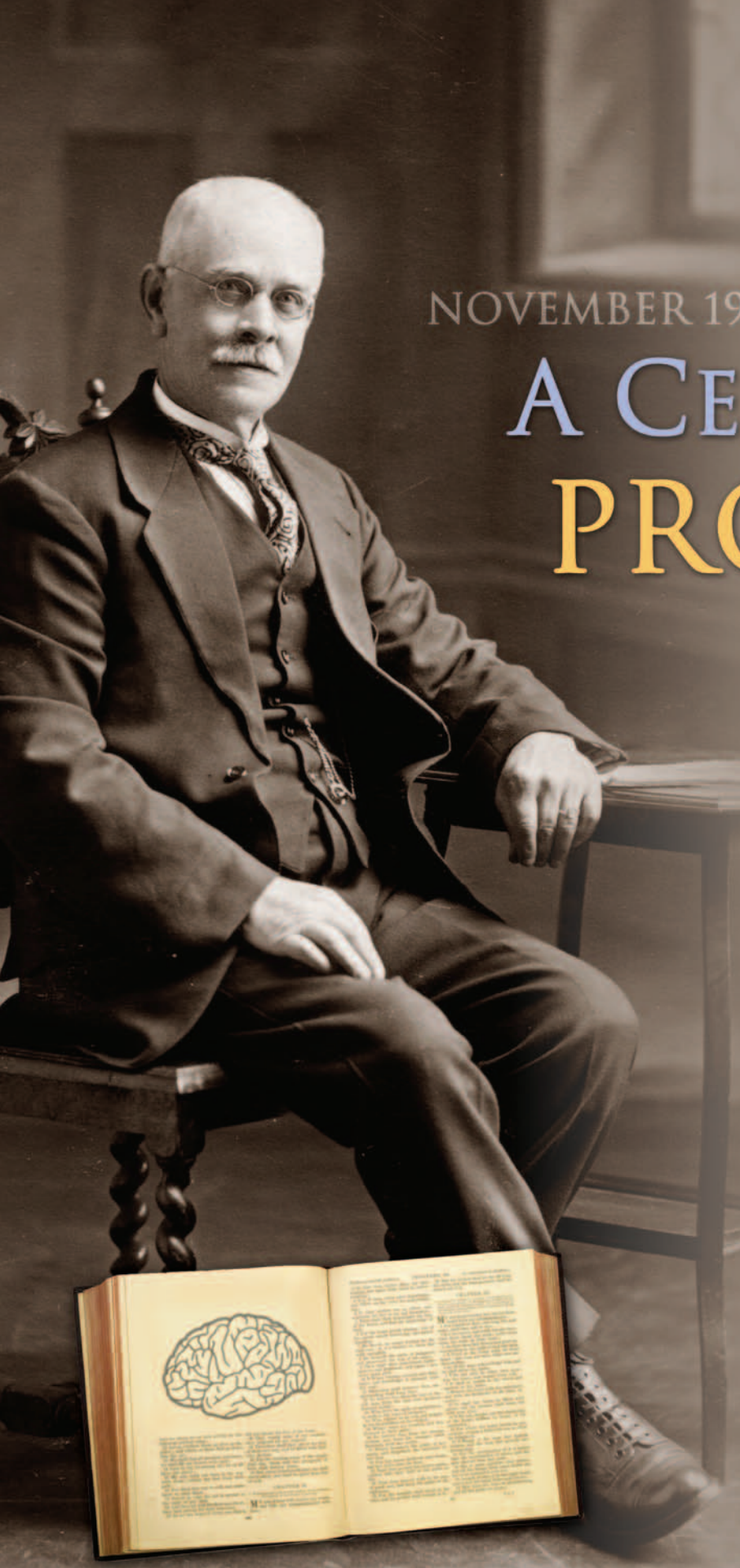


NOVEMBER 1906 - NOVEMBER 2006

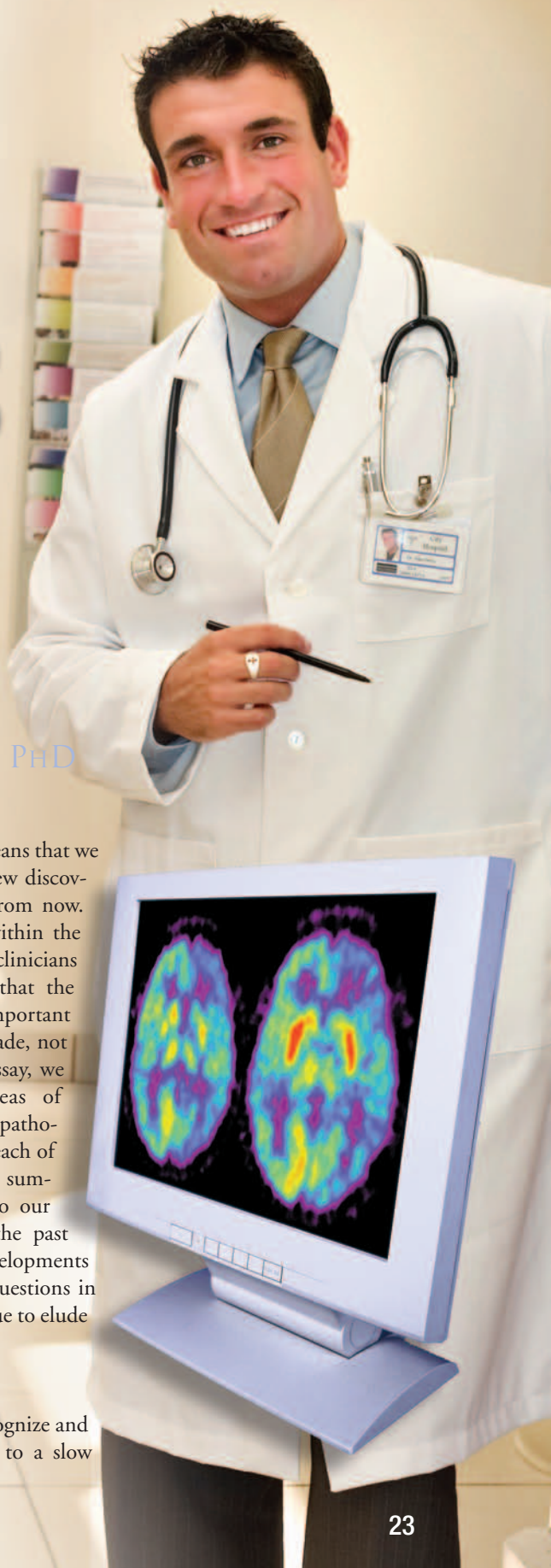
A Century Of PROGRESS

Auguste D., the first patient to be characterized with what would be become Alzheimer's disease (AD), was first examined by Alois Alzheimer on November 26, 1901. She died at the age of 58 on April 8, 1906, and shortly thereafter, Alzheimer began the examination of her brain. He presented his findings on November 3, 1906 at the 37th Assembly of Southwest German Psychiatrists in Tubingen. At that conference, he concluded his remarks by emphasizing that he was describing a "distinctive disease process"[1] through the correlation of clinical findings and pathological features.

Alzheimer's presentation was reportedly greeted with stony silence by the scientists in his audience and not a single question was asked. But in the 100 years since then, this disease has become the object of one of the most intensive investigations in medical history, stimulating questions from every conceivable scientific direction. Despite the explosion of attention and research, the promised "distinctiveness" of his discovery has only been partially fulfilled. Today, we still cannot accurately predict who will develop the disease before it begins, or definitively diagnose the disease among those with failing memories. The pathophysiology of the disease is still not fully understood, and there is as yet no treatment that can halt or delay the biological progression of the illness.

But the situation is far from bleak. Working in this field, one senses the approach of

Alzheimer's: & Pitfalls



On its 100th anniversary, AD is better understood yet more perplexing than ever. Here, two experts review the milestones we've reached and those that still lie ahead.

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breakthroughs in all these areas—not in the form of a "eureka" moment wherein a single mind conceives a recognizable solution, but rather in a great swelling wave of laborious progress by legions of dedicated participants: patients, families, clinicians and scientists. The correlation between diagnosis in life and specific pathology of the brain may not be perfect, but thousands of careful clinico-pathological correlations have rendered it exceedingly high, and new biomarkers will surely refine that further. Our understanding of the pathophysiology of the disease has been enhanced by dogged biochemical analyses of the structures Alzheimer described, and the ability to transfer the genetic production of some of these features from humans into mice. Dozens of potential treatments with a variety of mechanistic approaches are in advanced stages of development and new ways of imaging treatment success may be at hand.

The sense that research progress is accelerating so rapidly in this field means that we cannot easily predict where new discoveries will take us 100 years from now. But the palpable optimism within the community of scientists and clinicians specializing in AD suggests that the disease may yield its most important secrets within the coming decade, not the coming century. In this essay, we will reflect upon three areas of progress in AD: diagnosis, pathophysiology and treatment. In each of these domains, we will briefly summarize how we have come to our current understanding over the past century, point to exciting developments ahead, and reflect upon the questions in each of these areas that continue to elude us.

