aging (NIA) in the middle to late 1970s enabled initiation of targeted studies of normal aging and AD, with funding for AD-specific grants and the establishment of the first Alzheimer's Disease Research Centers (ADRCs) in 1984 in the USA; similar structures were established in other countries. A number of research groups described the distribution of amyloid plaques in the brain in AD in the 1980s and early 1990s.

First described in 1991, the Braak neuropathological staging system used maps of the regional distribution of neurofibrillary pathology, identifying their initial presence in the perirhinal and entorhinal cortex, then subsequent spread to different neocortical regions in a predictable pattern likely mediated by transsynaptic transmission of tau [7]. Braak staging has subsequently become the standard for research and clinical pathological studies, as well as for staging using Tau PET scans.

The development of non-invasive brain CT scans in the mid to late 1970s aided in separating out patients with cognitive impairment who had mass lesions and strokes, but there was little experience with early-stage AD except in a very few centers; the bulk of treatment was administered when patients were brought to medical attention because of the neuropsychiatric and behavioral disturbances that occurred later in the course of the disease. In those early days, researchers were still measuring the range of age-related cognitive decline that occurred in normal individuals, and the term senility confounded the distinction between the decline in cognitive function in normal aging and early AD symptoms. The uncertainty in the lay population about when cognitive or behavioral change represented something other than aging itself led to delays in seeking medical care until people had predominantly middle- and late-stage disease; many families thought that such changes in the elderly were "part of normal aging" and did not seek medical help until the changes were so severe that it became clear that something else more severe was happening.

Increasing outreach and publicity coupled with growing numbers of cases in the community led to wider knowledge of AD, and it became a subject of books, television shows, and movies. With increased awareness of the disease, older individuals came to the clinic in earlier and earlier stages of cognitive impairment, leading to the designation of a new transitional disease diagnosis, mild cognitive impairment, or MCI. There are many reasons elderly people may develop memory impairment besides AD, such as cerebral vascular disease and effects of medications. Since many people with MCI did not go on to develop dementia, MCI was best regarded as a risk factor for the development of

✉ Steven T. DeKosky
DeKosky@UFL.edu

Ranjan Duara
duara@msmc.com

1 McKnight Brain Institute, 1Florida Alzheimer's Disease Center and University of Florida College of Medicine, Gainesville, FL 32610, USA

2 Wien Center for Alzheimer's Disease and Memory Disorders, Mount Sinai Medical Center, Alton Rd, Suite 650, Miami Beach, FL 33140, USA

3 Dept of Neurology, 1Florida Alzheimer's Disease Research Center, University of Florida College of Medicine, Gainesville, FL, USA

4 Herbert Wertheim College of Medicine, Florida International University, Miami, FL, USA

AD. Distinguishing MCI of the AD type from other etiologies with less dire prognoses became easier with the use of longitudinal magnetic resonance imaging (MRI) scans, cerebrospinal fluid (CSF) analysis, and especially with the advent of positron emission tomography with amyloid tracers (amyloid PET). More clear identification of AD-related MCI enabled drug studies to begin at an earlier stage of the disease, enabling a better chance of therapeutic success since there would be no amyloid negative participants.

As increasing numbers of cases came to autopsy, it became possible to correlate the degree of cognitive decline with the neuropathological changes, as well as the multiple other pathological changes in the brains of normal and demented subjects, including alpha-synuclein, TDP43, and others. The data also helped clarify differences between aging and age-related dementias. In the mid-1980s, the introduction of MRI allowed both increased resolution and more sensitive determination of white matter alterations in AD. While the early studies from the ADRCs emphasized finding "pure" cases of AD and of vascular cognitive impairment (VCI; the modern term for vascular dementia), MRI enabled better determination of the presence of some vascular disease in the AD cases, a finding confirmed by neuropathologic studies [8].

Expansion of the ADRC program from the initial 5 centers in 1984 to over 30 centers in the nation by the early 2000s was coupled with a slow but steady increase in research funding from NIH. The epidemiological realities of the aging of the Baby Boomer population and the findings of the age-associated increase in the incidence and prevalence of AD, articulated to the neurological community in 1976 [9], spurred the organization of the Alzheimer's Association in 1980 (at its establishment, the Alzheimer's Disease and Related Disorders Association (ADRDA). Started by eight families from the Chicago area in the US, the Alzheimer's Association became a major lobbying force, continuously requesting increased NIH funding for dementia research in advance of the coming "silver tsunami" of dementia for which the country was unprepared. Indeed, despite yearly advocacy efforts at both the state and local level, funding increases were slow until the first "waves" of cases began to appear in physicians' offices and neurology clinics, as the earliest born Baby Boomers (the cohort born between 1946 and 1964) began reaching the age of risk after the turn of the century.

The Alzheimer's Association also developed their nascent dementia research program into a world-wide community of researchers and aided in sponsoring conferences and panels that brought researchers from around the world together to develop expert opinions, enumerate specific areas of needed research, and develop research proposals as well as provide funding opportunities for researchers. The research communities in several countries, notably the UK, France, Germany, Japan, Sweden, and the Netherlands, all developed programs to assess the disease and determine the needs of the caregivers and their communities as the numbers of patients increased and progressed through the disease. Even more broadly, recognition of the threat of this previously unforeseen increase in late life dementia spurred Alzheimer's Associations (with different names but similar goals) in the majority of countries in the world, and the development of Alzheimer's Disease International, a worldwide collaboration of nations' Alzheimer's Associations, focused on advocacy and education. In the USA and in many other countries, the Alzheimer's research centers were charged with conducting detailed baseline and longitudinal assessments, including clinical, DNA, and imaging and blood biomarker data for comparative studies between cognitively normal and impaired individuals. Brain autopsies enabled confirmation in these clinically well-established cases the bedrock findings in the disease: the presence of amyloid plaques and neurofibrillary tangles at autopsy as hallmarks of the disease. The ADRCs also provided education and outreach to health care workers and the community, and increasingly to underserved medical groups.

Mutations in the genomes of familial autosomal dominant AD (FAD) kindreds, first in the amyloid precursor protein (APP), then in the Presenilin 1 and Presenilin 2 proteins (components of the gamma secretase complex which "cuts" the APP molecule and releases the pathological 42 amino acid peptide Aβ42), were identified in the late 1980s and early 1990s. These discoveries also enabled the development of transgenic mice (using the new transgenic methodology), research with which led to use of anti-amyloid antibodies currently in clinical trials today. Multiple models of pathological protein expression were developed, including tau; mice with two transgenic proteins (e.g., Aβ42 and tau) followed. Over 200 such models exist today.

In the 1990s, many of the advances in understanding AD stemmed from new technologies, which in turn were related to advances in computer technology and speed; computerization of scientific instruments also led to increased throughput. Antibodies to beta amyloid (Aβ) and tau and phospho-tau (p-tau), developed for immunohistochemical analyses of brain tissue, were used to develop assays for the peptides in the CSF, enabling a more definitive diagnosis in living patients, and allowed more certainty for entry to research studies. The 2011 update to the 1984 criteria [10] maintained the clinical criteria from the 1984 paper — clinical research diagnoses were graded as Possible, Probable, and Definite AD. Definite AD required proof of the pathology so was only determined at autopsy. While these earlier criteria proved helpful in categorizing degrees of diagnostic certainty, the 2011 update added biomarkers that aided in diagnosis, including genetic advances (notably apolipoprotein ε4 (ApoE4)), the CSF

protein findings, MRI evidence of AD-compatible atrophy, and 18-fluorodeoxyglucose positron emission tomography (FDG-PET) patterns of regional metabolic decline.