Diagnosis

The ability of clinicians to recognize and diagnose clinical AD got off to a slow

start. Alzheimer's 1906 presentation to the 37th Assembly of Southwest German Psychiatrists in Tübingen was published in 1907 in the *General Journal of Psychiatry and Psycho-Forensic Medicine* under the title "On a Peculiar Disease of the Cerebral Cortex," providing the historical basis for the eponym by which we know the disease today.[2] In 1908, with his colleague Gaetano Perusini, Alzheimer evaluated three additional cases (at death, aged 46, 60 and 65) and these, along with the case of August D., were published by Perusini a few years later.[3] In revising his famous *Textbook of Clinical Psychiatry*, Emil Kraepelin noted these cases and several others that had been subsequently published of "presenile dementia" and first mentioned "Alzheimer's disease" as the name of the syndrome. Of note, Kraepelin discussed whether the anatomical findings were specific to presenile or senile dementia and presciently raised the possibility that this syndrome was "a peculiar disease process that is largely independent of age."[4]

Alois Alzheimer (left) and Auguste D. (right)

Yet, the generation of clinicians that followed considered Alzheimer's disease to be a form of presenile dementia, relegating senile dementia to atherosclerotic and mixed causes. In 1926, Ernst Grünthal observed that there was no histological distinction between Alzheimer's disease (presenile) and senile dementia, yet most of his patients were younger. In 1936, H. Pittrich presented the case of a 70-year-old patient with Alzheimer's disease who did indeed have characteristic histopathology, using the term unequivocally to describe a case of senile dementia.

Interest in the disease among clinicians languished until the 1960s when autopsy reports began to identify Alzheimer's disease as a common form of late-life dementia, rather than a rare condition.[5] While some experts blended the concept of senile dementia and Alzheimer's disease, others continued to hold that late-life dementia was developmentally normal (senility) or due to arteriosclerotic disease. Even today, practicing clinicians seeking to avoid the "A word" commonly attribute dementia to "atherosclerosis" or "hardening of the arteries" despite the absence of actual strokes on scans.

AD as a recognizable diagnostic entity gained traction in the 1980s and 1990s as a result of several factors. First, famous individuals such as Rita Hayworth and President Ronald Reagan developed the disease and their families courageously chose to share this information with the world. Second, the National Institute on Aging and the Alzheimer's Association conducted a tireless campaign to provide supportive care, raise awareness and encourage research. And third, the development of the first treatments specifically approved for AD, starting with tacrine in 1993, provided enormous incentives for the pharmaceutical industry to educate clinicians and the public about AD. To some, these trends represented an overly simplified "Alzheimerization" of a heterogenous group of dementing processes, even as they succeeded in raising awareness and resources for research.

But while the clinicopathological entity known as AD was gaining recognition as a common etiology of dementia over the past 40 years, there has been considerable confusion about what terms like "dementia" meant or should mean, and this confusion has bedeviled diagnostic efforts. To some, the term meant "senility" and was thought to be a common, even expected concomitant of the aging process. To others, dementia was a syndrome for any late-life cognitive decline, and for others, dementia became a synonym for AD. This nosological confusion was not improved by the fact that "dementia" was a label used by official diagnostic registries, such as the Diagnostic and Statistical Manual of Disorders (DSM), and as a basis for billing. In addition, many research studies have used DSM criteria for dementia, further compounding the confusion by setting precedents for the use of this term as a diagnostic entity in clinical research. This nomenclature was finally clarified in the *DSM-IV*.[6]

Today in the *DSM-IV*, and among specialists who evaluate patients with cognitive impairment, "dementia" is considered an acquired syndrome in which impairment of cognitive abilities is severe enough to interfere with the individual's customary occupational and social activities. As conventionally used, dementia implies "degenerative" and "progressive," but it is also sometimes used in the context of static conditions (such

as the cognitive impairment following stroke) or reversible conditions (such as cognitive impairment associated with overmedication or depression).[7] Most clinicians do not screen for cognitive problems in their practice unless they receive complaints from either the patient or the patient's family. This is unfortunate since the majority of patients with dementing illnesses do not complain about it to their health-care providers, and on average, family members do not seek medical attention for the patient until several years after the onset of symptoms. The differential diagnosis of dementia continues to challenge clinicians and is discussed at length in other publications.[7,8]

How good is our current ability to diagnose AD in living patients with dementia? Since Alois Alzheimer defined the disease by characterizing the pathology, the gold standard for determining the etiology of dementia in an individual patient is still histopathologic examination of the brain. However, the diagnosis of AD can be made in life with excellent sensitivity (between 80 and 100 percent) in most specialized centers, even in very mild individuals.[9-12] But in the largest study to date comparing the clinical diagnosis of AD to the neuropathologic findings, specificity of the clinical diagnosis was somewhat lower at 55 percent.[11] While most of the cases that were incorrectly diagnosed as AD had equally irreversible degenerative dementias, this study reminds us that many late-life dementias do not meet histopathological criteria for AD, and may represent different disease processes altogether.