Genetic advances led to the identification of the 3 genes responsible for autosomal dominant familial AD, of the powerful risk gene ApoE4 in 1992, and subsequently other genetic variants responsible for either increased or decreased disease susceptibility. The larger number of defined cases enabled large clinical trials to begin, starting with compounds directed at boosting cholinergic function; such studies led to the approval of several acetylcholinesterase inhibitors, such as donepezil, galantamine, and rivastigmine, and then memantine, a partial antagonist of the N-methyl-D-aspartate (NMDA) glutamate receptor, all in the late 1990s and early 2000s. Large-scale longitudinal assessments of cognitively normal individuals and people with AD in epidemiological studies provided new findings about the disease. These studies also identified the extent of variability of symptoms and longitudinal course in AD, especially factors associated with greater or lesser predisposition to AD, including environmental, genetic, developmental, and socioeconomic factors. The Alzheimer's Disease Neuroimaging Initiative (ADNI), established in 2005, not only enabled longitudinal studies of cognition, imaging and biomarkers, but made all the data freely available all over the world, to any investigator who wished to use it [11] The ADNI in the USA led to establishment of other ADNIs all over the world. They are still ongoing today.

By the early 2000s, the first studies aimed at disease modification — slowing or stopping progression of disease — were begun, aided by advances in MRI technology, which identified correlations of cognitive decline to regional volumetric changes in the brain, thereby allowing MRI scans to be used as an outcome variable in interventional trials. The first amyloid imaging tracer, Pittsburgh Compound B (PiB), was developed and published initially in 2004 [12]. It enabled definitive determination of amyloid plaques in the brain in vivo, thus, serving as a biomarker to aid diagnosis and allowing serial assessment of the ability of anti-amyloid medications to remove amyloid plaques from the brain. While a great deal has been learned about the clinical and pathophysiological mechanisms in AD, no new medications have been fully FDA-approved since memantine in 2003.

In the 2010s, therapeutics were extended to anti-amyloid, anti-tau, and anti-inflammatory interventions, and by 2020, over 100 medications were in various stages of development and trials [13]. Improvements in sensitivity of assays for biomarkers of AD are currently research tools, but with clinical approval will allow assessment of plasma levels of Aβ42 and tau and enable easier screening for current or incipient disease, and additional markers for assessment of response to therapeutics. The many studies aimed at decreasing amyloid plaques in the brain or interfering with amyloid metabolism have been negative for the most part. This has led to concerns that the amyloid hypothesis of AD, that stipulates that altered metabolism of amyloid leads to a cascade of events including the spread of pathological tau, oxidative stress, and neuroinflammation, is not correct. Evidence for certain variations in the metabolic pathway of amyloid precursor protein, leading to the deposition of Aβ as an initiator of the pathology of AD, is strong. The knowledge of downstream effects of Aβ, especially its effect on initiating alterations in tau protein, have led to anti-amyloid studies targeting treatment of AD cases at an early disease stage, i.e., in MCI and even pre-clinical stages (subjects who have normal cognition but are amyloid positive on PET scan or CSF analysis). But as noted above, therapeutic efforts have been broadened to anti-tau strategies and other interventions.

As with other complex diseases such as cancer or cardiac disease, there is a high likelihood that more than one medication will be needed to successfully delay the onset or slow the progression of the disease.

In this issue of Neurotherapeutics, experts in various areas of research and clinical care have contributed review articles presenting the current state of knowledge in multiple areas of AD investigation, reflecting the breadth of areas of current research in AD as well as prospects for the future. A brief summary of the reviews follows.

Heterogeneity in Alzheimer's Disease, Diagnosis, and Progression Rates: Implications for Therapeutic Trials

Duara and Barker [14] address heterogeneity in AD, as reflected in the genetics, neuropathology, demographics, cognitive and functional performance, neuropsychiatric features, and structural and fluid biomarkers. The heterogeneity described in each of these sections is followed by a review of the implications for clinical trials of the described heterogeneity. The article concludes with a discussion of ways to account for the variation in presentation and rate of disease progression when designing clinical trials.