At the present time, the diagnosis of AD is changing in ways both temporal and technological. On the temporal axis, symptoms of AD are being sought earlier in the lifespan. Instead of waiting for the development of clear-cut dementia, at which time neurons have been irrevocably lost, the field is moving toward the identification of early symptoms and preclinical risk factors. Persons with memory difficulties who appear to be functioning successfully are now characterized as having mild cognitive impairment (MCI) and often progress to full-blown dementia at a rate of about 15 percent per year, representing a rich opportunity for study and intervention.[13,14] At the same time a host of epidemiological studies have been identified that offer clues to the disease and to those who are at elevated risk. Risk factors implicated in recent years include female sex, head trauma and vascular risk factors such as diabetes; while there is evidence that education, exercise, dietary factors and some medications can offer protection against AD.

On the technological axis, there is an accelerating push to develop biomarkers, especially imaging modalities, that can help with the diagnosis of AD and the tracking of disease severity. The search for biomarkers is hampered because the pathophysiology of AD is not fully understood, but candidates include cerebrospinal fluid levels of amyloid-β, tau and phospho-tau, as well markers of inflammation and oxidation.[15] Great excitement has been generated by the discovery of compounds that bind to amyloid in the brain and can be visualized in subsequent positron emission scans, such as the Pittsburgh Compound-B (PIB)[16] and FDDNP (2-(1-(6-[(2-[F-18]fluoroethyl)(methyl)amino]2naphthyl)ethylidene) malononitrile).

There is also increasing interest in structural and functional imaging as a way of examining early and even preclinical disease.[17-19] Total brain volume, ventricular volume, entorhinal cortex volume and hippocampal volume have all been demonstrated to change at a predictable rate with clinical progression of AD. A new initiative from the National Institute on Aging, in conjunction with pharmacological and biotechnology companies, is sponsoring the Alzheimer's Disease Neuroimaging Initiative to examine the possibility of using structural or functional imaging at primary outcome measures in future treatment trials (see www.nih.gov/news/pr/oct2004/nia-13.htm).

In the future, successful identification of biomarkers will surely clarify the differential diagnosis of patients with dementia. If some of these biomarkers are found to change with the worsening of disease, they will also provide more reliable tracking measures for clinical trials. Those biomarkers that do not change with disease severity, or "trait" markers, such as genetic indicators, raise important ethical dilemmas if they are disclosed to people before treatment modalities are available. For example, the presence of a single APOE ε4 allele triples the risk of having AD, whereas two ε4 alleles increases that risk by about 15-fold, making APOE genotype the most robust risk marker for AD currently known.[20] But disclosure of genetic profiles for AD risk is controversial at the present time.[21,22]

Pathophysiology

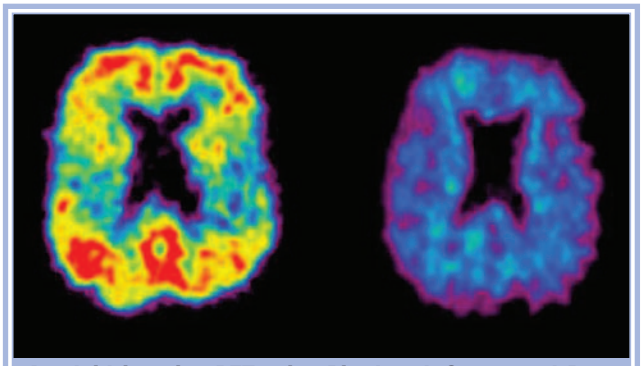
The pioneering neuropsychiatrists of the late 19th century were determined to find the etiology of mental diseases in the examination of the brain. Ironically, Alois Alzheimer's early scientific work was focused upon the notion that arteriosclerosis was responsible for many, if not most, cases of senile dementia. His beliefs did not change, but with the case of Auguste D., Alzheimer reported a syndrome in which progressive early dementia was associated with silver staining neurofibrils (later called tangles) and "millet seed-sized lesions… characterized by the deposit of a peculiar substance" (later called plaques) in the cortex. This combination of clinical dementia and the finding of "plaques and tangles" in the brain after death, most closely fits what we now call AD and has come to define the disease for most of us.

If AD was always such a common cause for dementia, why did it take over 50 years to be so recognized? One reason may have been the rise of psychoanalytic theories in the first half of the 20th century which inhibited the resolve of many to find pathophysiological explanations. Another reason may have

been that the silver stains used to see plaques and tangles were not routinely used by pathologists and these neuropathological hallmarks were not so readily recognized with the more routinely used hematoxylin and eosin stains. But even as the recognition of AD has grown into a juggernaut of world-wide awareness, what are we to make of those rare individuals who have AD-like clinical dementia but whose brains show neither plaques and tangles, nor any other obvious pathology? What are we to make of persons who appear to live their lives entirely without dementia (even with neuropsychological testing in their final years), but are found to have "AD pathology" upon autopsy? Nor are plaques and tangles simply present or absent. They exist on a spectrum from none to few to many, and attempts to standardize their number and distribution were not codified until the 1980s, with several revisions since then.[23-25] These cases, and these uncertainties with regard to pathological criteria, remain vexing reminders that while Alzheimer's formulation has laid the groundwork for identifying a clinicopathological entity that bear's his name, the puzzle has by no means been fully solved and that, even today, "Alzheimer's disease" is not a securely established pathophysiological entity in every case.

Once AD became identified as the most common cause of late life dementia, the presence of plaques and tangles was the logical starting point to seek clues about the pathophysiology of the disease. In the 1980s, plaques were identified as accumulations of amyloid and amyloid deposition has been gradually characterized as playing the critical causal role in the disease. The understanding of abnormal amyloid metabolism has accelerated over the past 10 years, partly through the study of the rare, dominantly inherited forms of familial AD and the ability to create transgenic mouse models of AD by transferring the human mutations into the DNA of mice. Leading theories suggest that the amyloid precursor protein (APP) is normally cleaved by an α secretase, but that in AD, abnormal cleavage by α and γ secretases produces a toxic amyloid-β or Aβ peptide with an tendency to assemble into even more toxic oligomers and polymers.[26, 27]

Neurofibrillary tangles (NFTs) were observed by Alois Alzheimer, but again, it was not until the 1980s that the major protein abnormality in NFTs was recognized to be a highly insoluble, hyperphosphorylated microtubule-associated protein called tau.[28,29] The intracellular deposition of tau and its disruption of the normal cytoskeletal architecture may be an important factor in the death of neurons, possibly through disruption of axonal transport. Tau abnormalities are known to be associated with other neurodegenerative diseases such as progressive supranuclear palsy and hereditary frontotemporal dementia with parkinsonism linked to chromosome 17, and NFTs may be more closely related to disease severity than amyloid deposition.



Amyloid-imaging PET using Pittsburgh Compound-B. Courtesy of William Klunk, MD, University of Pittsburgh School of Medicine.

It is perhaps ironic that Alois Alzheimer identified these two pathological entities in 1906 and that after 100 years, there remains an intellectual divide among scientists who believe that either Aβ or abnormal tau is the primary "cause" of AD. However, the preponderance of evidence suggests that these two pathologies are surely interlinked in humans with AD, and there is growing evidence that Aβ accumulates well before NFTs, and that the toxic oligomers induce synaptic failure and hyperphosphorylated tau.[27,30] As we shall see in the next section, while some drugs are being developed and tested to inhibit neurofibrillary degeneration, most of the new initiatives in therapeutics are directed toward targets within the amyloid cascade. Indeed, the various initiatives to develop therapies for AD may provide (or refute) "proof-of-concept" for competing theories of the mechanisms of disease.

Treatment

A century ago, Emil Kraepelin's description for the treatment of dementia is remarkably similar to what can be seen in any nursing home today:

"…careful physical care and supervision… with regulation of the entire way of life, especially nutrition…. Controlling fear with small doses of opium…

In delirious states of excitement the use of upholstered beds or duration baths…in the calmer forms…institutional treatment is in many cases unnecessary and should be replaced completely with care within the family…"[1]

The treatment of AD did not appreciably deviate from this formulation until the 1980s, when it was discovered that cortically projecting cholinergic cells in the basal forebrain's nucleus basalis of Meynert were particularly devastated in AD, and that the activity of choline acetyl-transferase, the enzyme responsible for the synthesis of acetylcholine, was markedly reduced in the cortices of AD patients when compared with

age-matched controls.[31] While deficits of many neurotransmitters were eventually found in the brains of AD patients, enthusiasm for a cholinergic interpretation of AD inspired many attempts to treat AD with cholinergic drugs, particularly the better tolerated cholinesterase inhibitors (ChEI).