Culture, Ethnicity, and Education in AD

Rosselli et al. [15] define culture as a "set of learned traditions and living styles shared by the members of a society," and describes how culture can be grouped by language, country of origin, race, ethnicity, and by the east–west and north–south divide. They explain how culture and education influence cognitive performance in different cognitive domains, as well as in cognitive assessment. The authors emphasize the influence of cognitive and brain reserve and its interactions with bilingualism and multilingualism on

cognitive function. They also note variations in the clinical presentation of AD in different cultures and ethnoracial groups and the disparities in presentation as a function of native language and country of origin. The influence of ethnoracial factors on biomarkers on genetic markers, such as apolipoprotein E (APOE) genotype, and fluid and structural biomarkers is discussed in detail. Finally, they describe how cultural and ethnoracial factors influence access to health care and clinical trials, and their implications for cognitive and clinical diagnosis and medical management.

Lewy Body Dementias: Controversies and Drug Development

Chiu et al. [16] note that although Lewy body dementia (LBD) is perhaps the second most common neurodegenerative dementia after AD, there remains substantial debate about its definition, distinction from Parkinson's disease dementia, and frequent misuse of terminology between the clinical syndrome (dementia with Lewy bodies) and the pathological condition (Lewy body disease). Although the pathologic hallmark in LBD is the presence of α-synuclein positive Lewy bodies in neurons and neurites in cortical, limbic, and brainstem regions, there remains debate about the causative role of alpha-synuclein in the pathology of LBD. The authors also highlight the many issues and challenges surrounding the design and implementation of clinical trials for symptomatic and disease-modifying therapies in LBD, including the clinical heterogeneity of LBD and its neuropathology, the lack of validated biomarkers, and outcome measures that would include biomarkers.

Vascular Cognitive Impairment

Rundek et al. [17] present recent developments in age-related vascular cognitive impairment (VCI), summarizing its mechanisms, diagnostic criteria, neuroimaging correlates, determinants of vascular risk, and current intervention strategies for prevention and treatment of VCI. They review the most recent and relevant literature in the field of VCI, and present evidence that VCI accounts for at least 20–40% of all dementia diagnoses, with chronic age-related dysregulation of cerebral blood flow, inflammation, and cardiovascular dysfunction as underlying mechanisms. They cite growing evidence indicating that cerebrovascular pathology is a major contributor to and acts additively and synergistically to promote neurodegenerative pathology, with hypertension, high cholesterol, diabetes, and smoking in midlife acting as major risk factors.

Salient Cognitive Paradigms to Assess Preclinical Alzheimer's Disease

Cid and Loewenstein [18] present the case that identification of the earliest cognitive changes in AD requires new approaches, other than traditional neuropsychological test paradigms that have worked well for identifying dementia and mild cognitive impairment in clearly symptomatic states of the disease. They review the development of novel cognitive paradigms including assessments of semantic interference, semantic intrusion errors, memory binding, and binding of face and name associations. The authors then present evidence that these new cognitive paradigms can be sensitive and specific, detect cognitive impairment in preclinical stages of neurodegenerative disease—even in culturally and linguistically diverse patient populations—and correlate with AD biomarkers in preclinical stages of the disease.

Primary Palliative Care in Dementia

Weisbrod [19] emphasizes that primary palliative care, as distinct from specialty primary care, "is the skill set all clinicians should develop in order to manage symptoms and guide discussions about prognosis, suffering, and planning for the future" in patients with dementia. He includes a review of techniques for communication with the patient and family and for determining the level of capacity of the patient and the family/caregivers to engage in difficult conversations regarding diagnosis, prognosis, and advanced care planning. While such conversations optimally take place over time, with increasing understanding of the course and severity of disease, individuals with cognitive impairment lose the capacity to make their own medical decisions much earlier than do people with other medical conditions such as cancer or cardiac failure. Thus, the balance must be between the preferred gradual introduction of the long-term topics and the need for earliest discussion so that the patient may participate, if possible. The article also reviews the management of pain and depression, difficult behaviors, prognostication, and advance care planning, including referral to hospice. The palliative care team must guide the way through a disease with many challenges, which include promoting the quality of life among these patients, including deprescribing medications of uncertain benefit. All the while, the palliative care team must advocate for respect for the patient's autonomy, and protection against uninformed consent.

The New Frontier of Perioperative Cognitive Medicine for Alzheimer's Disease and Related Dementias

Price [20] brings attention to the risk of cognitive impairment, delirium, and mortality among elderly individuals who undergo elective surgery, and to the importance of

perioperative screening to alert the need for postoperative vigilance and care. The well-documented increase in elderly subjects undergoing various elective surgeries, such as joint replacements, vascular repairs, and cosmetic procedures, presents an increasing number of potentially vulnerable patients to the surgical and post-op teams. The article summarizes a model program that could be developed to improve perioperative care, including a plan for identifying those individuals requiring perioperative cognitive intervention or increased vulnerability to postoperative complications, as well as training of medical professionals involved in both the perioperative setting and the immediate and long-term medical care and risks for patients undergoing anesthesia.

Emotional and Neuropsychiatric Disorders Associated with Alzheimer's Disease

Heilman and Nadeau [21] describe the impairments that have been found among AD patients in emotional communication, comprehension of affective prosody, and insight into their own cognitive and emotional deficits (alexithymia). They make the connection between these deficits and disorders of emotional and behavior including depression and anxiety, agitation, aggression, and psychosis. They point out how sleep disorders promote these behavioral disorders and independently become a challenging behavioral disorder among AD patients. They emphasize the association of disruptive behaviors with early institutionalization and the challenges to management of behavioral disturbances in and out of institutional care. Finally, they provide a comprehensive review of the pharmacological and non-pharmacological management of behavioral disorders in AD.

Behavioral Interventions in Mild Cognitive Impairment

Levy et al. [22] summarize the results of various studies of behavioral intervention techniques for persons with mild cognitive impairment and their partners. These include, especially, the Healthy Action to Benefit Independence and Thinking (HABIT®) program, a behavioral intervention, which found that quality of life was most affected by inclusion of wellness education. This had a greater impact on mood than computerized cognitive training (CCT), the greatest impact of which was on cognitive performance. Skill-based interventions, such as yoga, were found to have their greatest impact on improving functional status and lessening caregiver burden. Individual preferences for a particular combination of interventions could be optimized. As expected, and in some ways, a confirming finding was that better adherence in all these programs was associated with better outcomes and combinations of behavioral strategies.

Genomics and Functional Genomics of Alzheimer's Disease

Kamboh [23] provides a detailed review of the genomics of AD, including an extremely valuable complete timeline of discoveries in this field over the last 30 years, useful for researchers entering the field and for trainees looking to understand how the field evolved. In addition to the historical timeline, he provides the context and the associated insights these breakthroughs have provided regarding our understanding of the molecular pathogenesis of AD. Highlighted in the chapter are the early discoveries of gene mutations that lead to early-onset autosomal dominant AD, which account for a very small percentage of all cases; identification and confirmation of the elevated risk of late-onset AD (LOAD) provided by the ApoE E4 allele; and the discovery of the enormous genetic heterogeneity in LOAD, following the development and application of large genome-wide association studies (GWAS) in 2009. The article also highlights the application of these discoveries of AD risk genes to the functional genomics of AD and the molecular mechanisms that result in the pathology of AD. Finally, he describes how the genetic discoveries aid in the identification of targets for the development of new therapies for AD.

Neuropathology of Alzheimer's Disease

Trejo-Lopez et al. [24] review the neuropathology of AD, outlining the major advances in knowledge of the underlying pathophysiology of AD gained from detailed neuropathological studies. They describe how these discoveries have led to improvements in clinical diagnosis and treatment of AD, and in the development of biomarkers for in vivo use. The realization from these studies that neuropathological changes begin taking place decades before any clinical symptoms of AD become apparent has led to major changes in the classification of both the clinical and neuropathological aspects of AD. The progression of beta-amyloid (Aβ) plaque pathology captured in the Thal classification system, the progression of neurofibrillary pathology outlined by Braak and Braak, and their use for the widely used neuropathological classification to define stages of AD pathology are described. This review also emphasizes the role played by several additional pathologies which often accompany AD and contribute to the clinical manifestations of the disease. These include

limbic-predominant age-related TDP-43 (LATE), chronic traumatic encephalopathy (CTE), aging-related tau astrogliopathy (ARTAG), Lewy body disease, vascular pathology, and the key role played by immune response to pathological aggregates.