Between 1986 and 1992, several clinical trials demonstrated small, dose-dependent improvements after oral administration of tetrahydro-amino-acridine (tacrine), a centrally active ChEI.[32] The FDA approved tacrine in 1993 for use in AD despite the clinical trial results showing modest efficacy, a frequent dosing schedule, and a high prevalence of GI side effects, along with the need to monitor liver function studies for potential hepatotoxicity. The development and approval of tacrine lives on today in modern clinical trials because it helped to create a consensus among industry, academic, and government experts on standards for such trials. In particular, a standard for dual efficacy in clinical trials of symptomatic treatments for AD has emerged in which the FDA requires evidence of improvement on a measure of cognitive performance as well as on a scale of caregiver/clinician assessment.

A second generation of ChEIs (donepezil, rivastigmine and galantamine) that achieved the same improvements as tacrine with far fewer side effects was approved by the FDA and have become the standard of care for patients with AD. Memantine, an uncompetitive NMDA receptor antagonist, has also been approved for patients with moderate to severe AD. These compounds are now accepted as "symptomatic" treatments that help delay functional decline but probably do not influence the pathophysiology nor alter the biological course of the disease. Advocates for symptomatic treatments maintain that it is unethical not to treat patients with these compounds in order to prolong their remaining functional abilities, while critics point to modest efficacy, high cost and lack of discernable improvement in most patients.

There has been an increasing interest in the identification of agents that would be "disease modifying," meaning that they could slow the progression of the disease. Simply designing such studies is a challenge because without obvious improvement, a change in the slope of decline could take hundreds or even thousands of patients to demonstrate, even in a study lasting more than a year!

Given the cascade of pathophysiological steps hypothesized in the disease and the numerous clues from epidemiological studies, there are literally hundreds of compounds in various stages of development ranging from antioxidants to anti-inflammatories, from hormones to neuronal growth factors, and including agents that seek to influence Aβ production or clearing in a multitude of ways. Some of these treatments have been tested with high hopes and found wanting. For example, a large two-year placebo-controlled trial of vitamin E appeared to slow progression in AD patients,[33] but a follow-up trial to examine whether vitamin E slowed the progression of MCI to AD was negative.[34] And, despite consistent epidemiological evidence suggesting a protective effect for hormone replacement therapy in preventing or slowing AD, estrogen replacement neither improved the symptoms of patients with AD,[35,36] nor reduced the incidence of AD in normal women,[37] In fact, the incidence of dementia was increased among women taking hormone replacement, leading to the discontinuation of the study. Similarly, the association between anti-inflammatories and reduced risk of AD is striking in epidemiological studies,[38] but well-designed treatment trials have failed to find either improvements or disease modification.[39,40]

Cognitive activity is frequently hailed as an antidote to cognitive decline, and seniors exhorted to "use it or lose it" as if the brain were a muscle to be exercised. A number of well-designed studies have suggested that participation in leisure activities, cognitively stimulating activities, can reduce the risk (or delay the development) of AD, but these findings remain difficult to interpret because subtle, manifestations of AD could reduce interest and initiative in such activities many years prior to the onset of recognizable symptoms. Nevertheless, a number of recommendations have emerged to try to maintain "cognitive vitality" and may be useful, if only for morale of patients and their families.[41]

Some of the most promising therapies in development are those designed to decrease the production, deposition or clearance of or Aβ.[4] These include the APP β and γ secretase inhibitors, and the Aβ vaccination strategies. Secretase inhibitors are currently in clinical trials, but no results are available as this goes to press and there is concern that both g secretase inhibition and β-secretase inhibition could have a deleterious effect on other critical cell functions such as notch or nerve myelination, respectively.[43,44] Both active and passive vaccination with b-amyloid proteins promotes an immune response that can reproducibly reduce amyloid burden and improve cognition in transgenic mice.[45,46] An initial human trial of active vaccination with an Aβ vaccine AN-1792 was halted due to serious meningoencephalitic complications in some patients, however this approach may prove less toxic with alternative formulations or with passive immunization.