Microglia in Alzheimer's Disease: a Key Player in the Transition Between Homeostasis and Pathogenesis

McFarland and Chakrabarty [25] provide an in-depth review of the known relationships among microglial activation, a rapidly growing area of investigation in neurodegenerative disorders, and the impact of those processes on the clinical course and pathology of AD. They make the point that neuroimmune activation of the microglia is not simply reactive but may have a dynamic role, either pathogenic or beneficial, which may vary from one individual to another, based on numerous (especially genetic) factors. The different activation states of the immune system may have important roles in both healthy aging and in determining the course of AD. In general, chronic microglial activation leads to neurodegeneration, but in some circumstances, there appears to be a potential beneficial role to immune activation. The disparity in the effects of microglial activation in rodent models and the experience in human clinical trials of drugs that modulate the immune system remains largely unexplained; but it is an active area of investigation, which may aid in the discovery of more effective disease-modifying therapies for AD.

The Current Landscape of Prevention Trials in Dementia

Schneider [26] provides an extensive review of primary and secondary prevention trials for AD, including both pharmacological and non-pharmacological interventions. The pharmacological trials have based largely on the use of agents that target the Aβ cascade and to a lesser extent tau proteinopathy, anti-inflammatory agents, sex hormones, and Ginkgo biloba extract. The non-pharmacological trials include lifestyle modifications, including blood pressure management, increasing or maintaining socialization, and physical exercise and activity. The article also provides a thoughtful and detailed review of the advantages and disadvantages of different trial designs, as well as aspects of trial methodology, which may influence trial outcomes. Obstacles to providing an optimal trial design include the heterogeneity of progression of AD and its impact on the choice of inclusion and exclusion criteria, the outcome measures utilized, the size of the trial (important for power to determine an effect, especially with the variability of disease progression), the lack of validated drug targets, and the evolving diagnostic frameworks. All these factors have an impact on determining whether a prevention intervention will be successful. The article also provides a consideration of how future trials may be better designed and conducted more efficiently. The need for medications is acute, but the speed of determining the success or failure of a medication is constrained by the slow progression of the neurodegeneration. Dr. Schneider emphasizes that the most important reason a prevention trial fails is the lack of efficacy of the intervention that was chosen.

Disease-Modifying Therapies for Alzheimer's Disease: More Questions Than Answers

Golde [27] focuses his article on the scientific basis of AD "disease-modifying" therapy for treating active, manifest clinical disease and for primary and secondary prevention. The article also addresses the "open questions" that remain to explain the very limited success of current therapeutic approaches and the way forward to potentially overcome some of the reasons for the limited success achieved. These include a review of several widely disparate efforts to developing a successful treatment for and/or prevention of AD, including the following: (a) immunotherapy targeting Aβ; (b) inhibitors of Aβ aggregation and production; (c) immunotherapy targeting tau seeds (which are presumed to have prion-like spread from the entorhinal cortex to various regions in the neocortex); (d) the post-translationally modified (PTM) products of tau protein mismetabolism, which are presumed responsible for the aggregation and toxicity of tau protein and formation of neurofibrillary tangles; (e) the use of modulators of tau PTMs (including small molecules and antisense oligonucleotides), tau-chaperones, and tau aggregation inhibitors to prevent tau misfolding and aggregation; (e) the pros and cons of using immune modulators, including those that activate and those that inhibit innate immunity; and (f) the importance of the development and use of biomarkers which can help to "identify and stratify intent-to-treat populations who have dementia or preclinical stages of dementia and to enable tracking of the impact of the medication on underlying progression of the pathology."

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