Designing clinical trials to demonstrate primary or secondary prevention through disease modification remains an enormous challenge.[47] Clinical outcomes such as cognitive testing are highly variable and require large numbers and extended duration to demonstrate efficacy. Nevertheless, Phase III clinical trials of possible disease-modifying agents are underway for two agents that have shown encouraging results in Phase II trials. Alzhemed is a glycosaminoglycan (GAG) mimetic that competes with GAG binding sites to reduce soluble AB and

block fibril formation.[48] Flurizan (R-flurbiprofen) is a selective AB-42 lowering agent working through allosteric modulation of γ secretase.[49] One or both of these compounds could be available to clinicians within two years.

Conclusions

From the writings of Alois Alzheimer and his scientific peers, it is clear that none of them foresaw the worldwide importance of the clinicopathological syndrome that bears his name. One of the lessons of the last century is surely how the power of a name can generate fear, funding, hope and (hopefully) fully formed treatments. But that cohesion comes at a cost. By seeing the world of late life dementia through the prism of Alzheimer's disease, we may have overlooked important avenues of discovery, and adjustments to the definition of this disease may still be warranted. Despite the unsolved questions that remain and the technical challenges ahead, the future looks brighter now than at any time in the past century and we can hope that very soon, future anniversaries of the discovery of Alzheimer's disease will celebrate a disorder that has been vanquished. **PN**

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1. Maurer K, Maurer U. Alzheimer: The Life of a Physician and the Career of a Disease. New York: Columbia University Press, 2003.

2. Alzheimer A. Uber eine eigenartige Erkrankung der Hirnrinde. Allg Z Psychiatrie 1907;64:146.

3. Perusini G. Über klinische und histopathologische eigenartige psychische Erkrankungen des späteren Lebensalters. In: Nissl F, Alzheimer A, eds. Histopathologische Arbeiten _ber die Grosshirnrinde unter besonderer Ber_ksichtigung der pathologischen Anatomie der Geisteskrankheiten. Leipzig, 1911: 297-351.

4. Kraepelin E. Psychiatrie. Ein Lehrbuch fur Studierende und Aertze. Leipzig, 1910.

5. omlinson B, Blessed G, M R. Observations on the brains of non-demented old people. J Neurol Sci 1968; 7:331-356.

6. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Revised Fourth Edition. Washington, D.C.: American Psychiatric Association, 1995.

7. Green RC. Diagnosis and Treatment of Alzheimer's Disease and Other Dementias, 2nd edition ed. Caddo, OK: Professional Communications, Inc., 2005.

8. Cummings JL. Alzheimer's disease. New Engl J Med 2004;351:56-67.

9. Mendez MF, Mastri AR, Sung JH, Frey WH. Clinically diagnosed Alzheimer disease: Neuropathologic findings in 650 cases. Alzheimer Dis Assoc Disord 1992;6:35-43.

10. Becker JT, Boller F, Lopez OL, Saxton J, McGonigle KL, Alzheimer Research Program. The natural history of Alzheimer's disease: description of study cohort and accuracy of diagnosis. Arch Neurol 1994;51:585-594.

11. Mayeux R, Saunders AM, Shea S, et al. Utility of the Apolipoprotein E and the diagnosis of Alzheimer's disease. New England J Med 1998;338:506-511.

12. Morris JC. Is Alzheimer's disease inevitable with age? Lessons from clinicopathologic studies of healthy aging and very mild Alzheimer's disease. The Journal of Clinical Investigation 1999;104:1171-1173.

13. Petersen RC. Mild cognitive impairment as a diagnostic entity. Journal of Internal Medicine 2004;256:183-194.

14. Bennett DA. Mild cognitive impairment. Clinical Geriatric Medicine 2004;20:15-25.

15. Galasko D. Biomarkers for Alzheimer's disease - Clinical needs and applications. J Alz Dis 2005;8:339-346.

16. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Annals of Neurology 2004;55:306-319.

17. Atiya M, Hyman BT, Albert MS, Killiany R. Structural magnetic resonance imaging in established and prodromal Alzheimer's disease: A review. Alzheimer's Disease and Associated Disorders 2003;17:177-195.

18. Jack CR, Petersen RC, Xu Y, et al. Rates of hippocampal atrophy correlate with change in clinical status in aging and AD. Neurology 2000;55:484-489.

19. Jack CR, Petersen RC, Xu YC, et al. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. Neurology 1999;52:1397-1403.

20. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex and ethnicity on the association between apolipoprotein E genotype and Alzheimer's Disease: A meta-analysis. JAMA 1997;278:1349-1356.

21. Green RC. Genetic susceptibility testing for Alzheimer's Disease: Has the moment arrived? Alzheimer's Care Quarterly 2002;3:208-214.

22. Roberts JS, Cupples LA, Relkin N, Whitehouse PJ, Green RC. Genetic risk assessment for adult children of people with Alzheimer's disease: The Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study. J Geriatr Psychiatr Neurol 2005;18:250-255.

23. Khachaturian ZS. Diagnosis of Alzheimer's disease. Arch Neurol 1985;42:1097-1105.

24. Markesbery WR. Neuropathological criteria for the diagnosis of Alzheimer's disease. Neurobiology of Aging 1997;18:S13-S19.

25. Braak H, Braak E. Pathology of Alzheimer's disease. In: Calne DB, ed. Neurodegenerative Diseases. Philadelphia: W. B. Sanders, 1994: 585-613.

26. Haass C, Selkoe DJ. Cellular processing of amyloid b-peptide. Cell 1993;75:1039-1042.

27. Selkoe D. Alzheimer's disease is a synaptic failure. Science 2002;298:789-791.

28. Iqbal K, Grundke-Iqbal I. Pharmacological approaches to neurofibrillary degeneration. Current Alzheimer Research 2005;2:335-341.

29. Lee VM-Y, Trojanowski JQ. Progress from Alzheimer's tangles to pathological tau points towards more effective therapies now. J Alz Dis 2006;9:257-262.

30. Näslund J, Haroutunian V, Mohs R, et al. Correlation between elevated levels of amyloidß-peptide in the brain and cognitive decline. JAMA 2000;283:1571-1577.

31. Bartus RT, Dean RL, Beer B, Lippa AS. The cholinergic hypothesis of geriatric memory dysfunction. Science 1982;217:408-417.

32. Davis KL, Thal LJ, Gamzu ER, et al. A double-blind, placebo-controlled multicenter study of tacrine for Alzheimer's disease. N Engl J Med 1992;327:1253-1259.

33. Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The New England Journal of Medicine 1997;336:1216-1222.

34. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. New Engl J Med 2005;352.

35. Mulnard RA, Cotman CW, Kawas C, et al. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: A randomized controlled trial. JAMA 2000;283:1007-1015.

36. Henderson VW, Paganini-Hill A, Miller BL, et al. Estrogen for Alzheimer's disease in women: Randomized, double-blind, placebo-controlled trial. Neurology 2000;54:295-301.

37. Espeland MA, Rapp SR, Shumaker SA, et al. Conjugated equine estrogens and global cognitive function in postmenopausal women: Woman's Health Initiative Memory Study. Journal of the American Medical Association 2004;291:2959-2968.

38. Szekely CA, Thorne JE, Zandi PP, et al. Nonsteroidal anti-inflammatory drugs for the prevention of Alzheimer's disease: A systematic review. Neuroepidemiology 2004;23:159-169.

39. Aisen PS, Schafer KA, Grundman M, et al. Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. JAMA 2003;289:2819-2826.

40. Reines SA, Block GA, Morris JC, et al. Rofecoxib: No effect on Alzheimer's disease in a 1-year, randomized, blinded, controlled study. Neurology 2004;62:66-71.

41. Fillit H, Butler RN, O'Connell AW, et al. Achieving and maintaining cognitive vitality with aging. Mayo Clinic Proceedings 2002;77:681-696.

42. Christensen DD, Green RC. Disease-modifying therapy for Alzheimer's disease: Update on emerging treatments. CNS News 2005:21-26.

43. Tomita T, Iwatsubo T. Gamma secretase as a therapeutic target for treatment of Alzheimer's disease. Current Pharmaceutical Design 2006;12:661-670.

44. Willem M, Garratt AN, Novak B, et al. Control of peripheral nerve myelination by the B secretase BACE1 Science 2006;314:664-666.

45. Schenk D, Barbour R, Dunn W, al. e. Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. Nature 1999;400:173-177.

46. Janus C, Pearson J, McLaurin, et al. A beta peptide immunization reduces behavioural impairment and plaques in a model of Alzheimer's disease. Nature 2000;408:979-982.

47. Green RC, DeKosky S. Primary prevention trials in Alzheimer's disease. Neurology 2006;in press.

48. Aisen PS, Saumier D, Briand R, et al. A Phase II study targeting amyloid-B with 3APS in mild-to-moderate Alzheimer disease. Neurology 2006;67:1757-1763.

49. Wilcock G, Black S, Haworth J, et al. A placebo-controlled, double-blind trial of the selective AB42-lowering agent Flurizan (MPC-7869. R-flurbiprofen) in patients with mild to moderate Alzheimer's disease. In: Alzheimer's Association International Conferenence on Prevention of Dementia. Washington, DC, 2005.